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SUMARY

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Exterior

Amalia Peix - Instituto de Cardiología y Cirugía Cardiovascular, Havana – Cuba
Amelia Jiménez-Heffernan - Hospital Juan Ramón Jiménez, Huelva – Spain
Ana Isabel Venâncio Oliveira Galrinho - Hospital Santa Marta, Lisboa – Portugal
Ana Maria Ferreira Neves Abreu - Hospital Santa Marta, Lisboa – Portugal
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EDITORIAL

Translational Medicine – New Frontiers in Cardiology

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"A scientist is happy, not in resting on his attainments but in the steady acquisition of fresh knowledge."

Max Planck

Translational medicine is defined by the European Society for Translational Medicine (EUSTM) as "an interdisciplinary branch of the biomedical field supported by three main pillars: benchside, bedside, and community.[1] Frequently, translational medicine dedicated to cardiology is known as translational cardiology. The International Journal of Cardiovascular Sciences is dedicating a special thematic issue on translational cardiology due to the significant importance of this field in the last years. Searching PubMed for the keywords "translational" and "cardiology," the number of papers on translational cardiology were no more than 10 per year in mid-80's, with an increase to around 50 papers per year in mid-90's, 200 articles per year in the 2000's and, thereafter, a significant exponential increase in the absolute number of publications, close to 2,000 papers/year in 2019 (Figure 1). Cardiac journals are increasingly accepting translational papers covering different aspects of this exciting field, so diverse as cardiotoxic mechanisms[2] targeting RNA with antisense oligonucleotides and small interfering RNA in amyloidosis[3] or nitrosative stress as a modulator of inflammatory change in Takotsubo Syndrome[4] to name a few.

In this special edition, we present articles covering many areas in Cardiology, but with a common denominator: translational medicine. Intentionally, we covered several areas, from genetic/epigenetic to treatment of arrhythmias. The reason for this approach is that the intrinsic concept of translational medicine is not restricted to a single specialty; indeed, it applies to all areas of knowledge and their applications. The concept of translational medicine emerged and continues to evolve based on frequent observations, findings originated from hypothesis and laboratorial research, both in vitro and in vivo, but consumed decades before reaching the clinical arena. On the other hand, many original clinical observations remained without clarification of their basic mechanisms, either cellular, molecular or genetics. As a result, important clinical findings were considered "anecdotal" for considerable periods of time until mechanistic and trustful clinical studies were performed. Hence, significant clinical findings were never implemented in a broad sense; on the other hand, myth persisted until time demonstrated they were nothing more than myths. Evidently, these two circumstances contributed to the slow progress in medical care, i.e., on one hand, unrecognized truths, and proclaimed fallacies on the other. Lately, another question appeared, namely, the application of knowledge not only to the individuals but to the whole population as well. This closes the circle of translation: from basics to clinical application; from clinical observation to laboratory studies of their causes and mechanism. Finally, from knowledge generation to population uses. Thus, translational medicine deals with this complex array of hypothesis, rigorous scientific testing and population applicability.

Keywords

Translational Medicine/ trends; Translational Medical Research/trends; Basic Research/trends; Implementation Science/ trends; Access health technologies and informations/ trends.

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Academic institutions are already reviewing organizational structures, promoting innovative polices, to implement this concept. Under such concept, basic researches and clinical investigators must collaborate tightly and carry on investigative programs. This requires structural modifications in universities and research institutes. These changes depend on specific institutional policies; individual actions are not sufficient. In other words, we need profound philosophical modifications and, consequently, administrative policies in order to materialize the translational concept. Such materialization of the translational concept will accelerate scientific progress and its clinical application.

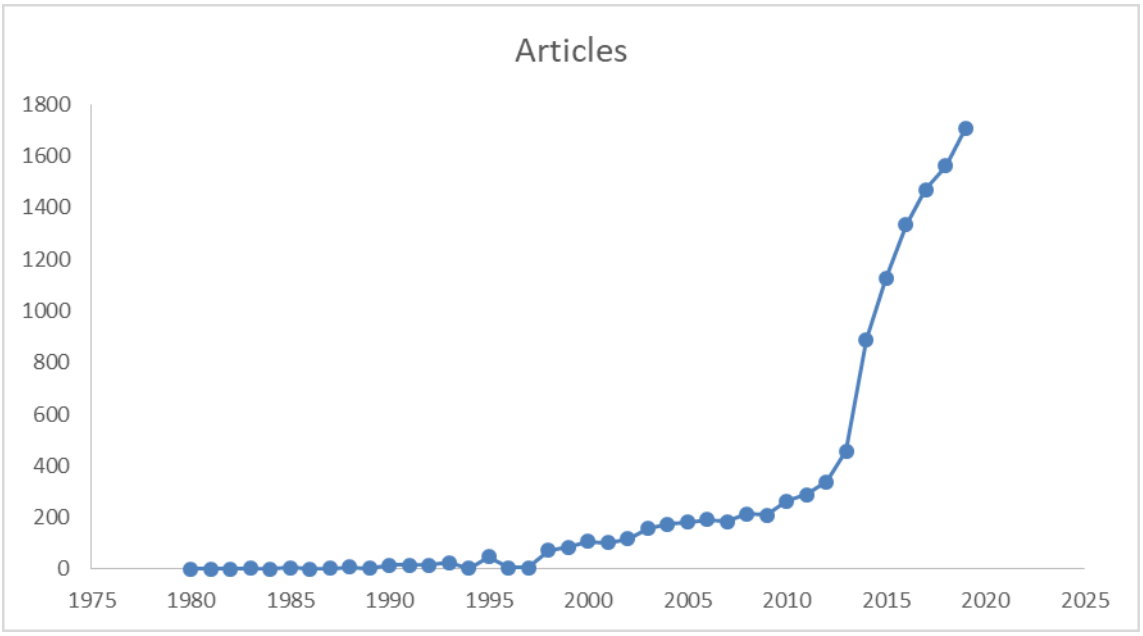

Figure 1 – Number of articles related to the term "translational and cardiology" that were indexed by PubMed per year (data extracted from PubMed).

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EDITORIAL

Heart Failure – Pathophysiology and Current Therapeutic Implications

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The concept of translational medicine involves promoting the rapid transfer of observations made in the areas of research and pathophysiological understanding to the medical practice. This approach is a reality in major Brazilian research centers which link academia and clinical practice.

Heart failure (HF) is a complex syndrome that can manifest itself as heart failure with preserved ejection fraction (HFpEF), acute heart failure, or chronic heart failure with reduced ejection fraction (HFrEF). Here, we will cover the type of HF whose pathophysiology is understood the best and thus has disease-modifying treatments: HFrEF.

In 1785, in the United Kingdom, the physician and biologist William Withering outlined one of the first major moves towards treatment options for HF when he wrote the book "An Account of the Foxglove and some of its Medical Uses With Practical Remarks on Dropsy and Other Diseases.[1]" Known as a kidney disease that caused fluid to accumulate in the body, HF was primarily treated with an extract of Digitalis purpurea, a plant popularly known as foxglove. In his research, Withering described some cases where he administered this compound, now known as digitalis, to HF patients and noticed improvements in the disease symptoms. Although no scientific data has proven, to date, a change in hard outcomes with the use of digoxin (an active compound of digitalis) , this medication still has a prominent place in the treatment of HF. Since 1980, more rigorous studies have been performed to demonstrate the safety and efficacy of digoxin: 4 large studies – DIMT (1993),[2] RADIANCE (1993),[3] PROVED (1993),[4] and DIG (1997)[5] – substantiated its clinical use, demonstrating clinical improvement of the patients and a reduction in hospitalization, although not in mortality (Table 1).

During the 19th century and at the beginning of the 20th century, literature on the treatment of HF was mostly inexistent; for a long time, patients with this salt and liquid-retaining disease were administered only digitalis to improve cardiac contractility and diuretics to relieve edema. Until the late 1960s, HF was thought to follow a cardio-renal pathophysiological model summarized in edema and congestion. It was not until the 1970s that this conception was modified by the cardiocirculatory view of the system as, in a simplistic view, a system connecting vessels to a pump. From the moment HF was understood as the failure of a pump, which in turn was based on the Frank-Starling mechanism and the behavior of the vessels connected to it, generating preload and afterload, there was a commitment to discovering vasodilators. This endeavor owes greatly to professor Jay Cohn, who for 22 years recruited researchers who demonstrated how vasodilator medications could improve left ventricular function. He further pioneered the interest in hormones as contributors to vasoconstriction and promoted the concept that neurohormonal inhibition could inhibit the structural remodeling of the heart.[6]

In 1986, Cohn *et al.* published one of the first major studies that laid the foundation for HF specialists: "Effect of Vasodilator Therapy on Mortality in Chronic Congestive Heart Failure.[7]" The use of hydralazine in association with isosorbide dinitrate demonstrated that peripheral vasoconstriction not only contributed to the worsening of HF symptoms but also favored the deterioration of left ventricular function and sudden death. With a 38% reduction

Keywords

Heart Failure/physiopathology; Stroke Volume; Translational Medical Research; Digitalis Glycosides; Diuretics; Myocardial Contraction; Edema.

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COMPARATIVE TRIALS: BETA-BLOCKERS				
TRIAL		US CARVEDILOL	MERIT HF	CIBIS - II
YEAR		1996	1999	1999
POPULATION		FC II, III, IV EF≤35%	FC II, III, IV EF≤40%	FC III, IV EF≤35%
N		1094	3991	2647
TREATMENT REGIMEN		(Carvedilol x Placebo) + ACEI/ARB + Digoxin + Diuretic	(Metoprolol x Placebo) + ACEI/ARB + Digoxin + Diuretic	(Bisoprolol x Placebo) + ACEI/ARB + Digoxin + Diuretic
FIRST ENDPOINT		Death or hospitalization due to cardiovascular causes	Reduction of mortality and symptoms in HF patients	Reduction of all causes of mortality in chronic HF
MORTALITY	DRUG	3.2%	7.2%	11.8%
	PLACEBO	7.8%	11.0%	17.3%
RRR		59.0	35.0	31.7%
ARR		4.6%	3.8%	5.5%
NNT		21	26	18

* FC - Functional class
* EF -Left ventricle ejection fraction
* ACEI/ARB -Angiotensin-Converting Enzyme Inhibitor /Angiotensin Receptor Blocker
* RRR - Relative Risk Reduction
* * ARR – Absolute Risk Reduction
* NNT - Number Needed to Treat

in mortality after 1 year, the hydralazine-nitrate combination proved that vasodilators were essential in the treatment of this disease.[7] In the struggle to change the natural history of HF, numerous trials were subsequently designed, validating the use of now well-established vasodilators. In the event of a drop in ejection fraction for a specific reason, vasodilation should facilitate the functioning of the cardiovascular system. However, it was observed that, in addition to improving functioning, it was necessary to stop the HF continuum, avoiding its perpetuation caused by the consequent dilation of the left ventricle.

It is worth mentioning that advances in the concept of vasodilation as well as new explanations for the mechanisms involved in HF and its real impacts on mortality were brought by studies performed in the 1990s. The highlight of the renin-angiotensin-aldosterone system was revealed by the SOLVD trial (Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fraction and Congestive Heart Failure) in 1991. This study was the first to demonstrate the benefits of using angiotensin-converting enzyme inhibitors (ACEIs) in the treatment of HF.[8]

A few years earlier, in 1987, great evidence had already been provided by the CONSENSUS trial (Effects of Enalapril on Mortality in Severe Congestive Heart Failure) that this class of drugs, in addition to improving the functional classification of patients with chronic HF, could also reduce mortality.[9] In this trial, which randomized only patients with class IV HF (according to the New York Heart Association [NYHA]), mortality in the placebo group was 52% after 1 year. Comparing the causes of death in the 2 groups, it was noteworthy that sudden death was equally present in both. The absolute reduction in total mortality was 27%. The SOLVD study then proved this tendency of reduced mortality in patients with chronic HF treated with enalapril when compared to placebo, despite also observing no significant differences in sudden death rates.

These studies opened an era of discoveries regarding vasodilators and, in particular, ACEIs and angiotensin receptor blockers (ARBs). Various studies have proven the superiority of this class of drugs: V-Heft II (A Comparison of Enalapril with Hydralazine–Isosorbide Dinitrate in the Treatment of Chronic Congestive Heart Failure),[10] in particular, compared the nitrate-hydralazine combination to enalapril, revealing unprecedented data regarding a reduction of sudden death in the enalapril group. Therefore, in addition to the vasodilation effect, anti-proliferative, anti-apoptotic and inflammatory cytokine inhibitor effects were added to the disease.

Still in the 1990s, the decade in which the pathophysiology of HF was elucidated the most, what was long postulated was designed, tested and proven: the effect of catecholamines on the development of HF.[11] Beginning in 1897, Starling described tachycardia and peripheral vasoconstriction as components of this syndrome and responsible for an increase in cardiac contractility as a compensatory response.[12,] In 1964, Dr. Eugene Braunwald wrote an editorial titled "The heart as an endocrine organ,[13]" on the occasion of the discovery that it was able to synthesize norepinephrine.[14] These findings led to the hypothesis that sympathetic activation played an important role in the progression of HF. Norepinephrine can have direct and indirect adverse effects on the circulation, and interfering with its actions can slow the progression of HF in animal models.[15,16] In 1996, the large US-CARVEDILOL study evaluated the effect of the beta-blocker carvedilol on the survival of patients with HF.[17] The study had an early end because the observed benefit surpassed that envisaged by its design: patients treated with carvedilol had a 65% lower risk of death than those who received placebo. This remarkable effect was indicated by a decrease in risk of death both due to the progression of HF and to sudden death. Since then, other beta-blockers such as extended-release metoprolol succinate (MERIT-HF, 1999)[18] and bisoprolol (CIBIS II)[19] have been tested for HF and have shown a significant effect in reducing hard outcomes (Table 2).

By the end of the 20th century, the horizons of HF therapy had completely changed, and the disease that previously attracted little effort from the scientific community for being known as "terminal" now could be treated with interventions that significantly reduced mortality. The famous renin-angiotensin system, which was popular during the discovery of HF and its decompensations, remained the center of attention. In 1999, the RALES study evaluated spironolactone, an aldosterone antagonist, in the course of HF and observed a 30% reduction in mortality. The exact mechanism through which this was achieved is not yet well understood, but it is known that spironolactone improves hemodynamics, cardiac remodeling, and natriuresis in patients with HF.[20]

Once the progression of the disease has been alleviated with established pharmacological therapies, the main cause of mortality in patients with HF is now recognized as sudden death from malignant arrhythmias. Two proposals have been made to reduce the risk of these arrhythmias: the use of antiarrhythmics such as amiodarone and the implantable cardioverter-defibrillator (ICD). In 2002, the MADIT-II study (Prophylactic Implantation of a Defibrillator in Patients with Myocardial Infarction and Reduced Ejection Fraction) compared patients with ischemic cardiomyopathy and a left ventricular ejection fraction (LVEF) < 35% who received an ICD as primary prophylaxis or were submitted to conventional therapy. This study showed a 31% reduction in the risk of dying from a malignant arrhythmia after ICD implantation.[21] In 2005, the SCD-HeFT trial (Amiodarone or an Implantable Cardioverter–Defibrillator for Congestive Heart Failure) demonstrated that ICD implantation in patients with NYHA class II HF reduced mortality by 12% in 5 years when compared to amiodarone, thus establishing its indication for ischemic and symptomatic patients[22] (Table 3).

Regarding cardiac stimulation devices, it is worth mentioning cardiac resynchronization therapy (CRT). Still quite debatable, despite being proven effective, CRT has brought benefits in improving survival, symptoms, and reducing hospital readmissions. However, some patients have been observed to not respond to this therapy in the clinical practice. One of the first trials to assess CRT was published in 2003 and was named MIRACLE (Cardiac Resynchronization in Chronic Heart Failure).[23] It aimed to assess whether patients with delayed intraventricular conduction would have clinical benefits with the implantation of this device. The study recruited 453 patients with ejection fractions (EFs) ≤ 35%, NYHA class III or IV, QRS ≥ 130 ms, and left ventricular end-diastolic diameter ≥ 55 mm. After 6 months, it was concluded that the device was capable of providing important clinical improvements to the HF syndrome: patients in the intervention group showed changes in quality of life, NYHA functional class, and the 6-minute walk test.

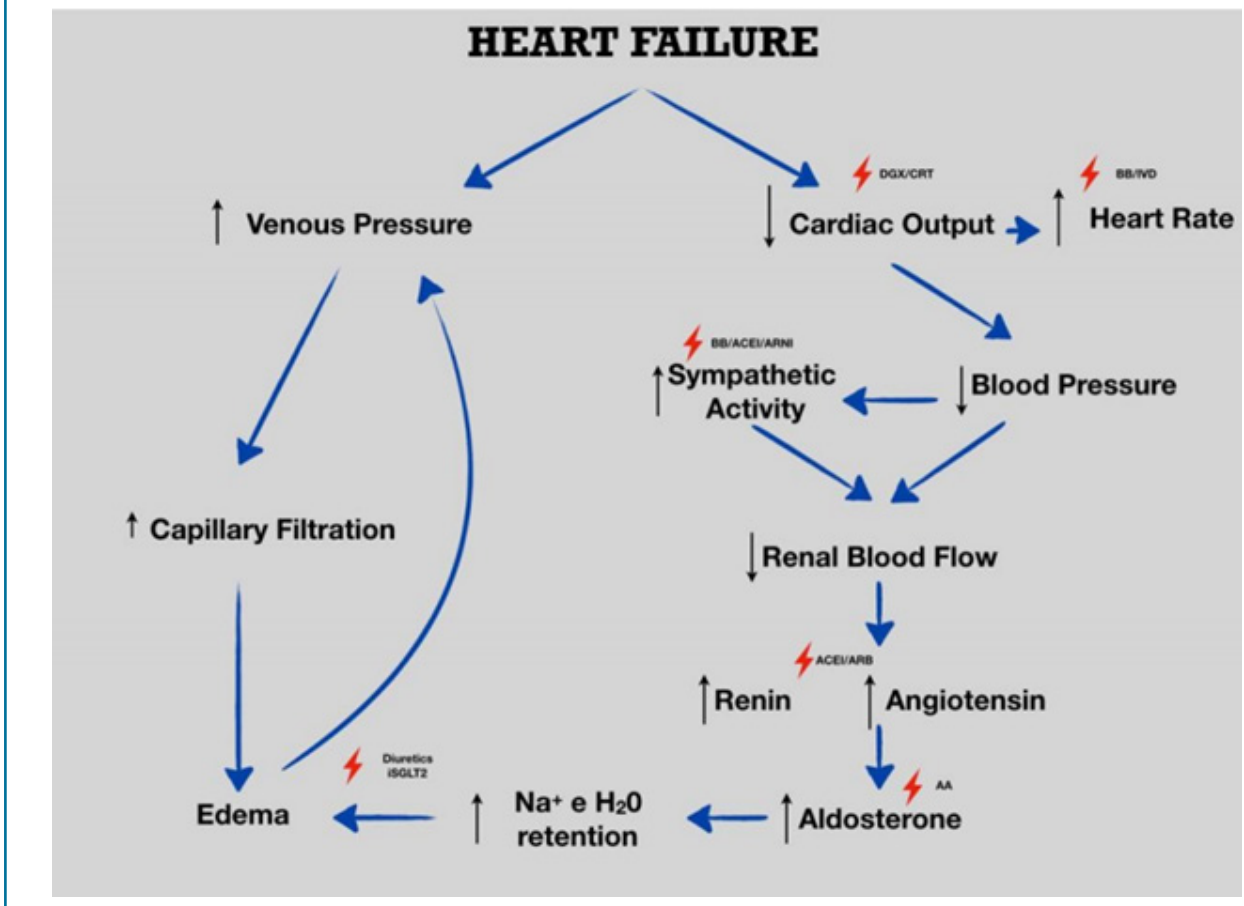
In order for this new therapy to be added to the HF treatment arsenal, other studies were conducted to verify if the device could modify hard outcomes. Since 2002, various studies have proven a reduction in the mortality of patients with QRS > 120 ms, who are sinus rhythm, belong to NYHA classes ≥ III, or are under optimized drug therapy (ODT): COMPANION (Cardiac-Resynchronization

COMPARATIVE TRIALS: DIGOXIN				
TRIAL	DIMT	RADIANCE	PROVED	DIG
YEAR	1993	1993	1993	1997
POPULATION	FC II, III	FC II, III EF≤35%	FC II, III EF≤35% + Sinus Rhythm	FC I - IV EF≤45%
FOLLOW-UP	6 Months	3 Months	3 Months	37 Months
N	161	178	88	6800
TREATMENT REGIMEN	Ibopamine x (Digoxin + Placebo)	Digoxin x Placebo	Digoxin Withdrawal (Placebo) x Digoxin	[Digoxin x Placebo] + Diuretics + ACEI
FIRST ENDPOINT	Efficacy and safety of this ibopamine in mild and moderate chronic HF	Effect of digoxin suspension in patients with chronic HF receiving [captopril or enalapril] + diuretic + digoxin	Efficacy in HF patients	Mortality
RESULTS	Digoxin increased exercise time / Mortality was not affected	Worsening of HF = functional capacity + worsening of the Ejection Fraction + increased cardiac frequency + weight increase.	Worsening of HF = functional capacity + greater treatment failure + worsening of the Ejection Fraction + increased cardiac frequency + weight increase	34.8% (digoxin) x 35.1% (placebo). Significant P for secondary outcome of HF hospitalization reduction

* FC - Functional Class
* EF - Left Ventricle Ejection Fraction
*ACEI - Angiotensin Converting Enzyme Inhibitor

Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure),[24] CARE-HF (The Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure),[25] MADIT-CRT (Cardiac-Resynchronization Therapy for the Prevention of Heart-Failure Events),[26] and RAFT (Cardiac-Resynchronization Therapy for Mild-to-Moderate Heart Failure).[27] The indication for CRT was established by the Brazilian Guidelines for Chronic and Acute Heart Failure with level of evidence IA for patients presenting the following: EF ≤ 35%, left bundle branch block, sinus rhythm, QRS ≥ 150 ms, and symptoms despite ODT.

In 2010, after observational studies,[28] heart rate (HR) was considered one of the factors with the worst prognosis in HF. A continuously high resting HR is responsible for the progressive worsening of not only the ventricular function but also coronary atherosclerosis and ventricular arrhythmias. Thus, considering the effect already provided by beta-blockers, a new drug acting only on the sinus node was proposed for selective inhibition of the If current. It has been validated for patients that are symptomatic despite therapeutic optimization, in sinus rhythm, and with a HR > 70 bpm. In the SHIFT study (Ivabradine and Outcomes in Chronic Heart Failure), 6558 randomized patients were randomly assigned to receive ivabradine or placebo, in a 1:1 ratio. After a 22.9-month follow-up period, patients who received the drug had a relative risk for the primary endpoint of 18%, with a number needed to treat (NNT) of 20 and $p < 0.001$.[29] In 2018, ivabradine



was incorporated by the Brazilian Guidelines for Chronic and Acute Heart Failure with a class IIA recommendation and level of evidence B.

Twenty-five years after the establishment of enalapril, biomarkers have taken center stage in the HF scenario. In 1988, professor Hisayuki Matsuo discovered a natriuretic peptide synthesized in the brain of pigs, which he named cerebral natriuretic peptide.[30] Later, confirming Dr. Braunwald's predictions from 1964, it was discovered in humans that the main source of this peptide was the heart, and it became known as B-type natriuretic peptide (BNP). In 2002, a prospective study evaluated BNP levels in 1586 patients who arrived at an emergency room with acute dyspnea, showing that these levels alone were more accurate than any historical or physical findings in identifying congestive HF as a cause of dyspnea. After the publication of this "BNP Multinational Study" trial in the New England Journal of Medicine, there was great impetus for the practical application of findings related to endogenous vasoactive peptides.[31]

In September 2014, McMurray *et al.* published PARADIGM-HF,[32] a fundamental study for HF specialists. Based on the inhibition of neprilysin (an enzyme responsible for the degradation of vasoactive peptides such as natriuretic peptides), as well as bradykinin, adrenomedullin, and angiotensin II, the new sacubitril-valsartan drug was proposed as another form of neurohormonal inhibition in HF. Similarly to US-CARVEDILOL, PARADIGM-HF was interrupted early (after an average follow-up period of 27 months) due to a significant reduction in mortality with a NNT of 21 for the primary event and 32 for mortality.

Every paradigm-modifying trial should be read and interpreted by each expert with a critical eye. PARADIGM-HF is no different. The entry of sacubitril-valsartan in the market occurred with great support from the pharmaceutical industry and, although the use of this medication is currently commendable in many cases, the traditional ACEI still holds its importance in the treatment of HF. The standard treatment of this syndrome comprising ACEI + beta-blocker + mineralocorticoid receptor antagonist has been put to the

COMPARATIVE TRIALS: ICD						
TRIAL	MADIT - II	SCD - HeFT				
YEAR	2002	2004				
POPULATION	FC I - IV + Primary AMI EF≤30%	FC II, III EF≤35%				
N	1.232	2.521				
DURATION	20 Months	45.5 Months				
TREATMENT REGIMEN	ICD X Drug Treatment (3:2)	Amiodarone x (Placebo + ICD)				
FIRST ENDPOINT	Mortality from any cause	Mortality from any cause				
P	0.016	0,07				
RRR	28.00%	ICD	24.00%	Amiodarone	3.50%	
ARR	5.60%	x	4.00%	x	1.00%	
NNT	17.8	p	14.0	p	100.0	

* FC - Functional Class
* EF:left ventricle ejection fraction
* ICD – implantable cardioverter-defibrillator.
* RRR - Relative risk reduction
* ARR - Absolute risk reduction
* NNT - Number needed to treat
*AMI - Acute Myocardial Infarction
*P - Placebo

test and, in well-defined cases, has already given way to the sacubitril-valsartan + beta-blocker + mineralocorticoid receptor antagonist triad.

Finally, the most recent major advance in HF drug therapies, the SGLT2 inhibitors, cannot go unmentioned. This drug class was developed primarily for the treatment of type 2 diabetes mellitus (T2DM), but a significant trend was observed in the improvement of patients with HF. As further explained below, it is currently being tested for the treatment of patients with HF regardless of the presence of T2DM.

The healthy human kidney does not excrete glucose because the proximal tubule contains co-transporters (SGLT1/2) responsible for its reabsorption, carrying it to the epithelial cell against a concentration gradient using ATP through the Na^+/K^+ pump. SGLT2 reabsorbs approximately 90% of the filtered glucose but is unable to do so when the glucose concentration in the ultrafiltrate is too low. In light of this knowledge, in 1987, Rossetti *et al.* used a murine model of diabetes to demonstrate that phlorizin, a competitive inhibitor of SGLT, could correct hyperglycemia, improve insulin secretion, and reverse insulin resistance.[33] This medication was not clinically tolerated in humans because it caused an intense diarrhea; however, it attracted attention to a possible target for the treatment of diabetes. As SGLT2 transports sodium and glucose in a 1:1 ratio, the higher the glycosuria, the greater the natriuretic effect. This knowledge has important implications for the treatment of patients with HF.

The EMPA-REG (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) study, published in 2015, was the first to demonstrate a significant cardioprotective effect of the use of SGLT2 inhibitors (SGLT2is). This drew the attention of the scientific community to a possible new drug for completing the quadruple arsenal for the treatment of HF.[34] Empagliflozin showed a 38% relative risk reduction in mortality from cardiovascular causes, 35% in hospitalizations due to HF, and 32% in mortality from any cause when compared to placebo. Subsequently, studies evaluated other gliflozins (canagliflozin and dapagliflozin) and pointed to a sustainable benefit in improving HF.

Recently, in 2019, DAPA-HF (Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction) was the first study to provide evidence of the benefit of gliflozins in non-diabetics, which should expand their indication (currently limited by glycated hemoglobin). In this study, McMurray *et al*. demonstrated that, after an average follow-up period of 18 months, this medication reduced the risk of cardiovascular death by 26% and avoided worsening HF (defined as emergency care that required intravenous

therapy or hospitalization for HF) compared to placebo. A very interesting finding was the size of this benefit, which was almost identical between patients with or without T2DM (25% and 27% reduction, respectively). When analyzed separately, cardiovascular death and worsening HF were significantly reduced in patients treated with dapagliflozin (18% and 30%, respectively). In addition, the treatment reduced the risk of death from all causes by 17%.[35]

The mechanism through which SGLT2is provide such impressive cardiovascular benefits is still unclear. It appears to be secondary to the hemodynamic effects provided by natriuresis and osmotic diuresis, which result in a reduction in intravascular volume and blood pressure. The consequent decrease in preload and afterload reduces pulse pressure and oxygen consumption in the myocardium. Although this mechanism is not yet fully elucidated, the fact is that all studies considering different SGLT2is demonstrated cardiovascular protection and a reduction in the development of HF (Table 4).

Finally, the big question remains: will we have a quadruple therapy dedicated to HF? Does the benefit of these new drugs have any bearing on the fact that all patients in the study are correctly using the standard therapy? The possibility of obtaining these answers is highly unlikely because taking a step back and comparing ACEIs or beta-blockers alone in each arm with new drugs is not ethically feasible. Moreover, the rapidly increasing body of knowledge on the pathophysiology of the HF syndrome also leads us to confront new dilemmas that we may not be able to solve (Table 5).

COMPARATIVE TRIALS: SGLT2is				
TRIAL	EMPA-REG	CANVAS Program	DECLARE - TIMI 58	DAPA -HF
YEAR	2015	2017	2018	2019
TREATMENT REGIMEN	Empagliflozin x Standard treatment	Canagliflozin x Standard treatment	Dapagliflozin x Standard treatment	Dapagliflozin x Standard treatment
FOLLOW-UP TIME	37.2 Months	28.8 Months	74.4 Months	18.2 Months
N	7024	10142	17160	4744
CARDIOVASCULAR DISEASE	100.00%	65.60%	40.60%	100.00%
HEART FAILURE	10.10%	14.40%	10.00%	100.00%
FIRST ENDPOINT	MACE, all-cause mortality, cardiovascular mortality, myocardium infarction, stroke, cardiovascular hospitalization, disease progression, or renal mortality.	MACE, all-cause mortality, cardiovascular mortality, myocardium infarction, stroke, cardiovascular hospitalization, disease progression, or renal mortality.	MACE, all-cause mortality, cardiovascular mortality, myocardium infarction, stroke, cardiovascular hospitalization, disease progression, or renal mortality.	Hospitalization or visit to the emergency room due to HF, hospitalization for HF, visit to the emergency due to HF or cardiovascular death
P (SUPERIORITY)	Not significant	Not significant	Not significant	<0.001
RRR	13.00%	15.00%	0.06%	23.00%
ARR	1.60%	0.46%	0.60%	4.90%
NNT	62.50	217.00	166.00	20.00
SECONDARY ENDPOINT (hospitalization due to HF)				
P	0.002	<0.001	**0.005	
RRR	35.00%	37.00%	18.00%	
ARR	5.10%	3.20%	2.50%	
NNT	19.00	31.00	40.00	

* MACE - Cardiovascular death, myocardium infarction or stroke
* RRR - Relative Risk Reduction
* ARR – Absolute Risk Reduction
* NNT - Number Needed to Treat
** cardiovascular death or hospitalization due to HF

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ORIGINAL ARTICLE

Dietary Fat Intake and its Association with Adiposity and Inflammatory Markers in Individuals at Cardiometabolic Risk

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Abstract

Background: Fatty acids are important components of diet that may influence the development of CVD.

Objective: To verify the relationship of dietary fatty acids with cardiometabolic markers in individuals at the cardiometabolic risk.

Methods: This cross-sectional study involved 282 subjects (116 M/166 F, 42 ± 16 years) attended the Cardiovascular Health Care Program, *Universidade Federal de Viçosa* (Brazil). Anthropometric and body composition measurements as well as metabolic and inflammatory markers were assessed by standard procedures. Demographic and lifestyle variables were obtained by semi-structured questionnaire. Food consumption was evaluated by 24h recall. Student's t-test or Mann-Whitney-U test and chi-square test were used, considering the statistical significance level of 5% probability.

Results: Individuals who eaten fat, fatty acids saturated and fatty acids polyunsaturated above recommendation (> 35, 7%, and 10% of caloric intake) were more likely to be overweight ($p < 0.05$). Those individuals with higher intake of medium-chain fatty saturated acids (≥ 1.05 g/d) had lower values ($p < 0.05$) of body mass index, waist circumference, waist-hip ratio and waist-height ratio and higher values ($p < 0.05$) of total leukocytes, C-reactive protein and total cholesterol, and LDL. Subjects with higher of palmitoleic acid intake (≥ 0.94 g/d) presented higher values of BMI, fat percentage and HOMA-IR ($p < 0.05$).

Conclusion: This cross-sectional study found different associations of dietary fat and cardiometabolic risk related to adiposity and inflammatory markers, according with chain-size and saturation, indicating the need the more detailed on the dietary assessment of obese patients to identify risk factors and established best strategies to control. (Int J Cardiovasc Sci. 2020; 33(5):447-456)

Keywords: Cardiovascular Diseases, Risk Factors; Metabolic, Syndrome; Obesity/prevention and control; Fatty, Acids; Biomarkers.

Introduction

The prevalence of overweight and obesity has grown at an alarming rate[1], and sedentary lifestyle and inadequate dietary patterns, with high fat and sugar intake contribute to the positive energy balance.[1,2] In addition, excessive fat accumulation, mainly in the abdominal region, has been implicated in the development of other chronic noncommunicable diseases (CNCD), such as diabetes (DM), dyslipidemias, systemic arterial hypertension and cardiovascular diseases (CVD).[3]

In this context, fatty acids are important components of diet that may influence the development of CVD, since fatty acids participate in important biological functions, such as energy substrate, regulation of metabolic pathways and inflammatory processes,

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hormone production, and participate in complex systems of intracellular signaling. Derivatives of fatty acids also act on the synthesis of prostaglandins, leukotrienes and thromboxanes,[4,5] being dietary fat important modulator of inflammatory status and cardiovascular risk.[6]

The medium chain fatty acids are absorbed in the non-esterified form and transported to the liver, bound to albumin, where they are rapidly metabolized. In turn, long-chain fatty acids undergo a process of esterification, forming triglycerides, which can remain in the bloodstream, carried by chylomicrons, or released into the tissues, acting as a form of fat storage in the body. Thus, excessive deposition of these lipids may lead to an increase in CVD.[7] However, little is known about the relationship between the consumption of medium and long chain fatty acids and cardiovascular risk parameters.

Dietary fatty acids can also be classified as saturated (SFA), monounsaturated (MUFA), and polyunsaturated (PUFA), according to saturation level. In this sense, high MUFA diet causes reduction in serum levels of total cholesterol, low density lipoprotein (LDL-c), triglycerides and increase in high density lipoprotein (HDL-c).[8,9] The PUFAs, especially those of the omega 3 series, are recognized by cardioprotective activity. However, SFAs are associated with proven deleterious effects, since they increase triglyceridemia and cholesterolemia, and have a proinflammatory action.[10] Regarding inflammation modulation by fat, Studies have found strong association of saturated fat intake with the synthesis of inflammatory biomarkers compared to polyunsaturated fatty acids.[11,12]

In this sense, the objective of the present study was to verify the relationship between dietary fatty acids and cardiometabolic markers in individuals at cardiometabolic risk treated at the Cardiovascular Assistance Program of the Federal University of Viçosa (PROCARDIO-UFV).

Methodology

Subjects

Participated in this cross-sectional study 282 patients included in PROCARDIO-UFV and had their first consultation until July/2016. PROCARDIO-UFV is a program that performs nutritional intervention to promote cardiovascular health in the academic community of UFV, registered in the Brazilian Clinical Trials Registry (ReBEC, number RBR-5n4y2g7).[13] The inclusion criteria in the program are: men and women; patients ≥ 20 years of age; students, workers and workers' dependents UFV; cardiovascular disease or occurrence of at least one cardiometabolic risk factor: overweight or obesity (Body Mass Index (BMI) ≥ 25 or 27 Kg/m²)[14,15] or/and dyslipidemia (Triglycerides (TG) ≥ 150 mg/dL or/and Total cholesterol (TC) ≥ 200 mg/dL or/and HDL-c < 40 or < 50 mg/dL for men and women)[10,16] or/and blood pressure ≥ 130/≥ 85 mmHg[16] or diagnosed hypertension or/and fasting glucose ≥ 110 mg/dL[16] or diagnosed diabetes mellitus.

The study did not include individuals who were not associated with the UFV, who did not present cardiometabolic risk or CVD, pregnant women, children and adolescents.

The study was approved by the Human Research Ethics Committees of the UFV (n° 066/2012/CEPH), in accordance to the Resolution 466/2012 of the National Health Council (CNS/Ministry of Health, Brazil) and to principles of the Declaration of Helsinki. All participants of the study read and signed the written informed consent form.

The data used were related to the first consultation. Of the 417 program users, 282 were selected for having complete data fatty acid intake.

Dietary Assessment

The volunteers responded to a 24-hour recall, reporting all food and drink consumed the day before (weekend or weekday) the consultation, as well as their quantities. In the present study, the daily intake of calories and total lipids (SFA, MUFA, and PUFA) were assessed using software, DietPRO, version 5.0i.

The determination of the intake of caprylic (C8: 0), capric (C10: 0), lauric (C12: 0), myristic (C14: 0), palmitic (C16: 0), stearic (C18: 1), SFA and oleic MUFA (C18: 1), linoleic (C18: 2, LA, family ω-6) and α-linolenic PUFA (C18: 3, LNA, family ω -3) and trans fatty acids were performed using the National Nutrient Database for Standard Reference (USDA) table.[17] The foods present in the recall and not listed in the USDA table had their composition estimated considering foods that presented nutritional composition and similar cooking methods.[17] In addition, the preparations were dismembered in their constituent ingredients and, in the case of not having the option of the composition for the cooked food, the raw food composition was used. The intake of each fatty acid was performed using a standard spreadsheet (Microsoft Excel®), developed specially for this aim.

Medium chain fatty acids were the sum of C8: 0 (caprylic acid), C10: 0 (capric acid) and C12: 0 (lauric acid).

And as long chain fatty acids the sum of myristic (C14: 0), palmitic (C16: 0) and stearic (C18: 0), monounsaturated fatty acids palmiticleic (C16: 1) and oleic (C18: 1) fatty acids (C18: 2, LA, family ω-6) and α-linolenic acid (C18: 3, LNA, ω-3 family). Adequate consumption of total fat, SFA, MUFA, PUFA and linoleic fatty acid was considered when the ingestion was between 25 and 35%; ≤ 7%; ≤ 20%; ≤ 10% of the daily energy value and between 1.1 and 1.6 g/day, respectively.[10] To assess the possible association of palmitoleic acid consumption and other variables of interest, the present study sample was categorized according to the median palmitoleic acid consumption (0.94g/day), medium chain fatty acids consumption (1.05 g/day) and long-chain fatty acids (LCFA) (18.92 g/day). The use of the median as a cutoff point has been used[18,19] based on the premise of the creation of risk groups in epidemiological studies.[20]

Anthropometry and Body Composition

Body weight and height were measured using a standardized protocol[21]

The Waist circumference was measured on the umbilical scar and hip ratio and waist-to height ratio were calculated. Waist circumference (WC) was measured from the umbilical scar in the horizontal plane.[22]

Abdominal obesity was considered WC greather than or equal to 80 and 90cm for women and men respectively.[23] Waist-to-height ratio (WH+R) and waist-to—hip ratio (WHR) were also calculated. WH+R and classified as high risk for (CVD) when ≥ 0,5 (both sexes); 0,85 (women) and 1.00 (men), respectively.[24,25] Total body fat (BF%) was assessed by tetrapolar electrical bioimpedance analysis, performed with standard protocol.[26] Obesity was diagnosed according to cut-off points proposed by Bray et al.;[27]: > 33 and 25% for women and men, respectively.

Metabolic Biomarkers

Fasting serum glucose, triglycerides, total cholesterol HDL, ferritin, uric acid and ultra-sensitive C-reactive protein (CRP-us) total leukocytes, were determined at the Laboratory of Clinical Analysis of the Health Division of the UFV, according to standardized protocol of this Laboratory.

Insulin resistance was estimated by the homeostasis-insulin resistance (HOMA-IR) model, which was calculated as follows: HOMA-IR = [fasting glucose (mmol/L)] fasting insulin (μUI/ml)]/ 22.5 and by the index triglycerides/glycemia (TyG), which was calculated as follows: Ln [fasted triglycerides (mg/dl) × fasting blood glucose (mg / dl)/2].[28]

Demographic and Lifestyle Variables

The variables age, sex, schooling, income, smoking, regular practice of physical activity and alcohol consumption were collected through interview of the participants.

Statistical Analyzes

The results were presented in absolute and relative frequencies, mean ± standard deviation and, or median (p25-p75). The normality of each variable was assessed by the Kolmogorov-Smirnov test. All dietary intake variables were adjusted by total caloric intake using the residual method, as proposed by WILLETT & STAMPFER.[29]

Non-paired Student-t and Mann-Whitney-U tests were used for comparison of two groups, where appropriate. Pearson's chi-square test was used to verify associations between socio-demographic variables, lipid consumption and nutritional status. All statistical analyzes were performed using the SSPS 21.0® program. We considered the level of statistical significance of 5% probability.

Results

Of the 282 subjects, 58.9% were female; 81.9% adults; 53.4% individuals reported practicing physical activity (self report) and 17.4% had diabetes. Of the overweight individuals, 76.6% were dyslipidemic (p = 0.028) (Table 1).

Table 2 shows dietary fat intake according to weight-status. Among the overweight individuals, 45.7% presented fat intake within the recommendation, but 79.7% of individuals consumed above recommendation to SFA.

The individuals (normal-weight and overweight) with higher consumption of medium chain fatty acids had lower values (p < 0.05) for BMI, perimeters of the waist, hip waist ratios, waist height ratios, ferritin, glycemia and uric acid. On the other hand, they had higher values (p < 0.05) of total leukocytes, total cholesterol, low density lipoprotein (LDL), HDL and CRP (Table 3). However, for long-chain fatty acids, only the total leukocyte count was significant (p = 0.038) for those with higher consumption (≥ 18.92 g/day) (data not shown). Individuals with higher intakes of palmitoleic

Table 1 - Characteristics PROCARDIO-UFV participants, according to body fat-status

Variables n (%)	Total (n = 282)	Normal-weight (n = 85)	Overweight (n = 197)	p-values
Sex				
Male	116 (41.1)	33 (38.8)	83 (42.1)	0.604
Female	166 (58.9)	52 (61.2)	114 (57.9)	
Age				
Adults	231 (81.9)	64 (75.3)	167 (84.8)	0.058
Seniors	51 (18.1)	21 (24.7)	30 (15.2)	
Schooling (n = 265)				
Illiterate incomplete/high school	62 (23.4)	17 (21.5)	45 (24.2)	
Complete high school	46 (17.4)	11 (13.9)	35 (18.8)	0.479
Graduated/incomplete graduated	157 (59.2)	51 (64.6)	106 (57.0)	
Income				
Did not inform	30 (10.6)	12 (14.1)	18 (9.1)	
Up to 2 wages	66 (23.4)	19 (22.4)	47 (23.9)	
2 to 4 salaries	103 (36.5)	25 (29.4)	78 (39.6)	0.399
4 to 10 salaries	71 (25.2)	25 (29.4)	46 (23.4)	
More than 10 wages	12 (4.3)	4 (4.7)	8 (4.1)	
Smoking (n = 281)				
Never smoked	189 (67.3)	65 (77.4)	124 (62.9)	
Have you smoked	80 (28.5)	14 (16.7)	66 (33.5)	0.014
Smokes currently	12 (4.2)	5 (6)	7 (3.6)	
Physical activity (n = 281)				
No	131 (46.6)	42 (49.4)	89 (45.4)	0.537
Yes	150 (53.4)	43 (50.6)	107 (54.6)	
Alcohol drink (n = 277)				
Never drinks	114 (41.2)	34 (41)	80 (41.2)	
Eventually	156 (56.3)	48 (57.8)	108 (55.7)	0.648
Daily	7 (2.5)	1 (1.2)	6 (3.1)	
Hypertension (n = 281)				
No	173 (61.6)	67 (79.8)	106 (53.8)	< 0.001
Yes	108 (38.4)	17 (20.2)	91 (46.2)	
Diabetes (n = 281)				
No	232 (82.6)	67 (79.8)	165 (83.8)	0.419
Yes	49 (17.4)	17 (20.2)	32 (16.2)	
Dyslipidemia (n = 281)				
No	56 (19.9)	10 (11.9)	46 (23.4)	0.028
Yes	225 (80.1)	74 (88.1)	151 (76.6)	

Variables expressed as absolute and relative frequency. P values in bold refer to statistical significance (p <0.05) using the Pearson chi-square test.
**Variables self-reported by participants.*

Table 2 - Lipid intake of PROCARDIO-UFV participants, according to body fat status

Fat intake	Normal-weight (n = 85)	Overweight (n = 197)	p-values
Total fat			
< 25 % CI (n = 93)	37 (43.5)	57 (28.9)	
25% -35% CI (n = 127)	38 (44.7)	90 (45.7)	0.011
> 35% CI (n = 60)	10 (11.8)	50 (25.4)	
Saturated fatty acid			
≤ 7% CI (n = 68)	29 (34.1)	40 (20.3)	0.013
> 7% CI (n = 212)	56 (65.9)	157 (79.7)	
Polyunsaturated fatty acid			
≤ 10% CI (n = 252)	82 (96.5)	172 (87.3)	0.018
> 10% CI (n = 28)	3 (3.5)	25 (12.7)	
Monounsaturated fatty acid			
≤ 20% CI (n = 275)	84 (98.8)	193 (98.0)	0.618
> 20% CI (n = 5)	1 (1.2)	4 (2.0)	

Variables expressed as absolute and relative frequency. p values in bold refer to statistical significance ($p < 0.05$) using the Pearson chi-square test. CI: caloric intake.

acid presented higher values for BMI, body fat (%) and HOMA-IR (Figure 1).

In relation to PUFA intake, 91.8% of study participants (n = 259) consume less than 0.6% of the total calories in α-linolenic acid, and 60.3% (n = 170) consume less than 5% of total calories in linoleic fatty acid. No significant relation was found between the recommended intake of α-linolenic acid (0.6-1.2% of total calories) and linoleic acid (5-10% of total calories) and cardiometabolic markers, neither there is significant result regarding the consumption of trans fatty acids (data not show).

Discussion

In this study, 45.7% and 87.3% of the individuals with overweight had consumption within the total fat and PUFA recommendations, respectively, and 79.7% above the recommendation for saturated fatty acids. This result shows the importance of dietary fat assessment regarding to its quality, since dietary fatty acid is more important determinant of cardiovascular risk than its total amount.[30,31]

In previous study, with adults aged 20 to 59 years and overweight prevalence of 76.79%, SFA intake remained within the established values. However, there was an inadequacy of the PUFA consumption being below the recommended level.[32] This difference in results can be explained by the fact that the authors used the recommendations of up to 7% of total calories in SFA and up to 10% of total calories in PUFA, in the study cited, 10% of total calories and 6 to 10%, respectively.

In the last decades, there have been medical and nutritional recommendations for the reduction of the consumption of SFA due to the action of these in the increase of the LDL-c in the increase of the risk of cardiovascular disease.[33] However, different SFA may have different effects on the lipid profile and cardiovascular risk factors.[34]

When compared to carbohydrates, lauric fatty acid (C12: 0) is what increases the LDL-c and consequently TC.[35] This may explain the fact that the individuals in the present study had a higher intake of saturated medium chain fatty acids (SCMA), among them lauric acid, with higher values of TC and LDL. Considering the high prevalence of dyslipidemic in this population (80.1%, n = 225), this finding may contribute to the prescription of diets, restricting foods containing higher amounts of these fatty acids, such as whole milk and its derivatives, coconut and their derivatives.

Lower values in the adiposity indexes (BMI, perimeters of the waist, hip waist ratios, waist height ratios) of the participants with the highest consumption of SCMA can be explained by the metabolism of the medium chain triglycerides. These are absorbed, mainly as free fatty acids, directly from the portal vein, thus reaching the liver faster than the long chain fatty acids. In the liver, oxidation is rapid because it does not need to be activated by coenzyme A, making it a good ketogenic substrate.[36,37] In clinical trials with men and women fed a diet containing medium chain triglycerides, mainly lauric acid, they achieved a reduction in body mass and abdominal fat, since these components are not easily incorporated into adipose tissue triglycerides.[38-40]

Inflammation is a prominent feature of many chronic diseases, high-fat and carbohydrate meals contribute to increased oxidative stress and inflammation.[41] A high-

Table 3 - Indicators of adiposity and cardiometabolic markers, according to the intake of medium chain fatty acids (n = 282)

Variável	Lower intake (< 1,05g/day)	Higher intake (≥ 1,05 g/day)	p
BMI (kg/m²)	29.48 (5.1)	28.20 (5.7)	0.049
Waist circumference (cm)	99.51(13.6)	94.09 (14.9)	0.002
Waist-hip ratio	0.96 (0.09)	0.91 (0.09)	< 0.001
Waist-height ratio	0.60 (0.09)	0.58 (0.10)	0.026
Total body fat (%)	30.30 (6.7)	31.66 (9.1)	0.222
Leukocytes (mil/mm³)	6,000 (5,120 - 7,035)	6,500 (5,425 - 7,750)	0.035
Ferritin (µg/L)	113.2 (54.9 - 237.7)	66.95 (30.5 - 153.0)	0.012
Uric acid (mg/dL)	4.5 (3.7 - 6.0)	3.9 (3.1 - 4.7)	0.002
Glycemia (mg/dL)	96.0 (87.0 - 108.0)	88.0 (80.8 - 97.0)	< 0.001
HOMA-IR	2.0 (1.2 - 3.4)	2.2 (1.5 - 3.0)	0.900
TyG	4.8 (0.3)	4.8 (0.3)	0.113
Total cholesterol (mg/dL)	195.2 (40.6)	215.6 (42.8)	< 0.001
LDL (mg/dL)	118.4 (37.4)	130.8 (37.6)	0.010
HDL (mg/dL)	44.7 (12.9)	51.4 (15.6)	< 0.001
TC/ HDL	4.64 (1.46)	4.49 (1.43)	0.402
LDL/HDL	2.81 (1.18)	2.75 (1.07)	0.696
Triglycerides (mg/dL)	140.0 (104.0 - 226.0)	146.5 (92.0 - 227.8)	0.597
CRP (mg/dL)	1.3 (0.3 - 3.2)	2.9 (0.8 - 5.8)	0.008

Data presented in mean and standard deviation or median (p25-p75). Values of p by t-test or Mann-Whitney.

fat meal has been suggested to increase inflammation, although there is currently no consensus regarding the specific changes in many of the pro-inflammatory markers that are often evaluated after a high-fat diet.[42]

SFA can cause inflammation of adipose tissue by processes involving, among others, the "toll-like receptor" TLR-4, a sensor that binds to bacterial lipopolysaccharide (LPS).[43] High fat diets, especially those rich in SFA, have been shown to increase LPS uptake in the intestine.[44,45] Evidence suggests that SFA and LPS share the same inflammatory signaling pathway as TLR4, thus promoting the expression of proinflammatory transcription factors such as nuclear kappa B and cyclooxygenase-2.[42]

The subjects with higher intake of medium chain fatty acids had a higher total leukocyte count. It has been demonstrated that CRP-us[46] and leukocyte count[47] can independently predict vascular risk in apparently healthy men and women, asymptomatic for cardiovascular risk factors.[46]

A study conducted by Raz et al.,[48] with 54 subjects with a BMI of 25 ± 0.9 kg/m², with a mean age of 41.7 ± 3.1 years, demonstrated a significant increase in CRP-us after a high-acid meal (51 g), it did not work when the meal was high in monounsaturated fatty acids.

We also found tha individuals with higher intakes of C16: 1 (≥ 0.94g/day) had higher values for BMI, fat percentage and HOMA-IR. Studies evaluating the palmitoleic MUFA intake and its relation with cardiometabolic markers have not been reported yet. However, some studies have pointed out that higher proportions of palmitoleic acid in blood or adipose tissue are consistently associated with chronic diseases outcomes, such as obesity,[49,50] hypertriglyceridemia,[51] hyperglycemia,[52] inflammation,[53,54] metabolic syndrome,[55,56] diabetes type 2,[57] disease coronary heart disease,[57] and heart failure.[58] In obese individuals

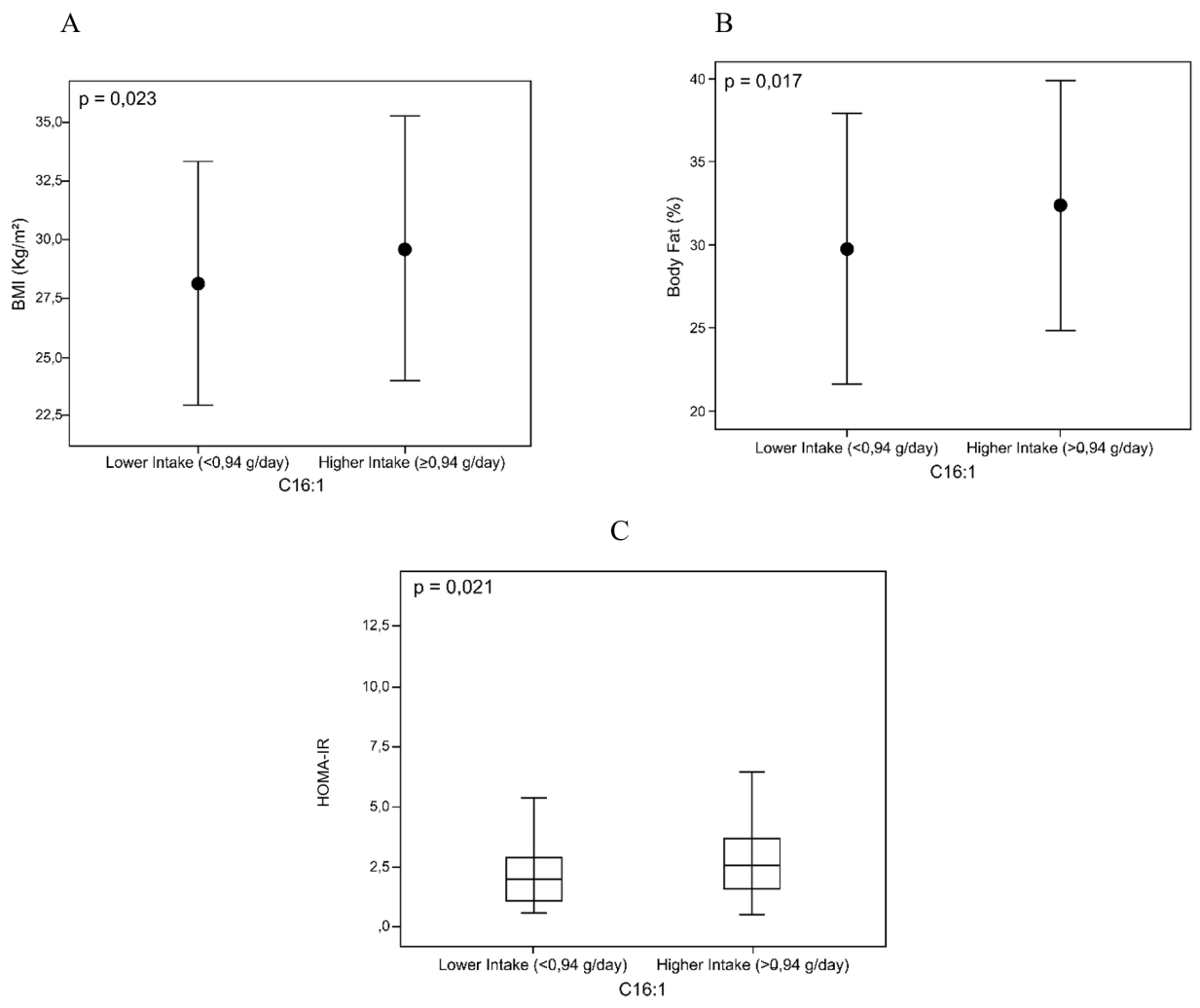

Figure 1 - Values of BMI (A), body fat (B) and HOMA-IR (C), according to intake of C16: 1 (palmitoleic acid). Data are mean and standard deviation or median (p25-p75), according to normality. Values of p by t-test or Mann-Whitney, where appropriate. C16: 1 was adjusted by caloric intake by residual method.

with significant weight loss, high palmitoleic acid in adipose tissue was associated with higher inability to maintain weight loss.[50] Moreover, in 18-week nutrition intervention study, with sixteen metabolic syndrome patients,[59] plasma palmitoleic acid was gradually increasing when participants fed related low-carbohydrate diet to high-carbohydrate diet (47 to 346 g/d).

The study has as its limitation the use of only a 24-hour recall that provides us with current and not habitual diet information, although this food survey has been extensively used in epidemiological studies to investigate food consumption relationship with chronic diseases.[60]

Conclusion

In this cross-sectional study, individuals with a higher intake of medium-chain SFA had lower values of indicators of adiposity, ferritin, uric acid, and fasting glucose, and higher leukocyte, CRP, CT, LDL, and HDL concentrations. While higher palmitoleic MUFA consumption was related to higher BMI, fat percentage and HOMA-IR values. Our results suggest the relevance of a detailed assessment of the dietary fatty acid profile in the high-risk cardiometabolic population, considering chain size and saturation.

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Author contributions

Conception and design of the research: Fortes FS, Almeida AP, Silveira BKS, Hermsdorff HHM. Acquisition of data: Fortes FS, Almeida AP, Silveira BKS. Analysis and interpretation of the data: Fortes FS, Almeida AP. Writing of the manuscript: Fortes FS, Almeida AP. Critical revision of the manuscript for intellectual content: Fortes FS, Almeida AP, Rosa COB, Hermsdorff HHM.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Universidade Federal de Viçosa* under the protocol number 066/2012/CEPH. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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ORIGINAL ARTICLE

An Approach to Technology Development and Current Medical Practice

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Abstract

Background: An approach to technology development and the current medical practice.

Objective: To consider the many stages of medical-applied technological developments and its main consequences related to the current medical practice and speculate on future developments.

Methods: Assessment of historical publications and individual and metanalysis of comparative evaluation of old versus new techniques.

Results: Documentation of progressive improvement in diagnostic skill and therapeutics toward less invasive procedures along the last decades, since the introduction of the scientific medicine.

Conclusion: Progress has been unequivocally documented albeit an effort to maintain time-proven established previous technique is advised, especially in favor of stimulating a personal patient-physician relationship. (Int J Cardiovasc Sci. 2020; 33(5):457-461)

Keywords: Technology/trends; Medical Practice; Medical Education; Physician-Patient Relations; Patient Participation; Electronic Health Records/trends; Telemedicine; Robotics.

Introduction

Conceptually, technology refers to the use of engineering tools, usually instruments, techniques and methods aimed at reaching a problem solution. Humans have evolved with successful application of new technologies – the fire, the wheel, the writing, the press, steam machines, the electricity – that allowed the development of humanity through the renaissance and the Industrial Revolution, and more recently by progressive use of new resources based on scientific computation and telecommunication and cutting-edge technologies.

Although these technology achievements have enabled great progress of humanity, one should not forget that they also brought along wars with devastating destructive power, threatening life and planet survival.

Trepanation tools, for example, are prehistoric and thus it is conceivable that technology was developed and employed in health care at the time of human gathering and is intrinsically linked to the development of medicine.

In the 18th century, patient clinical examination, as depicted by iconic portraits of the time, illustrates a more contemplative attitude, limited to asking questions about patient's sense of well-being and examining the tongue. The second half of the 19th century was marked by what is considered by many the beginning of scientific medicine, where physical examination including abdominal palpation, listening to the chest sounds (approaching the ear to patient's thoracic wall), and percussion was surpassed by revolutionary techniques and tools including the stethoscope, the thermometer, the microscope, the X-ray and the electrocardiograph.[1]

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Since then, a tremendous growth of technological resources has been observed in medical practice, especially with the introduction of computational science. This allowed the processing of an enormous amount of data in a short period of time and its wide use in health care.

In parallel, contrary reactions have come up against each innovation, as a necessity to establish the best method.

For instance, referring to the change of the remote primitive medicine, when knowledge and teaching of clinical medicine was limited to memorizing disease names and the corresponding herbal treatment, to the more scientific medicine, the social writer and poet Samuel Coleridge, strongly criticized doctors "for debasing and blinkered somatism".

From then on, new graphic registry methods, imaging techniques, the ultrasound and nuclear magnetic resonance have emerged as auxiliary diagnostic methods. Also, a multitude of therapeutic possibilities have led to minimally invasive procedures, including optical apparatus resources with less damage in the access, and robotic instruments with more precision in tissue repair.

Current scenario of the use of new technologies: usefulness and potential problems

In several medical fields that technological innovations have amplified our ability to diagnose, scrutinizing structures largely inaccessible until recent past, coming to the intimacy of vessels and tissues.[2-5] For instance, a large part of the improvement in coronary artery disease survival is due to new therapeutic resources and preventive strategies.[6]

An analysis of trends of recent use of biotechnology in medicine[7] clearly reveals a trend towards grafts, devices, new diagnostic and therapeutic resources and access systems.[8]

Problems arise when one considers the escalating, sometimes stratospheric costs of implementation of technology, to the point where reimbursement by the payees may not be possible, compromising advances in other areas of social interest throughout the world.

Consequently, it is clear the need for regulatory agencies evaluating the use of new technologies regarding their reliability, advantages and disadvantages, ideally from the perspective of an uncompromised academical milieu, beyond financial interests and intellectual bias. Besides, there is the challenge of providing equal use of resources to all that need them.

This is obviously a difficult task to be accomplished in any part of the world at this moment, even in the most developed countries.

Problems with technology in the near future

After the application of computing to aid the war effort and banking activity, the use of computing science in medicine has increased. For example, the creation of electronic medical records has amplified the possibilities of data management.

Many scores were built to calculate the odds of development of certain condition and prediction of future events. It is somewhat curious to verify that these scores have not been implemented in all hospital institutions, with rare exceptions.[9]

Despite that, the general perception is that with advances in computational processes and its greater capacity of handling large amounts of data, with provision of answers in shorter periods of time, there will be a progressive implementation of these new resources in medicine in a near future.

According to a survey by the Global Summit Telemedicine and Digital Health, 82.6 % of physicians use digital technology nowadays; 78.6 % are favorable to the use of new platforms, such as the "WhatsApp"; and 60% of the health institutes and 50% of the hospitals in the USA use telemedicine.

A Cochrane systematic analysis[10] compared the benefits of telemedicine with personal contact in distinct groups or situations as summarized in Table 2. Although telemedicine was more advantageous in some situations, the difference was not significant.

On the other hand, the use of artificial intelligence requires an adequate understanding and positioning of

Table 1 – Current scenario of use of new technologies: usefulness and potential problems

Improvement in diagnoses
Improvement in prognoses: survival and quality of life
Additional costs
Reimbursement
AdequacyAccess

Table 2 – Cochrane metanalysis of the comparison of telemedicine versus personal examination

HF	**16 studies 5239 patients.**	
	Mortality in 6 months	no difference
	Hospitalization in 8 months	no difference
	Quality of life in 3 months	improvement
HBP	**4 studies 1770 patients.**	
	BP control	improvement
LDL	**4 studies 1692 patients**	
	Control	improvement
DM	**16 studies 2768 patients**	
	Glicated Hb	Improvement

physicians involved in patient care and representatives of the medical class, as the Federal Medical Council in Brazil.

In the last book published before his death, "Brief answers to the big questions", the scientist Stephen Hawking dedicates one chapter to the implications of the use of artificial intelligence in human activities and states: "Although the primitive forms of artificial intelligence have already been applied and seems to be quite useful, I don't see with optimism the creation of something that is capable of level or surpass us". The author reveals his thoughts about the profound implication of artificial intelligence in human disqualification. In Medicine, one of the fearsome questions is whether the robots and algorithms will replace physicians.

On February 7th 2020, the FDA released for commercialization a software called Caption Guidance, from Caption Health Inc. Compatible with currently available sonographers, the software uses artificial intelligence and allows for health practitioners, mainly nurses, to perform high-quality echocardiographic studies, similar to the ones obtained by echocardiographists using the usual system. However, cardiologists or echocardiographists are still required to write the final report. This is considered the first artificial intelligence equipment applied to cardiology, and others are already expected.

It is well known that artificial intelligence has already been applied to other areas of medicine, such as radiology, which broadened the use of this resource with teleconsults and an almost infinite number of examples validated by experts.

It is not possible nor is there any reason to limit the progressive application of artificial intelligence in Medicine.

There should be an appropriate approach to understand and define the physician's position in this challenge of technological innovation. We should consider that, since the first auxiliary methods introduced, such as the electrocardiography and the chest X-ray, the physician plays a crucial role in establishing the correct final diagnosis. Occasionally, it becomes necessary to complement information given by the physician in order to get a better technical-clinical correlation of data. This situation has been more and more common with the appearance of new technologies, specially imaging methods, but also in laboratory. In all cases the physician tries to make the best diagnosis, making sure that something deserving a more immediate attention is not missing in his evaluation.

Because it is in the genuine essence of practicing medicine the willingness to help the patient is the most important professional endeavor.

However, all of this considered, we should now take a look at the cost of technological advances as a means of departing the physical contact between the physician and the patient.

Since the less scientific medicine depicted by Lukes Fildes (Figure 1) when the physician without resources did not go beyond attentive contemplation - yet well appreciated - to the more contemporaneous physical examination, a connection and a ritual have been established between the physician and the patient, where there is a clear message of personal and meticulous care. This is usually valued by the patient as a basis for a confident relationship.

We should add that the current physical examination is ever more based on information that technology has helped to clarify, and thus more efficacious considering the better understanding of disease mechanism, signs and symptoms, and capable of constructing a clinical picture that will lead to a safer and more efficacious utilization of the next auxiliary steps.

This emphasizes the increasing relevance of patient examination, and the importance of the medical

Figure 1 – The Doctor by Luke Fildes.

Figure 2 – A child portrait of the medical examination in the current era

learning be based on this understanding.[11] However, there are big challenges ahead of us.

We must understand that the basic principle in Medicine, and the one that will always be kept, is the task of delivering health care to the ones in need. Society must understand this and protect this professional for its own good, despite the development of artificial intelligence, in addition to guarantee an adequate formation in good medical schools and proper work environment.

Recently, the mischaracterization of medical activity has been identified as a cause of burnout and suicide among young students and doctors, as well as seasoned doctors.

The portrait published in Lancet [12] of a child during her medical interview for some illness contrasts to what Lukes Fildes had documented in the past. The child observes the distancing of the physician from her and her parents, while researching in the internet or filling out electronic forms in the computer, rather than paying due attention to herself, the patient.

This misuse of the technology must be condemned.

Author Contributions

Conception and design of the research: Feitosa G. Acquisition of data: Feitosa G. Analysis and interpretation of the data: Feitosa G. Statistical analysis: Feitosa G. Writing of the manuscript: Feitosa G. Critical revision of the manuscript for intellectual content: Feitosa G.

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ORIGINAL ARTICLE

Intestinal Microbiota and Cardiovascular Diseases

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Abstract

Background: Gut microbiota is essential to metabolize proteins, carbohidrates, aminoacids, fibers and essentially everything we eat. On the other hand, foods that we ingest powerfully influences gut miocrobiota.

Objetive: to analyze the contribution of human gut microbiota on cardiovascular disease.

Methods/Results: We summarized current knowledge regarding microbiota on cardiovascular diseases, emphazysing clinical relevance. The intestine harbors a great variety of bascteria and at the same time produces substances that can act locally as well as at a distance. Thus, the intestine is now considered an endocrine organ. The appropriate balance between the external environment and the composition of the gut microbiota is pivotal for human health. Alterations in gut microbiota are known broadly as disbiosis. A number of human diseases have been associated with disbiosis, including psychiatric, metabolic and chronic degenerative entities. In the cardiovascular system alterations of gut microbiota have been associated with atherosclerosis, hypertension, heart failure, obesity and diabetes. These influences occur through profound effect of gut microbiota upon the metabolism of proteins, carbohidrates, biliary acids, aminoacids and intestinal barrier among others.

Conclusion: Given the profund influences of gut microbiota upon mechanisms underlying cardiovascular diseases, microbiota is a potential therapeutic target.

Keywords: Cardiovascular Diseases; Gastrointestinal Microbiome/physiology; Risk Factors; Hypertension; Diabetes Mellitus; Obesity; Neoplasms; Alzheimer Disease; Metabolism; Atherosclerosis; Diet, Mediterranean.

Abstract

Recently, gut microbiota has emerged as an important mediator of several diseases such as diabetes, atherosclerosis, arterial hypertension, obesity, cancers and neuropsychiatric diseases including Alzheimer, autism and depression. Intestinal microbiota is formed by bacteria, fungi and viruses and its main function is to facilitate the absorption and metabolism of foods (protein, fat and carbohydrate). One example of the multiple actions of the gut microbiota is the bidirectional relationship between the intestine and the brain, the so-called "gut/brain axis". Furthermore, metabolites produced by gut microbiota can induce effects locally or at distance, which suggests that the intestine is an endocrine organ.

Given the participation of the gut microbiota in several diseases, there is great interest in strategies that may positively affect the gut flora and prevent or even treat diseases. Among these strategies, lifestyle change, but specially diet modulation has gained importance. In this article, we review the mechanisms through which intestinal microbiota participates in cardiovascular diseases and possible therapeutic interventions.

Introduction

For long time traditional risk factors such as hypertension, diabetes, smoking and hypercholesterolemia have been considered the main promoters of atherosclerosis, and their control has been the cornerstone treatment for cardiovascular

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diseases. More recently, a new independent risk factor has emerged: the gut microbiota.[1,2,3]

Intestinal microbiota is made up of trillions of cells – about 10 times more than all the cells of the human organism – consisting of bacteria, viruses, fungi and archea. The phyla Firmicutes (mainly Clostridia species) and Bacteroidetes represent about 90% of gut microbiota, which is also composed of Actinobacteria, Proteobacteria and Verrucomicrobia.[2]

Until recently, studies on intestinal microbiota relied on culture of bacteria, providing limited information regarding a small fraction of the gut microbiota. Lately, culture-independent techniques, such as the marker gene analysis (16 S rRNA gene sequences), metagenome and metatranscriptone enabled the identification of previously unculturable bacteria.[1]

Gut flora remains relatively constant during an individual´s lifetime. However, it changes considerably from childhood to adult life and then during aging (Figure 1).[4] Thus, total gut microbiota is estimated to be small during childhood, increases considerably during adult life and decreases in old age. Infants have unstable, distinct and heterogeneous microbiota, characterized by low levels of total bacteria. On the other hand, elderly subjects have high levels of E-coli and Bacteroidetes. In the study by Maritat et al.[4] the measured ratio of Firmicutes to Bacteroides was 0.4, 10.9 and 0.6 for children, adults and elderly, respectively. It is tempting to speculate that these two extremes may be related to vulnerability of children and old people.

More recently, clusters or enterotypes in intestinal microbiota have been identified (Figure 2). Arumugan et al.[5] studied fecal metagenomes of 39 individuals from France, Italy, Spain and Denmark by 16S ribosomal RNA-encoding gene. They identified three clusters that are not nation or continent specific. They also found that 12 genes correlated significantly with age and three functional modules with body mass index. There were three main enterotypes –Bacteroidetes/Roseburia, Akkermansia/Alistipes/Ruminococcus and Prevotella. The authors concluded that intestinal microbiota variation is generally stratified, not continuous. Wu et al.[6] also described the link between dietary habits and gut microbial enterotypes (see ahead).

Gut microbiota varies individually and in populations as well, mainly due to different cultures and diets. Diet is a major element; for instance, vegans and vegetarians have higher counts of certain Bacteroidetes compared to omnivores.[7-9] Ayenic et al.[9] compared gut microbiome in rural Bassa with urban individuals from Nigeria. In rural Bassa they documented a predominance of bacteria with high capacity for fiber degradation and almost absence of common members of urban/industrial microbiomes. They also observed an adaptation of intestinal microbiota to urbanization.

Intestinal microbiota also varies in different intestinal regions as in the upper and lower small intestine and the colon.[10] This distribution explains the preferential absorption and metabolization of proteins, lipids and carbohydrates throughout the gut. The question regarding the "normal

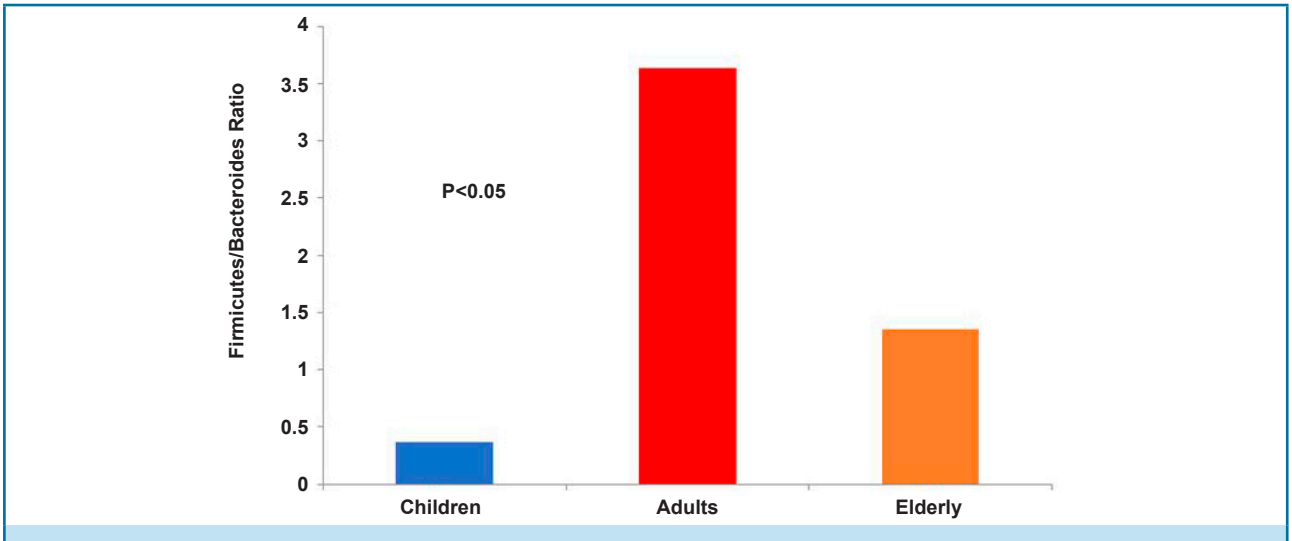

Figure 1 – Firmicutes/Bacteroides ratio in different phases of life. Modified from Mariat, et al.[4]

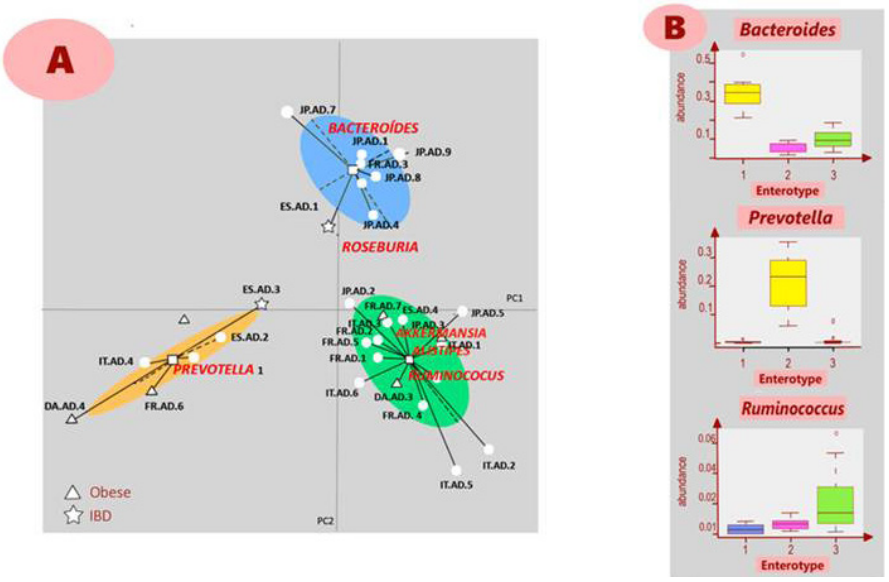

Figure 2 – Human enterotypes as identified by Arumugam at al.[5] Enterotypes are identified based on predominant bacteria namely Bacteroides, Prevotella and Ruminococcus (A,B). See text Modified from Arumugan et al.[5]

flora" is still open. Probably there are different enterotypes depending on diet, geographic location and genetic background.[2] On the other hand, the term "dysbiosis" describes a primary imbalance of gut microbiota. Some gut microbiota metabolites detected in plasma correlate directly with plasma trimethylamine-N-oxide (TMAO)[11] indicating the influence of gut microbiota on the pathogenesis of atherosclerotic disease.

Expansion of the knowledge in this area, both in mechanisms and identification of bacteria is expected in the near future. Understanding the functional role of bacteria and their relationship with plasma metabolome is pivotal issues for new research. However, our present understanding in this area is still superficial.

Main roles of the gut microbiota

The primary role of gut flora is the promotion and regulation of the absorption and metabolism of what we eat, *i.e.*, proteins, carbohydrates, fibers, nucleic acids, macro and micronutrients. Figure 3 summarizes the main functions of human gut microbiota. For instance, fermentation of non-digestible fibers and starch by microbiota in the colon leads to the production of short chain fatty acids (SCFAs), especially acetate, butyrate and propionate. Fatty acids are essential energetic sources of various organs including the heart, acting in the metabolism of proteins and carbohydrates.[12,13] Although only 5-10% of the energy consumed is from SCFAs, they play fundamental roles as in the signaling of molecules.[14]

The wide range of modulatory effects of SCFAs embrace the nervous system, blood pressure, histone deacetylases, inflammation, production of reactive oxygen species (ROS), inhibition of chemostasis, phagocytosis modulation, maintenance of intestinal barrier integrity and modulation of immune system responses.[2,14] SCFAs act through G-protein receptors, specifically the GRP41 and the olfactory receptor-78 (Olfr78). Olfr78, highly expressed in renal just-glomerular apparatus, mediates renin secretion induced by SCFAs. GPR41 and Olfr78 are also expressed in smooth muscle cells (SMC) of resistance vessels, and studies with KO mice indicate their influence on blood pressure. Thus, while GRP41 KO-mice are hypertensive, Olfr78 KO-mice are hypotensive.[1] Animal studies also indicate that SCFAs are essential in cardiac repair after myocardial infarction and immune response.[13,14]

Few interventions have focused on SCFAs; diet modulation represents the major tool to alter the gut microbiota. David et al.[15] examined, in 10 normal individuals, the effect of a shift from a plant-based diet to an animal-based diet. The animal-based diet increased bile–tolerant microorganisms, like Bacteroides, and decreased the levels of Firmicutes that metabolize polysaccharides, such as Roseburia. Consequently, there was a reduction in fecal acetate and butyrate when subjects were switched from plant to animal-based diets. This occurred within just a few

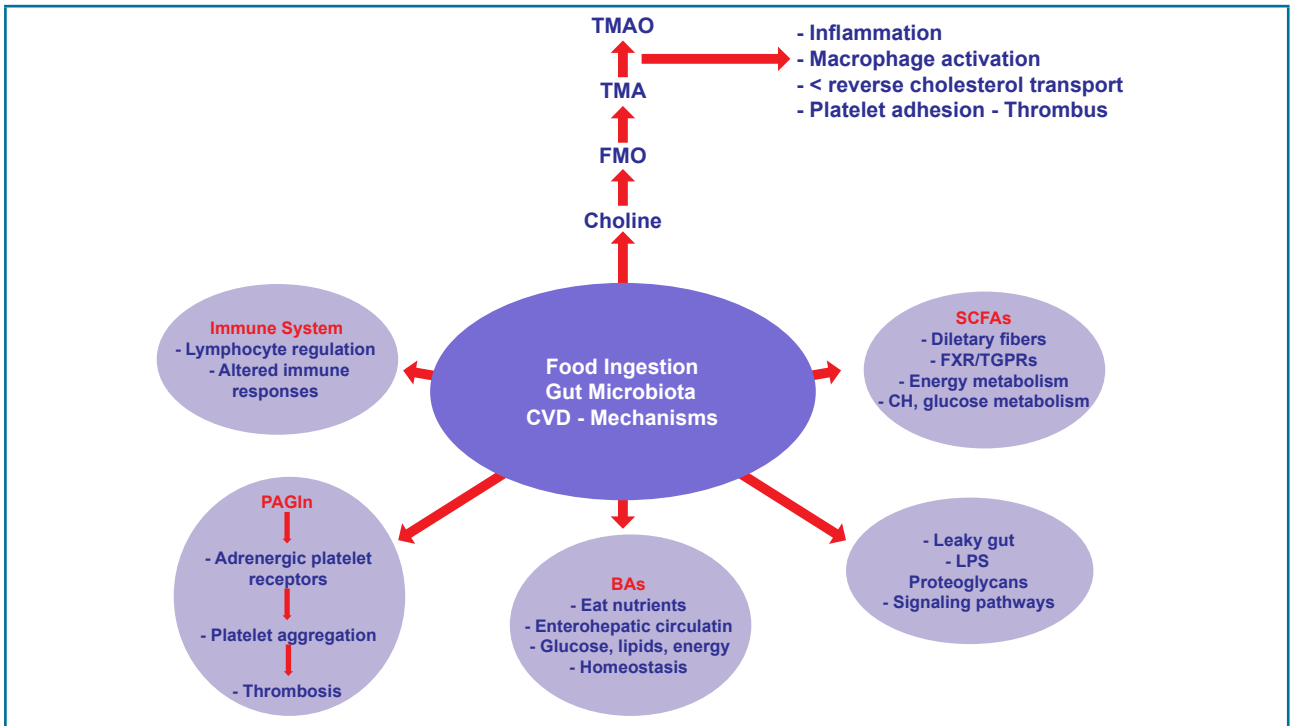

Figure 3 – Schematic summarized representantion of the main mechanisms through which gut microbiota may induce cardiovascular diseases (CVD). PAGIn: phenylacethyl glutamine; BAs: bile acids; SCFAs: short-chain fatty acids; FMO: flavin monooxygenases; TMA: trimethylamine; TMAO: trimethylamine-N-oxide; LPS: lipopolyssacharides.

days, indicating that human intestinal microbiota can be manipulated very rapidly.

In insulin–resistant patients with metabolic syndrome, fecal transplantation from lean donors led to improved insulin sensitivity and abundance of Roseburia, which is a butyrate–producing bacterium.[2]

Effects of bile acids upon intestinal microbiota

Bile acids (BAs) are synthesized from cholesterol in the liver. This is an important way to eliminate cholesterol from the body. The rate-limiting enzyme is hepatic cholesterol 7 α-hydroxylase ($CYP7A_1$). BAs are conjugated to taurine and glycine, which enhances their water solubility and their secretion into the bile; they facilitate fat digestion.[16] The main conjugated BA are chenodeoxycholic acid and cholic acid (primary BAs); the secondary or deconjugated BAs are lithocholic acid, ursodeoxycholate and deoxycholic acid. About 95% of the bile acids are reabsorbed in the terminal ileum and colon. These molecules are then recirculated to the liver through the portal vein; this process is known as the *enterohepatic circulation*.

BAs regulate energy metabolism through activation of the membrane Takeda G protein-coupled bile acid receptor 1 (TGR5) and the nuclear Farnesoid X receptor (FXR). Both TGR5 and FXR are highly expressed in the intestine and the liver. Humans produce a large conjugate BA pool which is maintained by a feedback mechanism of the FXR in the liver and intestine. BAS act as direct antimicrobial agents because of their detergent properties and hydrophobicity.[2]

BAs exert important effects as hormones dependent on activation of TGR5 and FXR by gut microbiota.[17] These receptors are implicated in lipid and glucose metabolism. In the ileum, FXR activation by BAs induces fibroblast growth factor 19, which circulates to the liver and reduces CYP7A1; such reduction then inhibits the synthesis of BAs, specifically lithocholic acid and deoxycholic acid.

One important observation is that reduced BAs levels in the gut are associated with inflammation and bacterial growth.[17] In this sense, obeticholic acid, a BA analogue and FXR agonist, was approved in the USA for treatment of bacterial translocation and inflammation in steatohepatitis. Also, FXR activation in mice decreased cholesterol absorption by 50%. FXR activation increases apoptosis and reduces inflammation and cell migration; FXR is expressed in endothelial cells, where it increases endothelial nitric oxide synthase (eNOS) expression and reduces endothelin-1 (ET_1). Glucose stimulates FXR and CYP7A1, but insulin inhibits them.[17]

On the other hand, TGR5 is involved in energy metabolism, and its activation has an anti-atherogenic effect. Given these multiple physiological functions, FXR and TGR5 are potential therapeutic targets. Both synthetic agonists and inhibitors have been tested, with conflicting results in animal models and humans. More research is still necessary to establish the role of the intervention on these receptors before clinical application.

Microbiota and Immunity

The immune system, either innate or adaptive, is clearly linked to gut microbiota, which plays a role in modulating the relation regulatory-to-effector T cells.[18,19]

To reach distant organs, microbial signals need to cross the intestinal epithelium. Structural components of the microbiota such as lipopolysaccharides (LPS) and peptidoglycans interact with mucosal surface cells through pattern recognition receptors (PRR). PRR recognize pathogen-associated molecular patterns (PAMPs), which modulate immune responses. LPS and peptidoglycans can trigger a cascade of downstream signaling pathways.[2]

Gut commensal microbiota maintains a balance of immune effectors, to protect the gut against dangerous invaders, and at the same time tolerate innocuous microbial antigens. A thick mucus layer in the intestinal mucosa, together with the epithelial wall, is essential to maintain homeostasis. The contribution of intestinal mononuclear phagocytes (MNPs) has being recognized as a potential targetable pathway in inflammatory disease.[18] The normal intestinal microbiota can inhibit innate lymphoid cells, which are major producers of interleukin-22 (IL-22), a cytokine that acts in epithelial cells to promote healing during infection. IL-22 also induces antimicrobial peptide production.[18]

In addition, commensals can affect the adaptive immune system by inducing T cell differentiation. Also, Clostridium clusters can induce colonic regulatory T cells (Tregs) that produce anti-inflammatory interleukin-10 (IL-10); to do this, Clostridium provides a transforming growth factor β (TGFβ) and high luminal concentrations of SCFAs, especially butyrate. Thus, SCFAs participate actively in the process called "homeostatic induction", in which bacteria exert immune effects through the differentiation of lymphocytes.[19]

Segmental filamentous bacteria (SFB) induce CD4+T helper cells in the ileal epithelial surface. CD4T helper cells produce IL-17, IL-17f and stimulate Th17 cells. All these cytokines are involved in inflammatory diseases such as inflammatory arthritis, psoriasis and inflammatory bowel disease.[18] These findings suggest that the inflammatory environment of the intestine modulate the differentiation of effector lymphocytes, highlighting the intimate interplay of gut microbiome and immunity.

Not only bacteria, but viruses can influence immunity; enteric viruses are frequent causes of human gastrointestinal diseases. Recent studies have also suggested interactions between viruses and bacteria – the so called "transkingdom interaction"; an example is the presence of virus-like particles correlated with significant changes in gut microbiome in intestinal bowel disease patients. Also, helminths such as Schistosoma mansoni and Trichinella have been found to modulate immunity.

These inflammatory cytokines can profoundly alter intestinal motility and permeability. One major effect of this phenomenon is the translocation of intestinal bacteria to plasma which can cause bacteremia and sepsis.

Taken together, these data indicate a significant modulatory role of gut microbiota - bacteria, viruses and helminths – in the immune system. Mechanistic studies are needed to further our knowledge in this emerging field.[18,19]

The real impact of gut microbiota in cardiovascular diseases

It has been recognized that gut microbiota is involved in the development of atherosclerosis, diabetes, hypertension, obesity, stroke, heart failure and neuropsychiatric diseases such as depression, autism and Alzheimer.[2] Even birth circumstances affect gut microbiota; in normal deliveries the child is exposed to the vaginal flora of the mother, which is beneficial to the health of the child. On the contrary, cesarean section deprives the baby of such exposure, and asthma and allergies have been encountered more frequently among these children. Furthermore, another gut microbiome metabolite, phenylacetyl glutamine (PAGIn), has been recently associated with cardiovascular disease in humans. PAGIn acts through adrenergic platelet receptors facilitating platelet aggregation and thrombus formation.[20]

A characteristic of the intestine and its microbiota is that they produce substances that act locally and others that act at distance, such as cytokines and noradrenergic products. These features led to the concept that the intestine is an endocrine organ.

Atherosclerosis

The metabolism of phosphatidylcholine, carnitine and choline found in abundance in red meat, milk and eggs has as its final compound trimethylamine-N-oxide (TMAO).

These substances enter the intestine and suffer a series of metabolic reactions under the influence of microbiomes. The fundamental reaction is the conversion of choline into trimethylamine (TMA), which is then metabolized by flavin monooxygenases (FMOs), especially FMO3, of the liver into TMAO.[1] TMAO production is entirely dependent on the gut microbiota. In experimental animals fed a choline enriched diet, TMAO production is abolished when animals received broad spectrum antibiotics.[3] The authors also showed that TMAO induced foam cell formation and atherosclerotic plaques in aortic root of rabbits. Seldin et al.[21] observed elevated inflammatory gene expression compared to controls in the aortas of LDLR$^{-/-}$ mice fed a choline diet. Chronic choline feeding led to inflammatory gene expression of cyclooxygenase 2 (COX-^{2}), E-selectin, monocyte chemoatractic 1 (MCP-1); macrophage inflammatory protein2 (MIP-2), TMAO and tumor necrosis factor α (TNF-α). In addition, acute injection of TMAO at physiological levels induced the same inflammatory markers and mitogen activated protein kinase (MAPK), extra-cellular signal related kinase (ECSRK) and nuclear factor kappa beta (NFK-β). To further explore the effects of TMAO, the authors[21] studied human aortic endothelial (HAEC) and vascular smooth muscle cells (VSMC) in culture. Treatment of these two cell lines with TMAO also induced gene expression of inflammatory markers: NFK-β; COX-2, interleukin 6, E-selectin and intercellular adhesion molecule (ICAM). In addition, TMAO enhanced endothelial recruitment of leukocytes.[21] These data indicate that TMAO activates inflammatory pathways in the vasculature, causing recruitment of endothelial cells and leukocytes, and atherosclerosis; these actions are mediated by NFK-β pathway.

Human studies documented participation of TMAO in atherosclerotic disease. Tang et al.[22] examined the effects of a phosphatidylcholine challenge (two hard-boiled eggs and deuterium-labeled phosphatidylcholine) in 40 normal individuals; they documented a significant increase in plasma and urine TMAO; in six of them, broad-spectrum antibiotics were administered, which completely suppressed TMAO increases. In a second study, 4,007 patients with documented coronary artery disease (CAD) were followed for three years and a graded increase in event risk in relation to TMAO plasma levels was documented, specifically death, non-fatal myocardial infarction or stroke (Figure 4).

In addition, TMAO levels correlate with atherosclerotic burden, as measured by the Syntax score, as well as to early atherosclerosis.[23,24] Furthermore, in a group of patients similar to those of the Courage trial,[25] i.e., with documented CAD and treated medically, higher TMAO levels were associated with worse prognosis due to cardiovascular events.

Emoto et al.[26] compared 39 CAD patients with 30 patients with risk factors and 50 normal controls. They

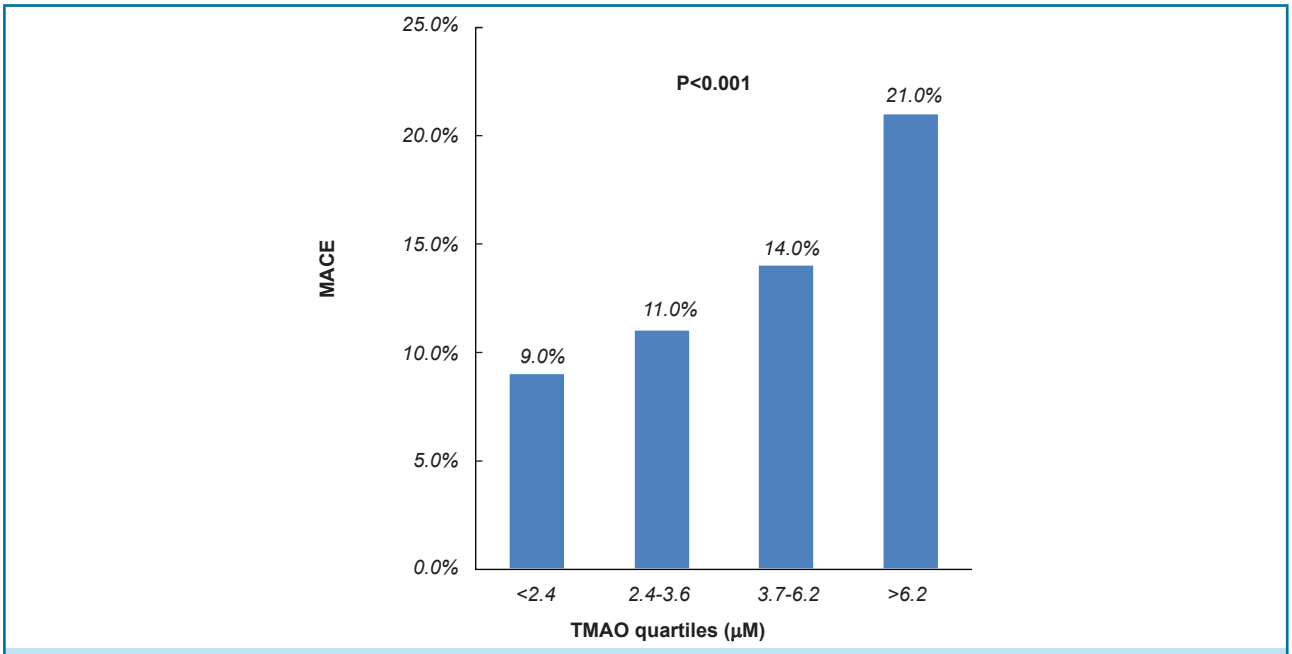

Figure 4 – Incidance of MACE (myocardial infarction, death and stroke) in 4007 CAD patients over 3 years period. Modified from Tang et al.[22]

observed that in CAD patients, order Lactobacillales was significantly increased and the phylum Bacteroidetes/ Prevotella was decreased when compared to controls.

On the other hand TMAO is an inductor of atherosclerosis or simply a marker of it. TMAO is clearly dependent on renal function and increases with age. Thus, individuals with even moderately decreased glomerular filtration rates have higher TMAO plasma concentrations.[2] Elderly individuals also have higher TMAO levels compared to middle age persons. One finding that supports the active role of TMAO as an atherogenic molecule is that it induces platelet hyperreactivity and thrombotic risk, both experimentally and in humans.[27,28] Furthermore, the ingestion of deep-sea fish increases urinary TMAO levels.[29]

The mechanisms underlying the atherogenic effects of TMAO include: a. induction of inflammation by expression of inflammatory genes in both vascular SMC and endothelial cells; b. induction of ROS production; c. impairment of bile acids synthesis through interference in the FXR/TGPR5 axis; d. increase in platelet adhesiveness and thrombus formation; e. impairment of reverse cholesterol transport; f. promotion of oxLDL receptors expression in macrophages facilitating foam cells formation[3]

Taken together these experimental and clinical studies indicate that dietary derived TMAO is closely associated with atherosclerosis, is entirely dependent on gut microbiota and is a marker of clinical outcomes; however, it is not yet entirely clear whether it is a marker or a true causative factor of atherosclerosis. It should also be mentioned the physiological functions of TMAO, specifically cell protection against hydrostatic and osmotic stress cells in deep sea fish and humans.[30,31]

Gut microbiota in diabetes and obesity

Patients with type 2 diabetes (DM_2) have typical intestinal flora compared with non-diabetic individuals; lower concentrations of butyrate-producing bacteria, such as Roseburia intestinalis and Faecalisbacterium, and higher concentrations of Lactobacillus gasseri and Streptococus mutans are found in DM2 patients. Also, insulin-resistant patients have increased concentrations of branched-chain amino acids,[32] which are associated with Prevotella copri and Bacteroids vulgatus.[33] In addition, in DM_2 individuals, postprandial glucose in response to diet can be modulated by intestinal microbiota.[34] Also, imidazole propionate, a metabolite produced by microbiota is elevated in DM2 and impairs glucose tolerance.[35]

Hypertension

It is well known that elevated salt intake is implicated in hypertension. In mice, high salt intake induced significant changes in gut microbiota associated with a reduction in Lactobacilus murinus. When this species was added to the diet, hypertension was no longer induced,[36] partially due to modulation of TH17 cells. Another mechanism involves G-protein coupled receptors (GRCRs) that are regulated by SCFAs. SCFAs can stimulate GPCRs, affect renin secretion and hence blood pressure;[37] in this line of evidence, KO mice for $GPCR_{41}$ showed systolic hypertension and SCFAs lowered blood pressure through regulation of $GPR_{41.}$[37]

Furthermore, Olfr78 and GPR41 are expressed in vascular SMC of resistance vessels; interestingly, propionate can cause vasodilation in mice through modulation of Olfr78 and GPR41. Also, high levels of oxLDL contribute to hypertension through inhibition of NO, which is a classic endothelial vasodilator. In summary, the link between diet, microbiota and hypertension includes two branches: a) production of SCFAs that are the final substances of fiber fermentation in the gut and their effects upon GRPs and Olf78 that are present in SMC and control blood pressure; b) increases in oxLDL from diet which inhibits NO and increases endothelin-1, which acts on SMC.

Cheema et al.[38] investigated metabolites associated with infused Ang II in mice. They found four up-regulated and eight down-regulated plasma metabolites; in feces there were 25 unregulated and 71 down regulated. These effects did not occur in germ-free mice. Thus, the relationship between AngII and hypertension is differentially regulated by microbiota-dependent metabolites, by complex mechanisms. Karbach et al.[39] also observed that gut microbiota facilitates AngII- induced vascular dysfunction and hypertension. Clinical observations have indicated that butyrate-producing bacteria is associated with lower blood pressure in pregnant women.[36]

Despite these strong mechanistic studies that support the interaction of diet, gut microbiota and hypertension, the role of human microbiota in hypertension needs further studies.

Heart failure

The participation of intestinal microbiota in heart failure (HF) has been suggested in many studies.[1] For instance a depletion of gut microbiota and its diversity has been observed.[40] Tang et al.[41] also showed that elevated TMAO in HF patients indicates higher long-term mortality risk, independent of traditional risk factors

and cardiorenal function.[41] Although mechanisms are not clear, one hypothesis is that bacterial translocation, inflammation and oxidative stress make these patients more vulnerable; that is an explanation well-suited to the "gut/brain axis hypothesis". In support of this hypothesis is the observation that HF patients are more prone to Clostridium difficile infection.[42]

Intervention on gut microbiota

Diet is the main tool to modulate intestinal microbiota. De Fillipis et al.[7] analyzed gut microbiota in 153 individuals who were omnivorous, vegetarians and vegans. There were significant associations between the consumption of vegetable-based diets and increased levels of fecal SCFAs, Prevotella and some fiber-degrading bacteria. On the contrary, higher urinary TMAO levels were observed among those who did not follow a Mediterranean diet. These data indicate that a Mediterranean type of diet influences gut microbiota and protect against atherosclerosis.[45]

Resveratrol, a polyphenol encountered in grapes, vegetables, berries and red wine may influence gut microbiota. Ingested resveratrol has low bioavailability due to its metabolization in the liver and intestine. Bifidobacteria infantis and Lactobacillus acidophilus are bacteria involved in the metabolism of resveratrol. Chaplin et al.[43] also showed, in animals, potential beneficial effects of resveratrol in fat accumulation, adipose deport extension, hepatic fat accumulation, glucose intolerance and insulin resistance, high blood pressure and lipids; in view of these effects, the authors concluded that resveratrol might be useful in metabolic syndrome.

Chen et al.[44] investigated the effects of resveratrol on TMAO and BA synthesis by gut flora in Apo $E^{-/-}$ mice. Resveratrol attenuated TMAO- induced atherosclerosis in these mice. Resveratrol also increased Lactobacillus and Bifidobacterium levels, which increased bile salt hydrolase activity, thus enhancing BA deconjugation and fecal excretion. In addition, resveratrol suppressed the FXR-TGR_5 axis and increased CYP7A1 and hepatic BAs neosynthesis. In antibiotic- treated mice none of these effects were noted. The authors concluded that resveratrol attenuated TMAO-induced atherosclerosis by decreasing TMAO levels and augmenting hepatic BA neosynthesis via gut microbiota remodeling. As indicated before, BA synthesis is an important pathway to eliminate cholesterol from the body.

Enterotypes have been linked to dietary patterns. Thus, the first enterotype described by Arumugan et al.[5] which is high in Bacteroides and low in Prevotella, is found in long-term Western diets, rich in animal proteins, choline and saturated fats; the second enterotype is high in Prevotella, low in Bacteroides and is associated with plant-based diets rich in fibers and simple sugars; the third enterotype has a slightly higher population of the genus Ruminococcus of the phylum Firmicutes.[45] Wu et al.[6] confirmed, in 98 individuals, that enterotypes are strongly associated with long-term diets, especially protein and animal fats with Bacteroides, in contrast to Prevotella which is preferentially linked to carbohydrate metabolism. Taken together, these data suggest that diet modulation, especially the Mediterranean diet, may beneficially influence the gut microbiota. Personalized diets according to the intestinal microbiota is a promising approach for glycemic control, as suggested by Zeevi et al.[34] In our group, we tested the effects of red wine on gut microbiota and plasma metabolomics in CAD patients (Wineflora Study). Preliminary results suggest a potential beneficial effect on gut microbiota by induction of anti-atherosclerotic bacteria.

Another possibility is *enzymatic blockade* of TMA formation by suppressing FMO3. However, this approach leads to TMA accumulation in plasma and consequent fish odor syndrome, which hampers its clinical application.[46]

Also, bacterial enzyme inhibitors, such as choline TMA lyase and carnitine TMA lyase, represent another approach to reduce TMA production.[47] However no human data is yet available. Another approach would be the use of long-term broad-spectrum antibiotics to suppress TMAO formation, as mentioned before. Unfortunately, this is not possible in clinical practice. Further, the use of antibiotics in patients produced no effects in preventing coronary events.[48]

Prebiotics and *probiotics* are potential ways to interfere with gut microbiota. Probiotics are substances that contain live bacteria such as Lactobacillus.[45] Tannock et al.[49] gave a milk compound containing Lactobacillus rhamnosus to 10 normal individuals; they observed transient changes in fecal microbiota, specifically lactobacillus and enterococcus, but no concomitant modifications in biochemical parameters. Experimental clinical studies have offered promising results related to BA metabolism. Prebiotics are foods such as fibers whose metabolism provide the growth of "protective bacteria"; for instance, ingestion of nondigestible fibers may induce the growth of commensals and alter intestinal motility.[47] Prebiotics and probiotics are in early phases of development but will likely constitute valuable alternatives for gut microbiota modulation.

Another intervention that impacts on intestinal microbiota is *bariatric surgery*, in which increased circulating levels of primary and secondary BAs were observed.[2]

Finally, *fecal transplantation* can be employed in especial circumstances.[50] Few experiments have been conducted on humans, showing inconsistent results. A series of technical and ethical problems, such as the definition of healthy donors, still need clarification. However, in special circumstances such as IBD resistant to conventional treatment, fecal transplantation may be a valuable alternative.

Conclusions

Gut microbiota plays a pivotal role in atherosclerosis, heart failure, diabetes, and obesity, acting as an independent risk factor. Gut microbiota is essential for metabolism of nutrients like proteins, carbohydrates, and plant derivates. It interferes directly in the metabolism of SCFA, BAs, inflammation and immune system. It also induces the formation of TMAO, an atherogenic molecule. The intestine is considered today an endocrine organ since it produces substances that act locally or at distance. The intestine and the brain maintains constant and bidirectional influences through the "gut-brains axis". Human intestinal microbiota is profoundly influenced by diet, and for this reason, diet modulation, especially by adopting a Mediterranean type diet, is the most promising approach to beneficially influence gut microbiota. However, there are no clinic studies analyzing the long-term effectiveness of dietary interventions on gut microbiota. Further research is needed to clarify the roles of intestinal microbiota in health and human diseases.

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Author contributions

Conception and design of the research: Luz PL. Statistical analysis: Favarato D. Critical revision of the manuscript for intellectual content: Haas EA, Favarato D.

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ORIGINAL ARTICLE

Early Outcomes of Modified De Vega Annuloplasty for Functional Tricuspid Regurgitation at a Brazilian Hospital

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Abstract

Background: Right valve diseases are not benign, the tricuspid regurgitation has a significant impact on morbidity and mortality of patients.

Objectives: This study aimed to report the short-term results of tricuspid annuloplasty using the De Vega technique modified by Manuel Antunes.

Methods: A descriptive-analytical study was performed to evaluate the results of the tricuspid valvuloplasty performed at the *Instituto de Medicina Integral Professor Fernando Figueira* between 2012 and 2017. Data were collected by reviewing charts and databases of the Department of Cardiology and Cardiovascular Surgery of the institution. Those with rheumatic diseases or infective endocarditis with tricuspid valve involvement, or reoperation of the tricuspid valve were excluded. Student's t-test and McNemar's were used for statistical analysis. A p-value < 0.05 was considered statistically significant.

Results: A total of 87 patients were studied, most of them were women (56.3%). The most associated heart valve diseases were mitral regurgitation (27.6%) and aortic regurgitation (20.7%). There was a significant decrease in the degree of tricuspid regurgitation in the postoperative period, with 83.3% of patients with none or mild regurgitation and only 1.1% with severe regurgitation (p = 0.0077).

Conclusions: In the current study, tricuspid valve annuloplasty using the modified De Vega technique was shown to be effective in the short term. Further studies are needed to evaluate the long-term results. (Int J Cardiovasc Sci. 2020; 33(5):472-478)

Keywords: Heart Valve Diseases/physiopathology; Cardiac Valve Annuloplasty/methods; Tricuspid Valve Insufficiency; De Vega Annuloplasty.

Introduction

In Brazil, a significant proportion of hospitalizations for cardiovascular diseases is due to heart valve diseases.[1] Among these, tricuspid regurgitation (TR) is more common than tricuspid stenosis, which is a rare condition. In the Framingham study, the overall prevalence of moderate TR was 0.8%, with a higher prevalence among women (up to 4.3 times greater than men). There is a frequent association of both tricuspid stenosis and TR with mitral valve disease.[1,2]

Historically, physicians and researchers have placed less importance to right heart valve disease because of

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its long, asymptomatic latency period, and the association of secondary TR with left heart valve disease. However, it has been recently observed that right valve diseases are not benign and have a significant and independent impact on morbidity and mortality.[3] Mortality increases with the severity of TR: one-year survival rate among patients without the disease was 91.7%; in patients with mild TR, 90.3%; moderate TR, 78.9%; and severe TR, 63.9%.[4]

TR does not cause many symptoms and is classified as primary (8 to 10% of severe cases) when results from organic tricuspid valve disease (e.g., endocarditis, rheumatic disease), and as secondary or functional (90% of severe cases), when it is caused by volume overload and/or pressure overload in the right ventricle generated by pulmonary hypertension, left heart failure or right ventricular ischemia. Most of signs and symptoms of TR become more evident due to an increase in the right atrial pressure, culminating in heart failure in more severe cases.[5-7]

Treatment options for tricuspid valve disease have increased. Annuloplasty techniques can be divided in two groups: the first group consists of techniques of implantation of a prosthetic ring to restore the shape and size of the tricuspid ring, like the Carpentier's technique, and the second group consists of techniques that do not use the prosthetic ring, as in the modified De Vega annuloplasty, by Manuel Antunes. In the classical De Vega's annuloplasty, two continuous sutures running along the anterior and posterior portions of the tricuspid annulus (he free wall of the right ventricle) are performed. Therefore, the septal portion of the annulus is spared for protection of the conduction system of the heart.[8] In 1983, aiming to improve the distribution of the tension of the valve suture, Manuel Antunes proposed the insertion of Teflon pledgets in each space between the suture lines, creating the modified De Vega technique.[9]

The De Vega technique is easily reproducible and applicable, low cost, relatively fast, and relatively free of complications. However, in a medium-term postoperative follow-up of annuloplasties, the incidence of recurrence of tricuspid insufficiency was higher after De Vega technique (17.2% -13.7%) compared with the modified De Vega annuloplasty (15.3% -7.7%).[10]

There are few studies in this area since the interest in right heart valve diseases has only recently increased. The present study was conducted with limited technology and scarce materials, provided by the Brazilian Unified Health System (SUS). Therefore, this research aims to add to the current knowledge on the theme and perform an early evaluation of tricuspid valve annuloplasty, performed with the modified De Vega technique, due to secondary tricuspid insufficiency.

Methods

A descriptive-analytical study was performed to evaluate the initial results of tricuspid annuloplasty using modified De Vega technique. The study was carried out at *Instituto de Medicina Integral Professor Fernando Figueira* (IMIP), and institute of integrative medicine, and data were collected by reviewing charts and databases of the Department of Cardiology and Cardiovascular Surgery at IMIP.

From May 2012 to April 2017, 87 consecutive patients who underwent modified De Vega procedure and other cardiac valve surgeries concomitantly in our institution were enrolled in the present study. Patients with rheumatic heart disease or infective endocarditis with tricuspid valve involvement or patients with a history of surgery for tricuspid valve disease were excluded.

All operations were performed with a conventional median sternotomy, cardiopulmonary bypass (CPB) with aortic and bicaval cannulation, and mild hypothermia (32° to 34°C). The aorta was cross-clamped and cold cardioplegia delivered. After the left heart valve surgery was finished, the aorta was released, and the heart was again perfused and beating.

The tricuspid annuloplasty consists of two continuous sutures using 3-0 or 4-0 polypropylene with Teflon-pledged sutures running along the anterior and posterior tricuspid annulus. The procedures were performed by five surgeons that used the same technique.

Preoperative echocardiography were performed in other institutions, and all postoperative echocardiography was performed at IMIP before hospital discharge.

The study complied with the principles of the National Health Council for research on human beings and was approved by the Research Ethics Committee of the IMIP. Certificate of Presentation for Ethical Consideration (CAAE): 58349516.7.0000.5201.

Statistical analysis

All statistical analysis was performed using Stata 12.1. The Kolmogorov-Smirnov test was used to test the normality of data. Continuous variables with normal distribution were expressed as mean and standard deviation. Descriptive statistics were used to characterize the patients, and proportions were used for categorical variables.

For the analysis of the differences between pre and post-operative values of left ventricular ejection fraction (LVEF) the Student's paired t-test was used. The McNemar´s test was performed to evaluate the efficacy of the treatment in reducing the degree of the tricuspid regurgitation. A p value of < 0.05 was considered statistically significant.

Results

A total of 87 patients were submitted to tricuspid valve annuloplasty evaluation, 49 (56.3%) were women. The median age was 41.8 years, the average height was 162.89 cm, the mean weight was 66.13 kg, and the median body mass index (BMI) was 24.83 kg/m^2.

Most patients had rheumatic disease (65.51%), followed by bacterial endocarditis (4.59%) (not tricuspid valve infective endocarditis, which was an exclusion criterion of this study) (Table 1).

Regarding comorbidities, 35.6% had systemic arterial hypertension, 21.8% chronic atrial fibrillation, and 18.4% of the patients were smokers. Heart valve diseases most associated with TR included mitral regurgitation (27.6%) and aortic regurgitation (20.7%). The most frequent signs and symptoms of heart failure were peripheral edema (35.6%), murmur in other locations than the tricuspid valve (14.9%) and nocturnal paroxysmal dyspnea (12.6%). According to the New York Heart Association (NYHA) criteria, most patients (n = 57, 93.4%) were classified as functional class II and III.

Of the 87 patients in the sample, 63 (72.4%) underwent tricuspid annuloplasty with mitral valve surgery, 22 (25.3%) tricuspid annuloplasty with aortic valve replacement, and 2 (2.3%) underwent surgery of the three (tricuspid, mitral and aortic) valves.

In 67 patients (77.0%), bioprosthesis was used to correct the other valve diseases.

The mean cross-clamp time was 68.29 minutes, and total cardiopulmonary bypass time was 129.04 minutes.

During the postoperative period, the mean intensive care unit (ICU) length of stay was 6.66 days, and mean hospital stay was 20.26 days. Fifty-eight patients (68.2%) used vasoactive drugs.

The main postoperative complications were respiratory tract infection (n = 16, 24.6%), followed by atrioventricular block (n = 14, 21.5%) and acute renal failure (n = 11 patients, 17%); only 3 (4.6%) patients required permanent pacemaker implantation. Overall 30-day mortality was 6.9% (n = 6) (Table 2).

Table 1 - Baseline characteristics of patients

Preoperative variables	n (% or ± SD)	n
Female	49 (56.3%)	87
Male	38 (43.7%)	87
Age (years)	41.8 ± 16.7	81
Anthropometric measurements		
Height (cm)	162.89 ± 7.25	57
Weight (kg)	66.13 ± 16.56	73
BMI (kg /m^2)	24.83 ± 5.70	57
Echocardiographic data		
LVEF (%)	56.19 ± 12.77	68
Etiology		
Rheumatic disease	57 (65.51%)	87
Infective endocarditis	4 (4.59%)	87
Rheumatic disease and infective Endocarditis	2 (2.29%)	87
Chagas disease	1 (1.14%)	87
Others (prosthesis dysfunction, congenital, etc.)	24 (27.58%)	87
Comorbidities		
Systemic arterial hypertension	31 (35.63%)	87
Chronic atrial fibrillation	19 (21.83%)	87
Smoking	16 (18.39%)	87
Diabetes mellitus	9 (10.34%)	87
Alcoholism	8 (9.19%)	87
Chronic kidney disease	6 (6.89%)	87
COPD	4 (4.59%)	87
Hypothyroidism	3 (3.44%)	87
Paroxysmal atrial fibrillation	1 (1.14%)	87
No comorbidities	16 (18.39%)	87
Others	10 (11.49%)	87

BMI: body mass index; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; SD: standard deviation.

Of the 87 patients in the sample, 34 patients (39,08%) underwent reoperations after tricuspid valve repair. Comparative analysis of reoperations with first heart surgeries revealed that the mean aortic cross-clamp time was 74.78 min in reoperation and 63.87 min in the first

Table 2 - Postoperative outcomes of the patients (n = 87)

Postoperative variables	n (% or ± SD)	n
Mortality in 30 days	6 (6.89%)	87
ICU time (days)	6.66 ± 6.32	66
Length of stay (days)	20.26 ± 20.36	50
Use of vasoactive drugs	58 (90.6%)	64
Echocardiographic data		
LVEF (%)	53,03±12.67	65
Complications		
Respiratory tract infection	16 (24.6%)	65
Atrioventricular block	14 (21.5%)	65
Permanent pacemaker implantation	3 (4.6%)	65
Acute renal failure	11 (17%)	65
Pericardial effusion	8 (12.3%)	65
Cardiopulmonary resuscitation	7 (10.8%)	65
Urinary tract infection	5 (7.7%)	65
Low cardiac output syndrome	4 (6.15%)	65
Cardiac tamponade	4 (6.15%)	65
Pneumothorax	4 (6.15%)	65
Mediastinitis	3 (4,6%)	65
Pleural effusion	3 (4.6%)	65
Sepsis	2 (3%)	65
Atrial fibrillation	2 (3%)	65
Stroke	2 (2.3%)	65
Free from complications	2 (3%)	65

SD: standard deviation; ICU: intensive care unit.

heart surgery. Mean cardiopulmonary bypass time was 143.36 min in reoperation and 119.20 min in the first heart surgery. Mean ICU time was 6.37 days for reoperations and 6.87 days for first surgeries, and the mean hospital stay was 23.06 days and 20.15 days, respectively. Thirty-day mortality was 12.2% among patients who underwent reoperation and 2.2% after the first heart valve surgery. In patients who underwent reoperation, the main complications were low cardiac output syndrome and cardiorespiratory arrest.

Analysis of echocardiographic data showed that there was no significant difference between pre- and postoperative mean LVEF (56.2% vs. 53.03%, respectively, p = 0.0774).

In the postoperative period, a significant reduction in the grade of TR was observed – 45 patients (83.3%) had none or mild residual lesion, eight patients (14.81%) had moderate TR and only one patient (1.85%) continued with severe TR (p = 0.0077) (Figure 1) (Table 3).

Discussion

The epidemiological profile of the patients submitted to cardiac surgery in this study agreed with that found in the literature. High-surgical-risk patients have comorbidities and advanced symptoms, in addition to the inherent factors involved in valve replacement surgeries, such as an extracorporeal circulation time. Data of the literature have shown that tricuspid insufficiency is more common in women,[2] there is a high prevalence of smoking in heart disease patients,[12] and the most common comorbidities in association with valve disease are systemic arterial hypertension, chronic atrial fibrillation, and diabetes.[13]

The symptoms of patients with TR are variable. In general, there is a predominance of repercussions of left heart disease in case of secondary disease,[14] and in advanced stage, the symptoms of right heart failure are prominent,[3] with emphasis on peripheral edema and heart murmurs found in this study6 associated with an advanced NYHA index (III and IV -57.4%),[15] which is an indicator of poor prognosis.[16]

The mean age found in this study (41.8 years) was lower than in other studies (56 years for valve surgeries and 58.7 years for heart surgeries).[13] This may be justified by the fact that most of our patients had rheumatic diseases which affect younger patients.

In addition, tricuspid valve surgery represents an additional risk factor when performed in patients with other systemic and valve diseases, especially mitral valve disease and aortic valve disease.[17,18] This association with the mitral valve is already well documented in the literature[1,2] and makes the approach of tricuspid valve surgery controversial,[19] since the correction of mitral valve disease per se could reduce the repercussions of the tricuspid injury.[20]

The present study demonstrated the effectiveness of tricuspid valve repair surgery by the modified De Vega technique, with a significant reduction in the degree of TR. Most patients achieved a favorable and expected

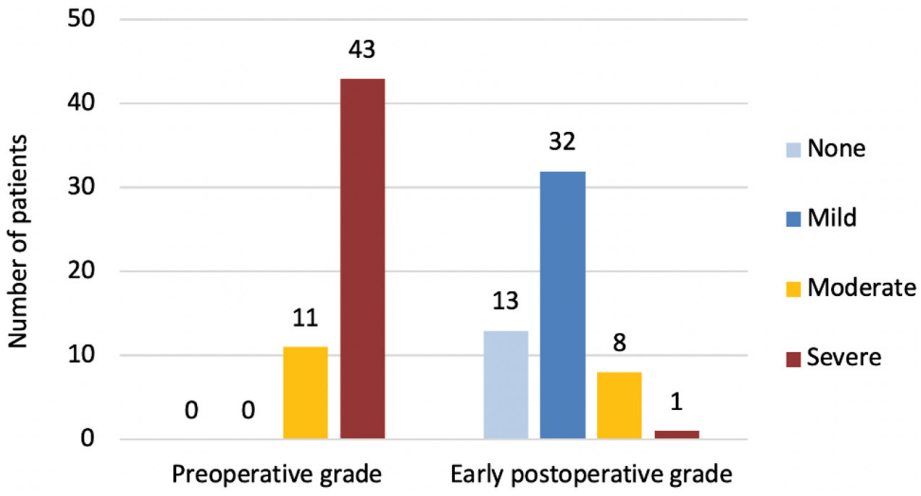

Figure 1 - Early postoperative changes in grades of tricuspid regurgitation.

Table 3 - Evaluation of tricuspid valve annuloplasty

Grade of the tricuspid lesion	Preoperative (n = 54)	Postoperative (n = 54)	p
Normal valve or mild lesion	0 (0%)	45 (83.33%)	0.0077*
Moderate or severe regurgitation	54 (100%)	9 (16.66%)	

*The McNemar´s test was used for categorical variables - normal valve or mild lesions x moderate or severe tricuspid regurgitation; *p < 0.05.*

outcome after valve repair, most of them had mild stenosis, normal valve or mild insufficiency in the post-operative period. Mild insufficiency, in the literature, has been identified as residual regurgitation, and may occur due to factors such as the degree of ring dilation, and right ventricular and left ventricular functions in the preoperative period.[21,22]

In addition, in our study, there was no significant decrease in the LVEF (p = 0.0774). The decrease in ejection fraction in the postoperative period of cardiac surgery is well recognized in the literature as an effect of extracorporeal circulation,[23] but little is known about the mechanism that leads to this dysfunction.[18,24]

Although the tricuspid valve repair has reached its goal, complications exist and may not be uncommon. The number of deaths in the recent postoperative period (up to 30 days) was 6.9% higher than in the international literature (2 to 4.5%).[18,24]

The most common complications in the early postoperative period after tricuspid valve repair in our sample were atrioventricular block, acute renal failure, respiratory tract infection, cardiorespiratory arrest and pericardial effusion. This is in agreement with previous studies, which also reported low cardiac output syndrome, bleeding, mediastinitis, sepsis and stroke,[18,25] which were also observed in our patients, without a significant frequency though.

The present study has some limitations. First, since it is a retrospective and observational study, the study has limitations inherent to its design. Second, there was a difficulty during data collection due to lack of information in the medical records, reducing the sample size for some variables.

Conclusion

Although the clinical profile of the study patients was characterized by severe disease, with multivalvular heart disease and a large percentage of reoperations, the modified De Vega technique for repair of functional tricuspid insufficiency was effective and reproducible in our environment. There were favorable results with a significant reduction in the degree of tricuspid insufficiency. Further studies are needed to evaluate the

outcomes of this surgery in the long term and in right heart valve disease.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the IMIP under the protocol number 58349516.7.0000.5201. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Author contributions

Conception and design of the research: Figueira FAMS, Ferraz, DLM. Acquisition of data: Alves KMB, Leandro GS, Santos LAB, D' Azevedo SSP, Silva TLS, Silva ITC, Tchaick RM. Analysis and interpretation of the data: Ferraz DLM, Monteiro VS, Cunha CBC. Statistical analysis: Ferraz, DLM. Writing of the manuscript: Alves KMB, Leandro GS, Santos LAB, Carvalho Junior JD, Oliveira JPSP, Walter FR, Ferraz DLM. Critical revision of the manuscript for intellectual content: Ferraz DLM.

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ORIGINAL ARTICLE

Lung Ultrasound as a Triage Tool in an Emergency Setting during the Covid-19 Outbreak: comparison with CT Findings

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Abstract

Background: Lung ultrasound (LUS) can detect interstitial alveolar changes confined to the subpleural region, like those described in Covid-19.

Objetive: To evaluate how LUS findings correlate with chest computed tomography (CT) in patients admitted to the emergency department (ED) with suspicion of Covid-19.

Methods: Cross-sectional study of 20 patients (median age 43 years; interquartile range, 37–63 years; 50% male). All patients underwent LUS and chest CT on the day of ED admission. Each hemithorax was divided into 6 segments with similar landmarks, and equivalent scores (sc) of lesion severity were defined for both methods. The number of affected segments on LUS (LUSseg) was divided into tertiles (0-1, 2-5, and ≥6), and compared with number of affected segments on CT (CTseg), LUSsc, CTsc, and percentage of affected lung parenchyma through visual analysis (CTvis). ANOVA or Kruskal–Wallis test for continuous variables, chi-square test for categorical variables, and receiver operating characteristic (ROC) curve analysis to define optimal cutoff points were performed. P<0.05 was considered statistically significant.

Results: Median LUSsc, CTsc, CTseg, and CTvis were significantly different between groups. A clear separation between groups was demonstrated; patients with <2 affected segments on LUS were defined as low risk. The ROC curve showed good discriminative power to predict ≥6 affected segments on CT, with an area under the curve (AUC) of 0.97 and 0.98 for >7 LUSsc and >3 LUSseg, respectively.

Conclusion: LUS findings correlate with chest CT, and can help identify patients with normal lung or minor pulmonary involvement secondary to Covid-19. (Int J Cardiovasc Sci. 2020; 33(5):479-487)

Keywords: Lung; Ultrasonography/methods; Triage; Pandemics; COVID-19; Pulmonary Alveoli; Pleura; Tomography, X-Ray Computed/methods.

Introduction

Since late 2019, the novel coronavirus disease (Covid-19) outbreak has posed a new challenge to health organizations worldwide. Hospitals are being reformatted to provide surge capacity for the population, in an attempt to avoid a collapse of entire health systems. Triage, separating the most serious cases (requiring hospitalization) from those who can safely stay at home in self-isolation, plays a particularly important role in the management of available hospital beds in this setting. Triage protocols are based on clinical, laboratory, and imaging data, with chest computed tomography (CT) considered a sensitive tool to detect and quantify the extension of pulmonary involvement in Covid-19.[1,2] This high accuracy notwithstanding, scanners need to undergo a time-consuming high-level disinfection after each scan, slowing the workflow in overloaded emergency departments. Lung ultrasound (LUS) has been suggested as an attractive tool to rule out

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more extensive pulmonary involvement in patients with high clinical suspicion for Covid-19.[3,4] LUS is a ready-to-use bedside technique that relies on the visualization of artifacts that arise from the pleural line.[5]As the vast majority of interstitial syndromes involve the pleura and as most pulmonary lesions in Covid-19 are located in the subpleural region, LUS is especially suited to demonstrate those lesions.

Within this context, the aim of the present study was to evaluate whether LUS findings correlate with CT findings in patients admitted to an emergency department with clinical suspicion of Covid-19.

Methods

Patient Population and data collection

This was a cross-sectional study of 23 patients admitted to our emergency department with clinical signs and symptoms suggestive of Covid-19. The sample size was determined by convenience. All patients underwent LUS and CT on the same day. Patients were excluded if CT clearly showed evidence of non-Covid-19 pathology. The following clinical data were collected for analysis: age, gender, heart rate, respiratory rate, peripheral oxygen saturation (obtained by pulse oximetry), and duration of symptoms. Relevant symptoms suggestive of Covid-19 were fever, cough and dyspnea. Hypertension, diabetes mellitus, heart failure, chronic obstructive pulmonary disease (COPD), asthma, and obesity were considered risk factors for severe Covid-19.

Lung ultrasound

LUS was performed using a Vivid E9 XD Clear system (GE Healthcare, USA) with a 3-5 MHz convex probe. Patients were scanned in upright position whenever possible or in supine position and subsequent lateral decubitus to access posterior regions. Each hemithorax was divided in six regions: anterior, lateral and posterior with anterior and posterior axillary lines set as landmark of those regions and 4th intercostal space subdividing them in superior and inferior[6] (Figure 1a). The transducer was held perpendicular to the chest wall, with the marker pointing cephalad. Each region was carefully scanned by sliding the probe so as to cover as much pleural surface as possible. The liver and spleen were used as landmarks of transition between lung and diaphragm. Dynamic images were obtained and stored to detect typical LUS findings as described in the literature,[5] such as lung sliding, B-line movement, and subpleural and translobar consolidations. Each region was scored semiquantitatively according to increasing degrees of severity of LUS findings, as follows: 0, A-line profile (considered a normal finding); 1, >2 B-lines per intercostal space; 2, coalescent B-lines; 3, subpleural consolidation; and 4, translobar consolidation[7]. The scores of each segment were added to yield the final score (sc). The total number of abnormal segments (seg) was also added and compared with CT. Patients were divided into tertiles according to the number of affected segments on ultrasound (LUSseg): group I, 0-1 segment; group II, 2-5 segments; and group III, ≥6 segments. The presence of pleural effusion was also documented. Pleural thickening or irregularity was not considered for scoring purposes.

Computed tomography

CT was performed using a 64-slice SOMATOM Confidence® RT scanner (Pro-Siemens Healthineers, Germany). Percent lung involvement was defined through visual analysis according to the distribution of affected lung parenchyma and stratified into four categories: 0% (normal lung), less than 25% of lung affected, 25-0% of lung affected, and >50% of lung affected.[8] The number of affected segments was also evaluated using the same anatomical landmarks as for LUS (Figure 1b). A 12-segment model was used for CT instead of the traditional 5-lobe segmentation used in radiology reports, aiming to ensure comparability of analysis with LUS to define the anatomic distribution of the lesions. A cutoff value of >6 segments on CT was defined for "extensive pulmonary involvement". As in LUS, each segment was scored according to increasing severity of CT findings, as follows: 0, normal findings; 1, peripheral ground-glass opacities; 2, "crazy paving"; 3, subpleural consolidation ; and 4, translobar consolidation. Again, as in LUS, the score values of all segments were added to yield the final CTsc. The number of affected segments on CT (CTseg) was added for comparison with LUSsc (Figure 2) LUS scanning and analysis was performed by three echocardiographers experienced in LUS (MLA, MPLB, and TBA), who were blinded to CT findings. CT analysis was performed by two experienced radiologists (DCM and LAC) who, in turn, were blinded to LUS findings.

Statistical analysis

Data analyses were performed in IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA).

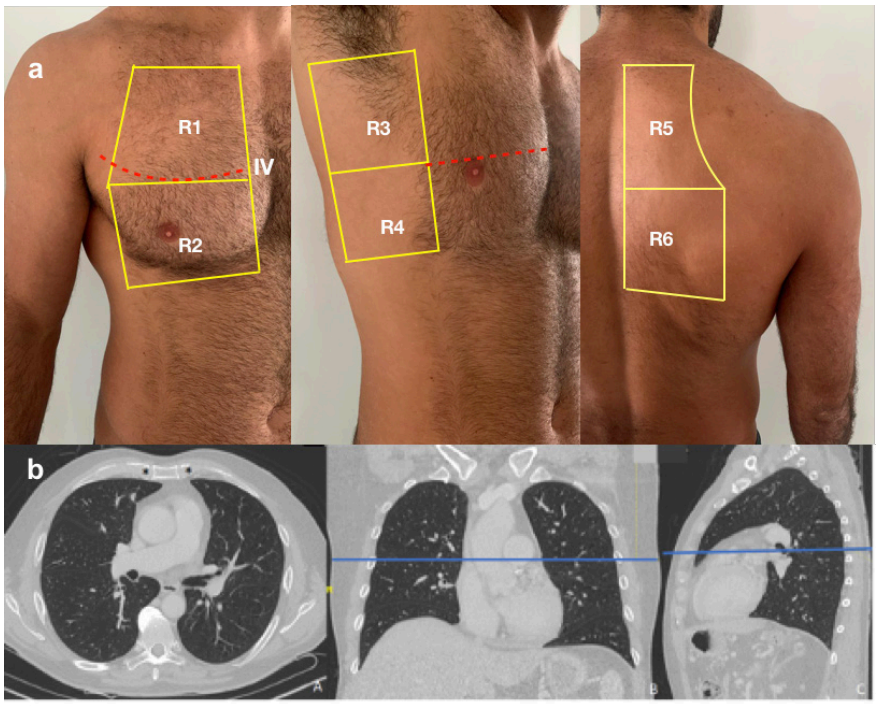
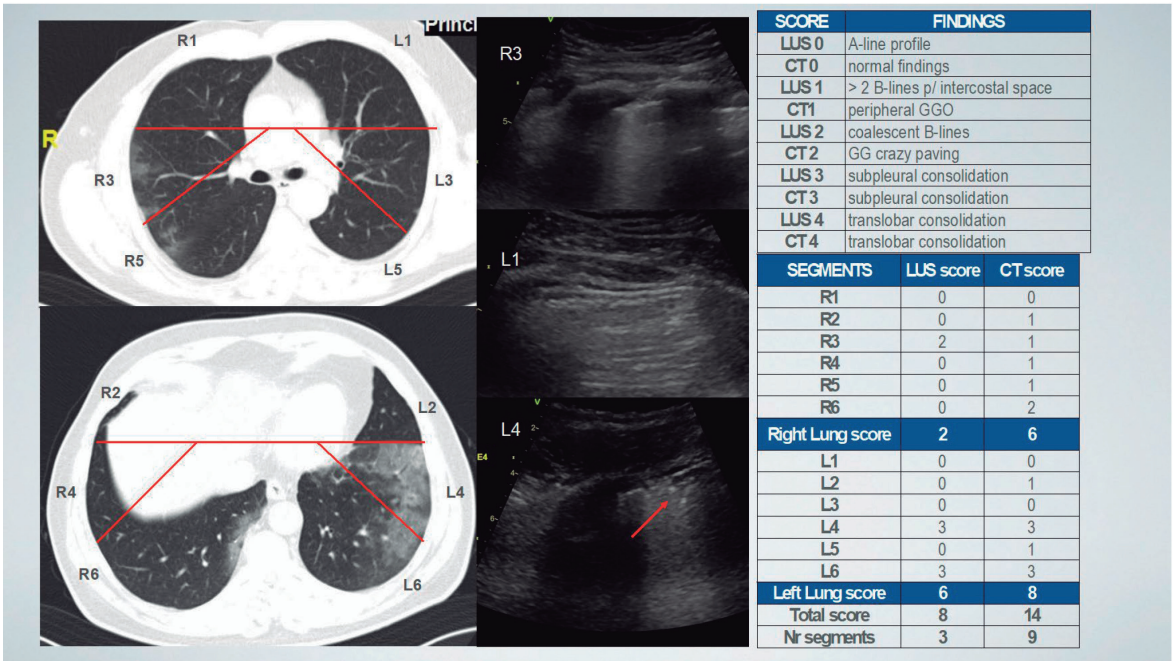


Figure 1 – Segmentation model for lung ultrasound (a) and corresponding CT (b). The anatomical landmarks are the 4th intercostal space and the anterior and posterior axillary lines.



SCORE	FINDINGS
LUS 0	A-line profile
CT 0	normal findings
LUS 1	> 2 B-lines p/ intercostal space
CT1	peripheral GGO
LUS 2	coalescent B-lines
CT 2	GG crazy paving
LUS 3	subpleural consolidation
CT 3	subpleural consolidation
LUS 4	translobar consolidation
CT 4	translobar consolidation

SEGMENTS	LUS score	CT score
R1	0	0
R2	0	1
R3	2	1
R4	0	1
R5	0	1
R6	0	2
Right Lung score	2	6
L1	0	0
L2	0	1
L3	0	0
L4	3	3
L5	0	1
L6	3	3
Left Lung score	6	8
Total score	8	14
Nr segments	3	9

Figure 2 – Example of 61 year old male patient showing CT segmentation and corresponding LUS showing subpleural in a patient with predominant peripheral ground glass opacification (GGO) and subpleural consolidation restricted to L4 and L6 as demonstrated by both methods. Left panel: CT segmentation and findings; middle panel: LUS findings in 3 segments and right panel: scoring according to findings and structured scoring table, right lung (R) and left lung (L).

Continuous data were presented as mean ± standard deviation (SD) or median and interquartile range (IQR), according to the normality of data distribution as evaluated by the Shapiro–Wilk test. Categorical data were presented as absolute and relative frequencies. Continuous variables were compared by means or medians of one-way ANOVA or Kruskal–Wallis tests, as appropriate, while categorical variables were compared with a chi-square test. Receiver operating characteristic (ROC) curve analysis and the Youden index were used to assess optimal cutoff points for LUSseg and the best LUSsc to detect ≥6 affected segments in CT. All statistical tests were two-sided, and a P-value <0.05 was considered statistically significant.

Results

Patient population

Three of 23 patients were excluded due to CT findings typical of pneumocystis infection (one patient), bilateral moderate pleural effusion secondary to heart failure (one patient), or residual changes of previously documented pneumonia (one patient). The remaining group had a median age of 43 years (IQR, 37 to 63 years) and was 50% male. The median duration of symptoms was 7 days (IQR, 6 to 8 days). Baseline clinical characteristics and differences between the groups are listed in Table 1. No difference was observed between groups except for female gender (more prevalent in group I) and lower oxygen saturation (more prevalent in group III).

Lung ultrasound and computed tomography characteristics

LUS and CT measurements based on LUSseg are shown in Table 2, Figure 3, and Figure 4. Median LUSsc, CTsc, CTseg, as well as CT visual analysis categories, were significantly different between groups. Using ROC curve analysis to predict ≥6 segments on CT (Figure 5), LUSsc and LUSseg showed good discriminative ability, with AUCs of 0.97 and 0.98 respectively. A LUSsc >7 and a LUSseg ≥3 showed similar sensitivity (81.8%) and specificity (100%) in predicting lung involvement in ≥6 CT segments.

Table 1 – Clinical characteristics of the sample, based on the number of segments affected on lung ultrasound

	Group I (0/1 segments) (n=9)	Group II (2/5 segments) (n=4)	Group III (≥6 segments) (n=7)	p-value
Age in years, median [IQR]	38 [36-48]	47 [39-58]	63 [38-74]	0.241‡
Female gender, n(%)	7 (77.8)	3 (75)	0 (0)	0.005*
Symptom duration in days, median [IQR]	7 [5-11]	8 [3-13]	7 [7-8]	0.911‡
Heart rate, bpm	88±15	86±15	94±21	0.709§
Respiration rate, bpm	18±3	20±6	24±8	0.134§
Peripheral oxygen saturation, median [IQR]	99 [98-100]	98 [93-98]	94 [91-95]	0.009‡
Fever, n (%)	7 (77.8)	3 (75)	7 (100)	0.383*
Cough, n (%)	9 (100)	3 (75)	7 (100)	0.122*
Dyspnea, n (%)	8 (88.9)	1 (25)	4 (57.1)	0.072*
Hypertension, n (%)	2 (22.2)	0 (0)	4 (57.1)	0.109*
Diabetes, n (%)	2 (22.2)	1 (25)	1 (14.3)	0.890*
Heart failure, n (%)	0 (0)	0 (0)	0 (0)	1.00*
COPD, n (%)	0 (0)	0 (0)	1 (14.3)	0.376*
Asthma, n (%)	2 (22.2)	0 (0)	0 (0)	0.257*
Obesity, n (%)	2 (22.2)	1 (25)	2 (28.6)	0.959*

*COPD: chronic obstructive pulmonary disease; IQR: interquartile range; *chi-square test; §one-way analysis of variance (ANOVA); ‡Kruskal–Wallis test.*

Table 2 – Lung ultrasound and computed tomography parameters and their relation to the number of segments affected on lung ultrasound.

	Group I (0/1 segments) (n=9)	Group II (2/5 segments) (n=4)	Group III (≥6 segments) (n=7)	p-value
Pleural effusion on lung ultrasound, n (%)	0 (0)	0 (0)	1 (14.3)	0.376*
LUS score, median [IQR]	0 [0-1]	7 [3-10]	18 [14-23]	0.002‡
Pleural effusion on CT, n (%)	0 (0)	0 (0)	1 (14.3)	0.376*
CT score, median [IQR]	0 [0-4]	13 [11-14]	27 [24-31]	<0.001‡
CT visual analysis, n (%)				0.002*
<25%	9 (100)	3 (75)	0 (0)	
25%-50%	0 (0)	1 (25)	5 (71.4)	
>50%	0 (0)	0 (0)	2 (28.6)	
CT number of segments, median [IQR]	0 [0-2]	9 [5-11]	12 [11-12]	<0.001‡

*CT: computed tomography; IQR: interquartile range; LUS: lung ultrasound. *chi-square test; ‡Kruskal–Wallis test.*

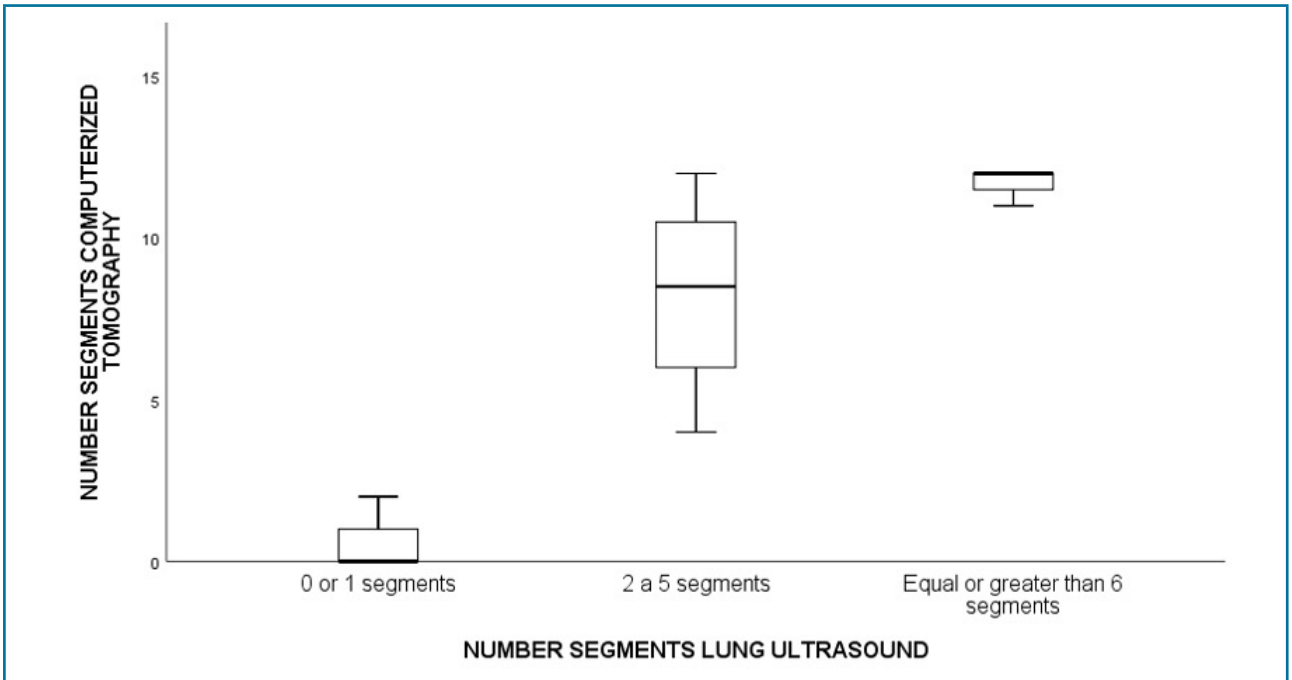


Figure 3 – Distribution of number of affected segments on lung ultrasound and computed tomography. The chart shows the median (horizontal bars), the 25th and 75th percentiles (lower and upper limits of the boxes), and lower and upper absolute values (error bars).

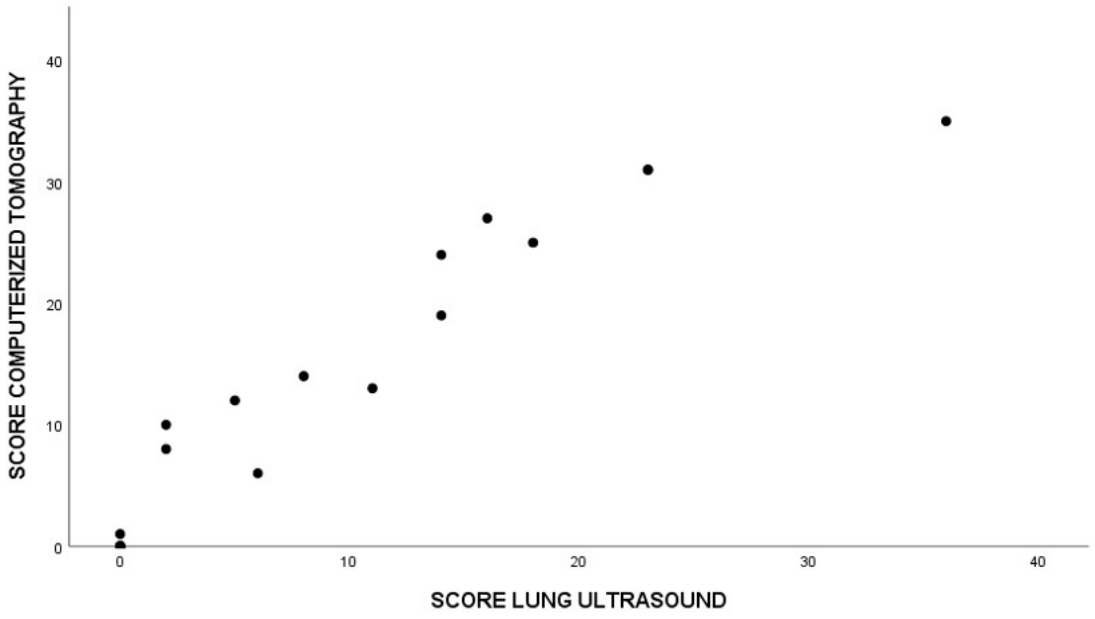


Figure 4 – Scatter-dot plot of lung ultrasound score and computed tomography score, showing proportionally ascending values according to extension of involvement.

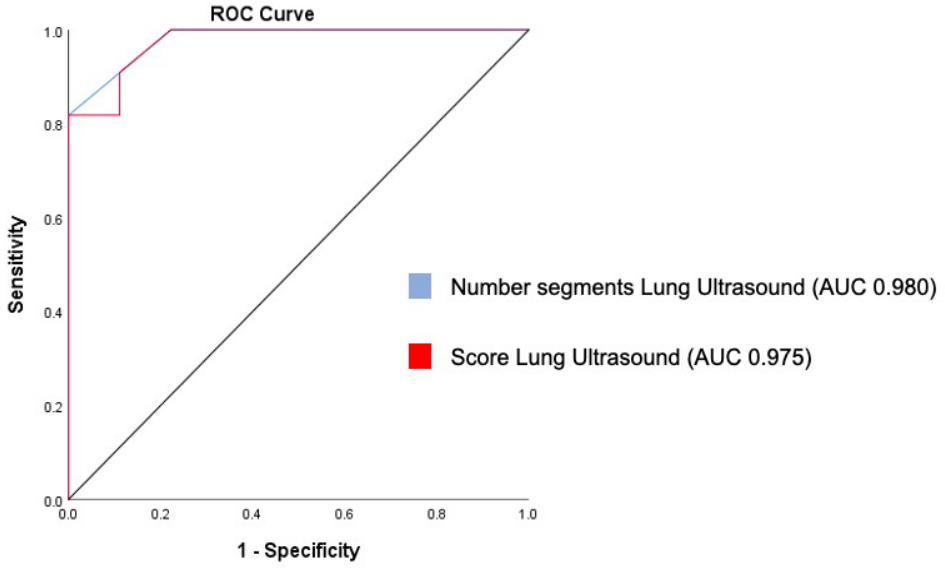


Figure 5 – Receiver operator characteristic analyses of lung ultrasound to identify ≥6 affected segments on computed tomography.

Discussion

This study provides important information about the relationship between CT and LUS findings in Covid-19. A low LUSsc and LUSseg was able to predict normal findings or minor pulmonary involvement on CT, thus classifying the patient into a low-risk group. There was a clear separation between the groups with minor pulmonary involvement (group I) and severe pulmonary involvement (group III), as shown in figure 3. On the other hand, LUS was less able to distinguish group II from group III, which might in part be explained by the sample size or by an actual lack of ability of LUS to detect those findings located deeper in the lung rather than in close relation to the subpleural space. This also explains the different scores yielded by CT and LUS. Nevertheless, as shown in figure 4, there is a linear, ascending proportion of both scores with increasing lung involvement. To better understand the limitation imposed by the physics of ultrasound, figures 6a and 6b present two identical CTsc and their LUS correlates, showing a different spatial distribution of the lesion, with CT findings in figure 6a being missed on LUS. However, this discrepancy did not change patient classification and, consequently, did not affect decision making. The presence of ≥3 abnormal segments or a score >7 on LUS showed good sensitivity and specificity in identifying more extensive involvement on chest CT.

Value of lung ultrasound to predict affected segments in chest computed tomography

LUS is an attractive tool that can be used in a variety of settings, including intensive care units and emergency departments[9]. Compared with echocardiography, LUS has a shorter learning curve for those not experienced with ultrasound imaging. The worldwide experience with Covid-19 has shown just how pivotal quick, safe decision making can be in affecting the workflow of an overwhelmed emergency department. Symptoms alone may not be good markers of disease severity, and oxygen saturation as the sole objective parameter may not be indicative of

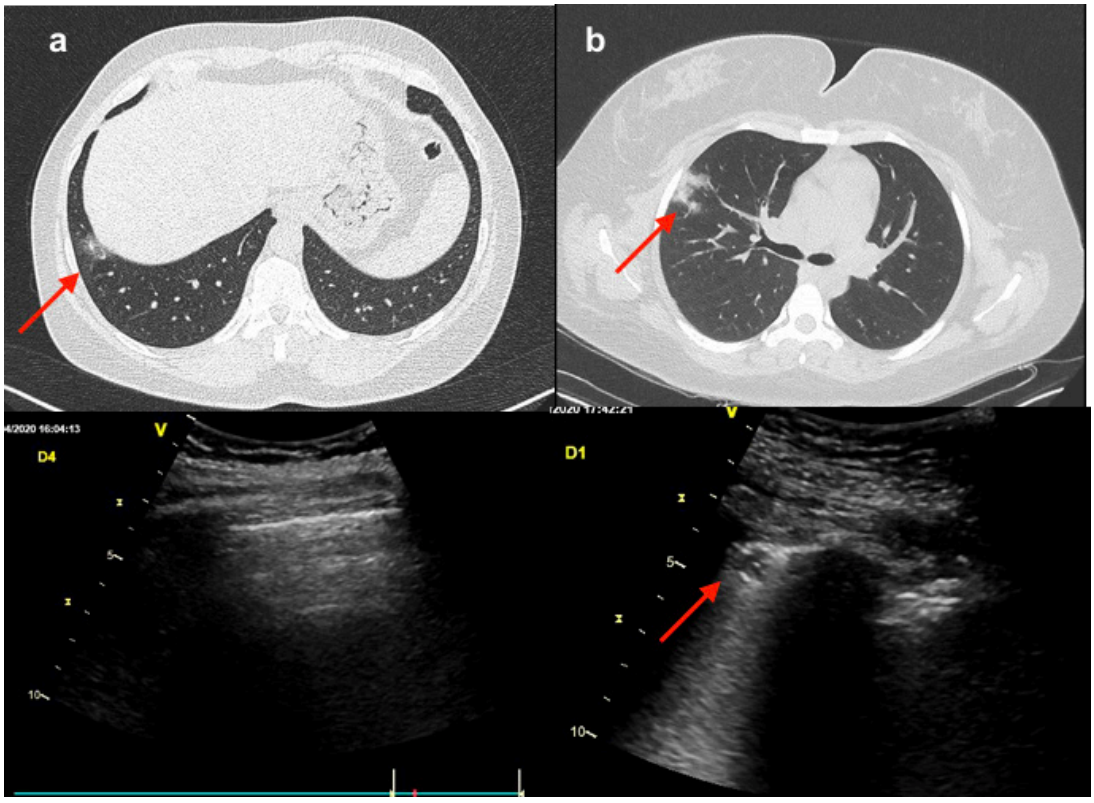


Figure 6 – Representative CT and corresponding LUS images of 2 patients with minor pulmonary involvement. Case (a) was a 42-year-old female with a deep lesion in the lung and a normal A line profile on LUS. Case (b) was a 27 year old female with subpleural consolidation, also demonstrated on LUS (red arrow), as well as coalescent B-lines

the actual anatomical picture. CT is the most sensitive imaging method to evaluate the extension and severity of pulmonary involvement[10], but the time required for disinfection[11] and patient transportation logistics mean CT will not be available for all those who need chest imaging. In this context, LUS can help identify those patients with less severe disease who can be sent home safely with instructions to self isolate, thus saving hospital beds for patients who really need them. Using LUS as a first-line imaging method in clinically stable patients who present with adequate oxygen saturation, reserving CT and other tests for those who present with two or more abnormal segments on LUS, seems a logical workflow. This strategy can potentially help hospitals and their staff cope with an extremely high patient volume scenario, reduces radiation exposure, is consistent with rational use of resources, and enhances physician confidence to discharge those patients at low risk. Further studies are needed to specifically evaluate the safety of LUS to support discharge of such patients.

This strategy has been previously described by Buonsenso et al, who suggested the use of LUS as a triage method in the emergency department[11]. Positivity for SARS-CoV-2 infection on laboratory tests was not considered in the present study, as our aim was to compare imaging methods as a triage tool for those with a high clinical likelihood of Covid-19 rather than to define the presence or absence of disease. Fang et al showed that laboratory testing has lower sensitivity when compared to CT findings,[12-14] depending on the time course of symptoms and cannot provide quick answers.

Limitations

Our study encompassed a limited sample size, and findings require reproduction in a larger population. On the other hand, LUS yielded robust data to rule out extensive pulmonary involvement in patients with suspected Covid-19, which was the main purpose of this study. A greater sample size could hypothetically refine the classification of extension and severity scores, identifying those who are considered to have less severe pulmonary involvement and can recover at home but still warrant closer surveillance, as the disease could potentially progress. LUS findings in Covid-19 are not specific for this disease, being present in other interstitial syndromes including other viral pneumonias, pneumocystis infection, hypersensitivity pneumonitis, and diffuse alveolar hemorrhage. These findings thus have to be considered in the context of the present outbreak, and laboratory testing to confirm Covid-19 is still mandatory to support long-term decision making and epidemiological data analysis.

The risk of exposure to the virus is an important issue to be considered. To mitigate this risk to acceptable low levels, patients should always wear a surgical mask and sonographers should wear full personal protective equipment (PPE) while scanning.

Conclusion

The results of this study suggest that LUS findings correlate with chest CT findings, and that can LUS therefore help identify those patients with clinical suspicion of Covid-19 infection who have unaffected lungs or minor pulmonary involvement. Further studies are needed to specifically evaluate the safety of LUS as the sole imaging triage tool for ED screening without the need for subsequent CT, allowing patients to be discharged home to recover or undergo further surveillance.

Author contributions

Conception and design: Alcantara ML, Bernardo MPL. Acquisition of data: Alcantara ML, Bernardo MPL, Autran TB. Analysis and interpretation of data: Alcantara ML, Bernardo MPL, Autran TB, CHagas LA, Machado DC. Statistical analysis: Lustosa RP. Writing of the manuscript: Alcantara ML. Critical revision of the manuscript for intellectual content: Lustosa RP.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of *Hospital Pró-Cardíaco* under protocol number 3168.4620.0000.05533. All procedures of this study were conducted in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from participants included in the study.

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ORIGINAL ARTICLE

Analysis of Conduction Intervals in Normal Electrophysiological Studies: Establishment of Reference Values the Brazilian Population

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Abstract

Background: In the investigation of cardiac rhythm disorders, a normal electrophysiological (EPS) study is associated with a favorable prognosis. One of the normality criteria is established by conduction intervals within expected range.

Objective: To establish reference values in EPS for the intracavitary conduction intervals (PA, AH and HV) in a Brazilian population.

Methods: A retrospective cohort study of the first 1,500 patients submitted to EPS ablation was performed at Instituto de Cardiologia do Rio Grande do Sul, Brazil. The EPS was considered normal if the test was performed for diagnostic purpose; absence of induced arrhythmias; and conduction intervals within the expected range. The REDCap software was used for data collection and management, and the SPSS Statistics 22.0 used for data analysis. Continuous variables were compared with Student's t-test for independent samples and categorical variables with the chi-square test (X^2). Values of $p \leq 0.05$ were considered significant.

Results: A total of 124 (8.3%) with EPS considered normal were included; mean age was 52 ± 21 years, and 63 were male. The mean values in milliseconds of PA, AH and HV were 23 ± 9, 88 ± 25 and 44 ± 7, respectively. The PA, AH, and HV percentile ranges were 13 - 25, 81-107 and 40 - 52, respectively. When the patients were divided into three age groups (1 to 18 years, 19 to 64 years and 65 or more), we observed that the group of older patients had significantly higher values of PA, AH and HV compared with younger patients.

Conclusion: This study showed that intracavitary conduction intervals in a sample of the Brazilian population were similar to previously published studies. Elderly patients tend to have higher values of intracavitary conduction intervals in EPS. Future studies including broader age ranges could enable the acquisition of more reliable and reproducible reference values. (Int J Cardiovasc Sci. 2020; 33(5):488-494)

Keywords: Electrocardiography/methods; Arrhythmias, Cardiac; Syncope/physiopathology; Syncope/therapy; Predictive Value of Tests; Treatment Outcome; Brazil/epidemiology.

Introduction

Electrophysiological study (EPS) is a useful test in the evaluation of the cardiac conduction system.[1,2] Moreover, it has an additional role in investigating symptoms such as palpitations, lipothymia and syncope, especially in established structural heart disease or when electrocardiogram (ECG) shows abnormalities that suggest an arrhythmic cause for these symptoms.[3]

A normal EPS is characterized by the following: no triggering of sustained arrhythmias (with clinical repercussion), no evidence of accessory pathway or ectopic focus, and sinus and nodal functions presenting expected normal responses as defined by the literature. In certain situations, patients with a normal EPS have a better prognosis regarding mortality.[4] Thus, knowledge

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of the normal, or reference intervals is fundamental to the interpretation of EPS results for each patient. Normal intervals should be established from a healthy population and address pathological implications of values out of these ranges.[5] The PA interval evaluates the conduction time of depolarization in the right atrium, from the sinus node to the atrioventricular (AV) node. The AH interval determines the conduction time within the compact AV node to the His bundle. The His-ventricular (HV) interval estimates the conduction time through the His-Purkinje system.

Several studies on cardiac electrophysiology have sought to establish a consensus of values of electrical stimulation conduction that would be associated with a higher risk of adverse events.[6,7] However, these values have not been established from systematic sampling yet, and the reference values commonly used were those obtained in studies published in the 60's and 70's.[8] No studies including diverse populations have been conducted and so far, no study has been performed in Brazil.

The aim of the present study was to establish the pattern of normal intracavitary values by EPS in the Brazilian population.

Methods

Patient selection

A historical cohort study of the first 1,500 patients undergoing EPS and / or ablation was performed at the Electrophysiology Service of the Institute of Cardiology of Rio Grande do Sul - ICFUC. The study included patients undergoing EPS from June 1997 to October 2010. The data used in this study were obtained from the reports of the electrophysiology laboratory and the hospital medical records.

Electrophysiological study

The EPS included: measurement of sinus node recovery time; measurement of intracavitary intervals (PA, AH, HV); assessment of the induction of supraventricular and ventricular arrhythmias by programmed stimulation; identification of accessory pathway; and determination of atrial, ventricular and AV node refractory periods. The tests were performed as previously described.[9,10]

The EPS was considered abnormal in any of the following situations: sinus bradycardia and abnormal sinus node recovery time;[1,2] HV interval ≥ 70 ms or atrioventricular block (second- or third degree) during atrial pacing;[3] induction of sustained ventricular tachycardia or ventricular fibrillation;[4] induction of any type of supraventricular tachycardia that caused hypotension or symptoms;[5] presence of accessory pathway. This normality pattern used in our study was based on previous studies in the literature.[11] Besides that, all patients underwent a drug withdrawal protocol prior to the EPS; those with dromo- or chronotropic effects were discontinued for a period of five half-lives prior to the study. Patients with abnormal EPS were excluded from the study.

The PA interval was defined as the interval from the onset of the P wave to the first atrial deflection recorded on the HIS bundle ECG;[2] HA, measured at the HIS-bundle ECG, was defined as the interval from the first rapid atrial deflection to the beginning of HIS deflection;[3] and HV interval of the HIS bundle, measured from the onset of ventricular depolarization by ECG or local ECG, whichever was earlier.

To record signals and pacing maneuvers, multipolar catheters were placed within the upper right atrium, His bundle region and right ventricular tip. All data were digitally recorded using Prucka - Cardiolab system (GE Prucka; GE Healthcare, Waukesha, WI) with a 30 Hz - 500 Hz pass filter. The few traces not digitally available were measured again from the printed reports, by the same electrophysiologist.

Our study population was divided into three age groups, following the World Health Organization age groups definition[12] – 1-18 years, 19-64 years and 65 and over. The purpose of this division was to assess the potential effect of age on driving intervals and how this could influence the establishment of normal values.

Statistical analysis

Data were stored in a dedicated database designed with the help of the RedCap platform (Research Electronic Data Capture - hosted at the University Foundation of Cardiology - RS). Tables of absolute frequencies and percentages for characterization of general sample were prepared. Data were exported to Excel 2010 software (Microsoft Excel. Redmond, Washington: Microsoft, 2010. Computer Software) and then analyzed using the SPSS 22.0 software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Continuous variables with normal distribution were expressed as mean and standard deviation and

those with non-normal distribution as median and interquartile range. Variables with normal distribution were compared using the Student's t-test for independent samples, and data with non-Gaussian distribution were analyzed with the nonparametric Kruskal-Wallis test. Categorical variables were expressed as percentages and compared with the chi-square test (X^2) with subsequent Bonferroni correction.

In all comparisons, we considered a critical alpha of ≤ 0.05 and a beta error of 0.8. Values with $p \leq 0.05$ were considered significant.

Results

We evaluated the first 1,500 patients from 7,090 cases in our service. Of these, 124 had EPS considered normal, that is, no changes in the conduction system or evidence of sinus node dysfunction (Figure 1). From the cases initially considered normal, three were excluded from analysis due to lack of clinical or demographic data. In the analysis of the pattern of normal intracavitary values - PA, AH, HV -, we identified those patients whose test results within the expected range. Outlying HV values were reviewed by one experienced electrophysiologist and then another four patients, with significant conduction disturbance and / or HV > 70 ms, were excluded.

Characteristics of the individuals included in the study are summarized in Table 1.

Intracavitary interval values and distribution

The mean values of PA, AH and HV were, respectively, 23 ± 9 ms, 97 ± 34 ms and 45 ± 8 ms. The 25th and 75th percentile range for PA, AH, and HV was 18 to 26, 76 to 114, and 40 to 52, respectively (Table 2). Distribution curves of the ranges are shown in Figure 2.

In the analysis of conduction intervals by age group, the group of patients older than 65 years showed significantly higher values of all intervals when compared to the youngest group (PA, p = 0.048; AH, p = 0.004; HV, p = 0.001). The youngest group also had shorter HV intervals when compared to the intermediate

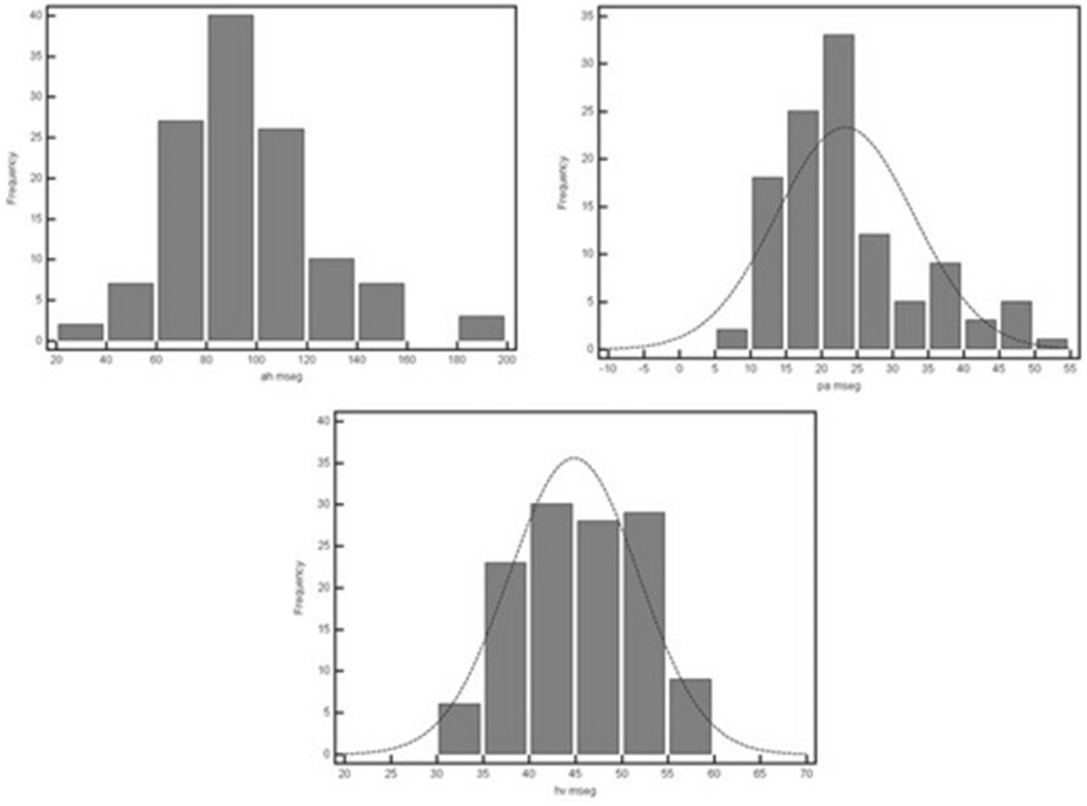

Figure 1 - Protocol and patients included for analysis.

Table 1 - Clinical and demographic characteristics of the 124 patients included in the study

	n = 124	(%)
Male sex	63	50.8
Average age in years	52 ± 21	
EPS indication		
Pathway system rating	85	0.8
Syncope	15	12.1
Evaluate sinus function	10	8
Supraventricular tachycardia Hx	2	1.6
Hx PCR	2	1.6
Pre-excitation on ECG	2	1.6
Vertigo	1	0.8
Palpitations	1	0.8
Atrial flutter Hx	1	0.8
Hx of ventricular tachycardia	1	0.8
Other	4	4

EPS: electrophysiological study; Hx: previous history; CRP: cardiopulmonary arrest; ECG: electrocardiogram.

age group (p = 0.008). Table 4 shows the comparison of conduction intervals between the age groups.

Discussion

The normal patterns of intracavitary values used by the ICFUC electrophysiology service are based on international parameters, which were described and compiled between the 1960s and 1980s (Table 3).[10,13-18]

Table 2 - Intracavitary conduction interval by percentiles

Normal	Average	P 25	P 50	P 75
PA	23 (± 9)	18	21	26
AH	97 (± 34)	76	91	114
HV	45 (± 8)	40	46	52

PA interval defined as the interval from the onset of the P wave to the first atrial deflection recorded on the HIS bundle electrocardiogram; the AH interval determined the conduction time within the compact AV node to the His bundle; the HV interval of the HIS bundle was measured from the onset of ventricular depolarization by ECG or local EC.

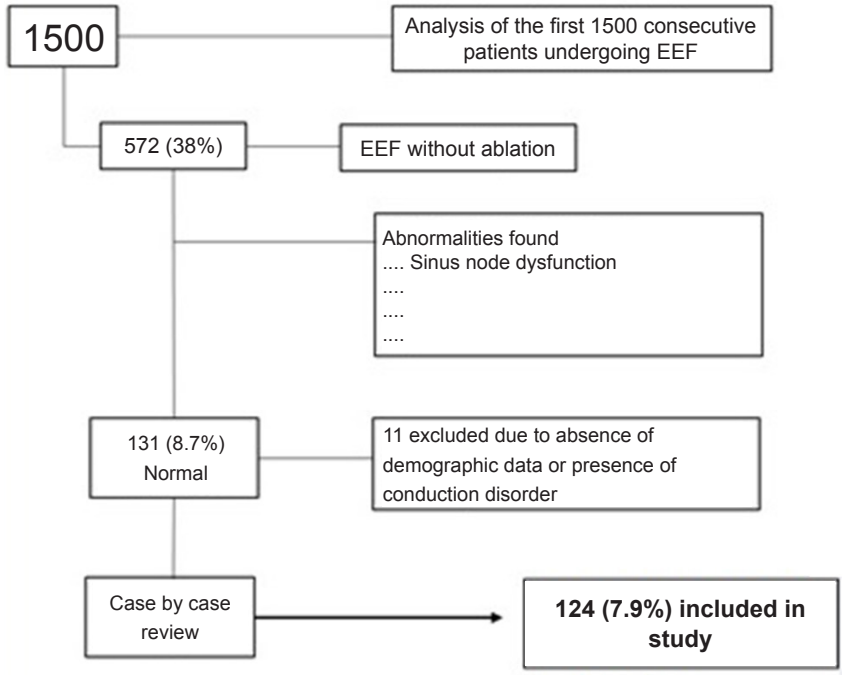

Figure 2 - PA, AH and HV interval distribution according to frequency.

These studies have limitations, since intracavitary values were obtained not only from healthy patients but also from patients with some type of AV block or infra-Hisian block. Therefore, it is important to analyze the results with caution, not only to establish the patterns of our own population, but also to reevaluate the pattern of normality, considering that the studies were conducted decades ago.

The prevalence of cardiovascular diseases increases with age.[10] The cardiac conduction system is affected by the increase in elastic and collagenous tissues associated with aging. There is more than 90% reduction in the number of cells with automatism by the age of 75 years. Age-associated calcification may affect the conduction system and increase the prevalence of atrioventricular block.[11] The PR interval, a marker of atrioventricular conduction, increases from 159 ms (on average) at 20-35 years of age to 172 ms at 60 years of age.[12] We believe that the differences in AH and in HV intervals between age groups observed in our study reflect these changes (Figure 3).

Table 3 - Intracavitary conduction intervals according to different studies; data compiled by Josephson et al.[10] and updated by the authors

Laboratory	PA	AH	HV
Narula	25-60	50-120	35-45
Damato	24-45	60-140	30-55
Castellanos	20-50	50-120	25-55
Schulenburg	85-150	35-55	-
Peuch	30-55	45-100	35-55
Beckeit	10-50	50-125	35-45
Rosen	9-45	54-130	31-55
Josephson	9-45	54-130	31-55
IC -FUC	18-26	76-114	40-50

PA interval defined as the interval from the onset of the P wave to the first atrial deflection recorded on the HIS bundle electrocardiogram; the AH interval determined the conduction time within the compact AV node to the His bundle; the HV interval of the HIS bundle was measured from the onset of ventricular depolarization by ECG or local EC.

Clinically, changes in conduction intervals should be interpreted in the context of the symptoms.[13] Shorter PA and AH ranges could reflect increased adrenergic tone or supranormal conduction. Shorter HV intervals generally represent the presence of accessory pathway. HV values are useful in the evaluation of patients with syncope and have a moderate accuracy to predict future occurrence of total atrioventricular block when the values exceed 70 ms.[14]

The present study has some limitations. First, the study made a retrospective analysis of a prospectively collected data, and thus did not have a uniform methodology or adequate review; second, it presented data from a single center, with a single team, which increases the reliability of the measurements, but decreases the external validity of the results; third, the study did not evaluate the presence of comorbidities and the use or not of drugs; also, it did not present a multivariate analysis of possible independent factors that could influence interval values. Finally, all patients included had an indication for electrophysiological study with or without ablation regardless of participation in the research, that is, they did not necessarily represent a healthy population. This may have influenced the values considered "normal".

Table 4 - Comparison of conduction intervals between different age groups

Range (ms)	Age group			Difference (p value)		
	1 to 18 years n = 10	19 to 64 years n = 75	>64 anos n = 75	1 and 2	1 and 3	2 and 3
PA	19 (± 6)	22 (± 9)	27.5 (± 11)	0.640	0.048	0.009
AH	94 (± 19)	88 (± 25.5)	106 (± 30)	0.398	0.004	0.403
HV	38 (± 6)	44 (± 7)	47 (± 6)	0.008	0.001	0.107

*PA interval defined as the interval from the onset of the p wave to the first atrial deflection recorded on the HIS bundle electrocardiogram; the AH interval determined the conduction time within the compact AV node to the His bundle; the HV interval of the HIS bundle was measured from the onset of ventricular depolarization by ECG or local ECG. *p values were obtained by the Kruskal-Wallis test.*

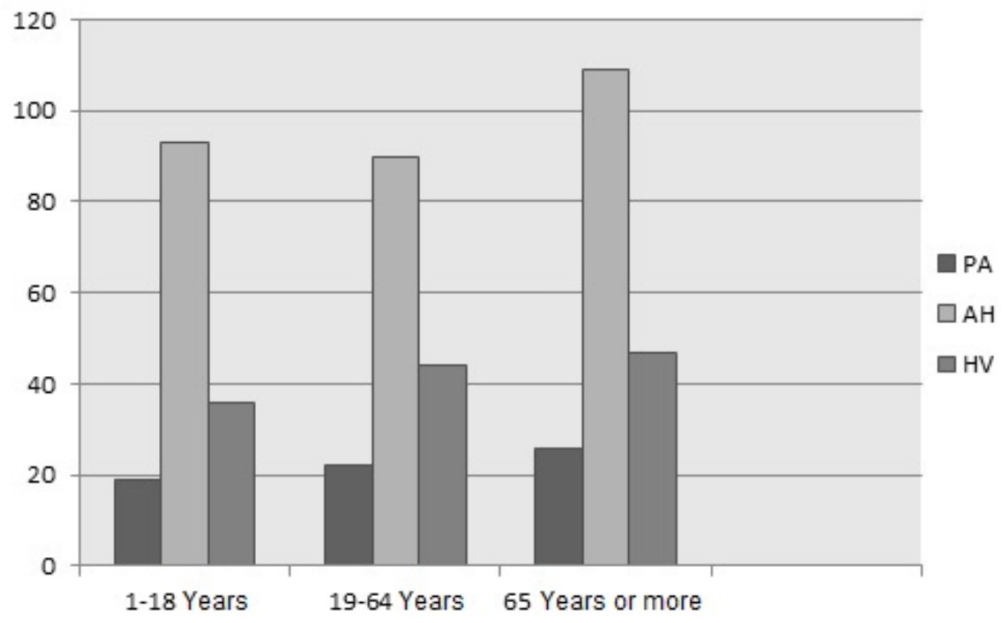

Figure 3 - Intracavitary intervals according to age group (ms).

Conclusion

This study showed that intracavitary conduction intervals in a sample of the Brazilian population were similar to previously published studies. Elderly patients tend to have higher values of intracavitary conduction intervals in EPS. However, it was not possible to infer from this study whether there is an association between the number of existing comorbidities and the increase in conduction intervals. Future studies including broader age ranges could enable the acquisition of more reliable and reproducible reference values.

Author contributions

Conception and design of the research: Leiria TLL, Lima GG. Acquisition of data: Santos CBL, Trombetta JS, Osterkamp G. Analysis and interpretation of the data: Leiria TLL, Trombetta JS, Lima GG. Statistical analysis: Leiria TLL, Sant'anna RT. Writing of the manuscript: Leiria TLL, Santos CBL, Pires LM, Lima GG. Critical revision of the manuscript for intellectual content: Sant'anna RT, Kruse ML.

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EDITORIAL

Intracardiac Conduction Intervals: An Electrophysiological Mirror of the Brazilian Population

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Editorial referring to the article: Analysis of Conduction Intervals in Normal Electrophysiological Studies: Establishment of Reference Values the Brazilian Population

In the current edition of the International Journal of Cardiovascular Sciences, Leiria et al.[1] have published a historical cohort of 124 electrophysiological studies considered normal, and evaluated three parameters of intracardiac conduction: (1) PA interval; (2) AH interval and (3) HV interval. The reference values for baseline electrophysiological parameters in the Brazilian population are of great interest due to their unique characteristics.

Since the description of the electrical potential in the end portion of the atrioventricular (AV) node by, Dandamudi and Vijayaraman[2] related Wilhelm His Jr., in 1893, which would come to be named the bundle of His, cardiac electrophysiology has added knowledge to both the diagnosis and treatment of the different forms cardiac arrhythmias, and to the field of artificial cardiac stimulation.

With the evolution of the catheters and sheaths used to perform cardiac electrophysiology procedures, the electrophysiological study has increasingly become part of the propedeutics of cardiac arrhythmias and, in some clinical conditions, it can stratify the risk of sudden cardiac death.[3]

For conducting the electrophysiological study, multipolar electrodes catheters are inserted into the cardiac cavity under fluoroscopy guidance through deep venous accesses (more rarely, arterial punctures). These catheters are connected to an electrophysiology polygraph, where both the intracardiac electrical potentials and the 12-lead surface electrocardiogram are recorded.[4]

The PA interval represents the depolarization time of the right atrium, from the sinus node to the atrioventricular node; the AH interval reflects the conduction time from the compact AV node to the His bundle and the HV interval represents the conduction time from the onset of the His bundle to the ventricular myocardium, with normal values described in the literature, as follows: 9 to 145 ms, 45 to 140 ms and 35 to 55 ms, respectively.[3,4] In this cohort, the authors found: 23 ± 9 ms, 97 ± 34 ms and 45 ± 8 ms for the PA, AH and HV intervals, respectively.

It is known that several factors can influence electrophysiological parameters, among them, age, sex, sympathetic tone and medication use. In this context, Taneja et al.,[6] conducted the first study to demonstrate that the HV interval is greater in men than in women.[6] Similarly to the present study, the authors also found larger AH and HV intervals in older patients.

The AH interval is strongly related to a patient's autonomic system, and its increased absolute value does not necessarily reflect the function of the AV node, whereas an HV interval greater than 70 ms may represent infra-Hisian block, associated with a worse prognosis, and the need for a definitive pacemaker implant.[7]

Some aspects deserve consideration: one of them is that the present study reflects the reality of a single center and, in the retrospective analysis of the data, comorbidities and drug use were not evaluated. The presence of structural heart disease, fibrosis of the conduction system, diabetes mellitus, renal failure, metabolic status, among others, can dynamically alter the baseline electrophysiological intervals of patients.

Keywords

Cardiac Electrophysiology. Cardiac arrhythmias. Cardiac Electrophysiological Techniques.

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Some questions seem certain in the literature: some non-modifiable variables, such as age and gender, influence the electrophysiological parameters of healthy individuals.[6] Therefore, these variations must be taken into account when carrying out diagnostic and therapeutic electrophysiological studies. In this scenario, electrophysiological maneuvers of programmed atrial and ventricular stimulation can provide better information on the conduction system.

In this sense, the findings of the present study opens opportunities to learn more about the intracardiac conduction intervals in the Brazilian population.

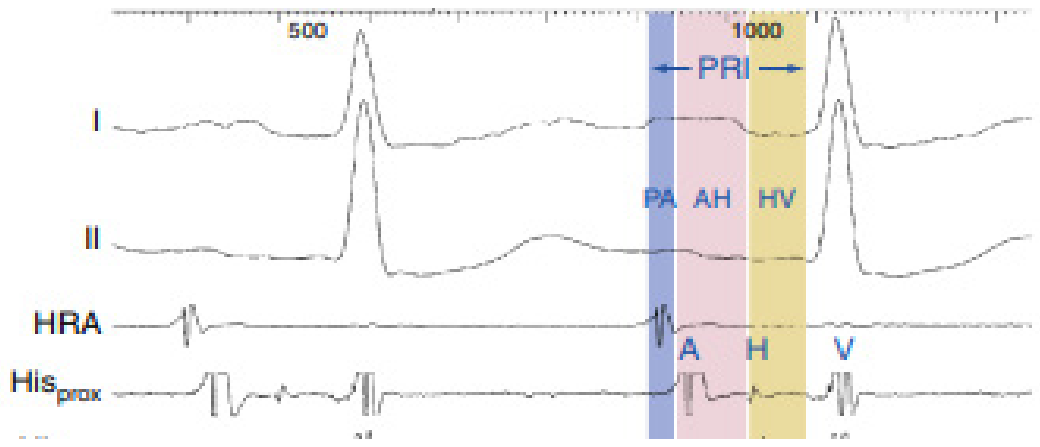

Figure 1 – Association between the surface electrocardiogram and the intracavitary electrical potential:The PA, AH and HV intervals. (Adapted from Zipes et al.) 5 I and II: Peripheral derivations of the surface electrocardiogram; PRI: PR interval; PA: PA interval; AH: AH interval; HV: HV interval; HRA: Electrical potential of the high right atrium; HisProx: Electrical potential of the proximal HIS bundle.

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ORIGINAL ARTICLE

Does Tight Glucose Control During the First 24 hours of Hospitalization Reduce Scintigraphic Infarct Size in STEMI Patients?

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Abstract

Background: Hyperglycemia at the time of admission is related to increased mortality and poor prognosis in patients diagnosed with ST-segment elevation myocardial infarction (STEMI).

Objective: We aimed to investigate whether tight glucose control during the first 24 hours of STEMI decreases the scintigraphic infarct size.

Methods: The study population consisted of 56 out of 134 consecutive patients hospitalized with STEMI in a coronary care unit. Twenty-eight patients were treated with continuous insulin infusion during the first 24 hours of hospitalization, while the other 28 patients were treated with subcutaneous insulin on an as-needed basis. The final infarct size was evaluated with single-photon emission computed tomography (SPECT) in all patients on days 4 to 10 of hospitalization. The groups were compared and then predictors of final infarct size were analyzed with univariate and multivariate linear regression analysis. A p-value < 0.05 was considered statistically significant.

Results: The mean glucose level in the first 24 hours was 130 ± 20 mg/dL in the infusion group and 152 ± 31 mg/dL in the standard care group (p = 0.002), while the mean final infarct size was 20 ± 12% and 27 ± 15% (p = 0.06), respectively. The multivariate linear regression analysis demonstrated that the mean 24-hour glucose level was an independent predictor of the final infarct size (beta 0.29, p = 0.026).

Conclusion: Tight glucose control with continuous insulin infusion was not associated with smaller infarct size when compared to standard care in STEMI patients. (Int J Cardiovasc Sci. 2020; 33(5):497-505)

Keywords: ST-Elevation Myocardial Infarction/mortality/mortality; Hyperglycemia; Hospitalization; Insulin; Tomography, Emission Computed,Single Photon/methods; Myocardial Perfusion Imaging.

Introduction

Hyperglycemia has become a predictor of mortality and morbidity in patients with acute coronary syndrome (ACS).[1] High blood glucose levels cause increased mortality, larger infarct size, unsuccessful reperfusion, and prolonged hospitalization.[2,3] Glucose has direct harmful effects on the myocardial tissue by increasing the levels of oxygen radicals, free fatty acids, ketones, and lactate. Also, it enhances platelet aggregation and activates other mediators in the coagulation system, leading to unsuccessful reperfusion.[4]

Hyperglycemia is caused by increased sympathetic activity as a consequence of disease severity. It has been shown that mortality increases with glucose levels higher than 140 mg/dL both at the time of admission and in the

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first 24 hours.[5] Current guidelines recommend glucose-lowering therapy when admission glucose levels exceed 200 mg/dL[6] Guideline recommendations are based on this therapeutic threshold to avoid hypoglycemia, as shown in the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation) study.[7] However, the population of that study consisted of critically ill patients treated in intensive care units rather than patients with ST-segment elevation myocardial infarction (STEMI).

Previous studies have not comprehensively investigated whether intensive blood glucose control aiming for levels lower than 140 mg/dL in the first 24 hours of STEMI is beneficial in relatively low-risk patients. Evaluation of scintigraphic infarct size with single-photon emission computed tomography (SPECT) in STEMI patients is a valuable outcome for pilot studies aiming to search for new treatment modalities with a limited number of patients.[8] In our study, we aimed to investigate the effects of tight glucose control with continuous insulin infusion during the first 24 hours of hospitalization on final infarct size in STEMI patients.

Methods

Study population

Of 134 consecutive patients presenting with STEMI, 56 were included in the study. Their mean age was 55.1 ± 11 years, and 44 (78.6%) were male. They all had successful reperfusion demonstrated angiographically in the infarct-related artery during the first 6 hours of chest pain . Inclusion criteria were having admission glucose levels higher than 140 mg/dL (irrespective of having a prior diabetes diagnosis), being diagnosed with myocardial infarction (MI) for the first time, and being hemodynamically stable. Local ethics committee approval was obtained for the conduct of the study. Written informed consent was obtained from all patients included in the study. STEMI diagnosis was made as per the criteria stated in current guidelines. The success of reperfusion was defined in patients receiving thrombolytic therapy as 70% or more resolution of the ST-segment elevation on electrocardiography and relief of ischemic chest pain within 90 minutes of treatment. All patients underwent primary or rescue percutaneous coronary intervention (PCI) or an early invasive strategy. In patients treated with primary or rescue PCI, Thrombolysis in Myocardial Infarction grade 3 (TIMI-3) flow in the infarct-related artery was accepted as successful reperfusion. The patients in whom TIMI-3 flow and ST-segment resolution on ECG could not be achieved were excluded from the study. All study patients were treated with standard anti-ischemic therapy, including treatment with beta-blockers, renin-angiotensin converting enzyme inhibitors, statins, and dual antiplatelet agents.

Blood glucose regulation

In half of the study patients (n = 28), blood glucose levels were regulated with insulin infusion, targeting levels between 80-140 mg/dL. Insulin infusion was administered in line with the Yale University infusion protocol. The protocol has been described elsewhere and proven to be safe for avoiding hypoglycemia.[9,10] The Yale University infusion protocol allows nurses to adjust the infusion dose without a need for order. In the remaining 28 patients, short-acting insulin was administered subcutaneously on an as-needed basis upon the clinician's discretion. Blood glucose was measured every time with the same glucometer at the bedside. Enteral alimentation with a cardiac and diabetic diet started 4 hours after PCI provided that the patient was clinically stable. After the first 24 hours, blood glucose levels were checked 4 times a day in all patients. Subcutaneous insulin was administered when needed in all study patients according to the standards of care.

Myocardial perfusion scintigraphy

All study patients underwent myocardial perfusion scintigraphy with SPECT using 10 mCi of technetium-99m sestamibi on days 4 to 10 of hospitalization. Tomographic images were obtained using a dual-head gamma camera with a high-resolution collimator (Siemens Medical Solutions, Erlangen, Germany). After the standard view images were acquired, the percentage of the final infarct size was calculated automatically with a software (Emory Toolbox). All scintigraphic images and associated calculations were acquired and performed in the nuclear medicine laboratory of Istanbul University Institute of Cardiology. All estimations were conducted by a single experienced operator, who was blinded to the study patients.

Statistical analyses

Continuous variables were expressed as mean ± standard deviation or median with 25–75 percentiles based on their distribution. Categorical variables were described as percentages and numbers. Kolmogorov-Smirnov test and/

or histogram was used to define the distribution of the data. Group comparisons were performed using a two-sample t-test or Mann-Whitney U test according to the distribution of the data, while a chi-square test was used for the categorical variables. We chose a large effect size (0.50, because of the small dataset), with α = 0.05, n = 56, and 7 predictors for linear regression models. Power was calculated as 0.87. The association between final infarct size (dependent variable) and predictors was evaluated with univariate and multivariate linear regression models. The assumptions of our linear regression model were the following: a near-normal linear relationship exists between the independent and dependent variables, which was assessed with a scatter plot. Little or no important collinearity was detected among the independent predictors, and no variable in the variance inflation factor (VIF) model was over 5. Residuals had a near-normal distribution, and no important autocorrelation was found in Q-Q plot among residuals. Potential pathophysiological and clinical predictors of the final infarct size were included based on the results of previous studies and the results of univariate linear regression analysis with data from the present study. In all statistical analyses, a p-value < 0.05 was considered statistically significant. R software with Hmisc and rms packages, version 3.2.2 (R Project, Vienna, Austria), was used for statistical analysis.

Results

In total, 56 out of 134 STEMI patients were included in the study. Their mean age was 55.1 ± 11, and 44 (78.6%) were male (Figure 1). Half of the participants (n = 28) were treated with insulin infusion. There were no statistically significant differences in demographic and clinical characteristics and biochemical results between the two groups (Table 1). The mean admission glucose levels were 192 ± 47 mg/dL in the insulin infusion group and 178 ± 49 mg/dL in the standard care group (p = 0.3). The mean blood glucose levels in the first 24 hours were 130 ± 20 mg/dL in the insulin infusion group and 152 ± 31 mg/dL in the standard care group (p = 0.002). The mean admission glucose level was 217 ± 57 mg/dL in the diabetic patients and 163 ± 21 mg/dL in the nondiabetic patients (p < 0.0001). The mean 24-hour glucose level was 153 ± 29 mg/dL and 133 ± 21 mg/dL in the diabetic and nondiabetic patients, respectively (p = 0.006). In the insulin infusion group, blood glucose levels lower than 60 mg/dL were detected twice; however, no patients manifested symptomatic hypoglycemia. Mean 24-hour glucose levels lower than 140 mg/dL were found in 20 out of 28 patients in the insulin infusion group and in 13 out of 28 patients in the standard care group (p = 0.05). The mean final infarct

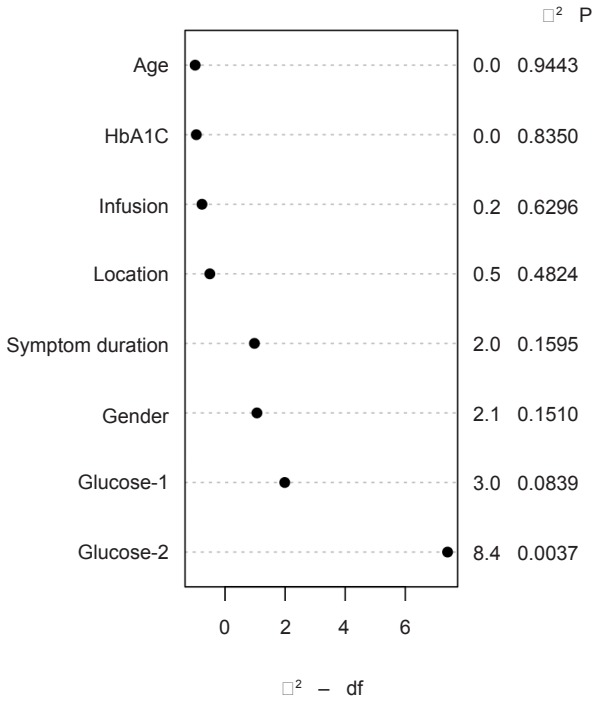

Figure 1 – Glucose-1: admission glucose; Glucose-24: mean 24-hour glucose; HbA1C: glycated hemoglobin.

Table-1 Characteristics of study patients grouped according to blood glucose control regimen

	İnsulin infusion	Usual care	P value
Age (years)	55.4±12.2	55±11.7	0.885
Gender (female/total [%])	6/22	6/22	1
BMI(kg/m^2)	27.5±3.9	27.4±5.4	0.822
DM (n,%)	14/28	9/28	0,277
HT (n,%)	11/28	13/28	0,787
HL(n,%)	7/28	9/28	0,768
Smoking (n%)	16/28	12/28	0,408
Pre-infarct angina (n%)	12/28	15/28	0,422
Symptom duration (minute) (median, IQR)	160 (112-240)	160 (120-180)	0,971
Sistolik blood pressure (mmhg)	129± 25	125±28	0,529
Diastolik blood pressure (mmhg)	79±15	74±14	0,288
Heart rate (beat/ per-minute)	74±15	80±16	0,137
STMI localisation (Anterior/total)	12/28	12/28	1
Admission Glucose (mg/dl)	192 ±47	178±49	0.303
24 hour Average Glucose (mg/dl)	130±20	152±31	0.002
Total cholesterol(mg/dl)	205±50	191±43	0.274
HDL (mg/dl)	38±8	39±14	0.89
LDL (mg/dl)	139±38	124±33	0.12
Triglyceride (mg/dl)	164±48	174±76	0.134
HBA1c (%)	6.9±2.1	6.4±1.9	0.434
Creatinine (mg/dl)	1.1±0.5	0.9±0.2	0.136
Haematocrit (%)	39±7	39±8	0.863
Creatinine phosphokinase (peak)[mg/dl]	2390±2156	2884±2335	0.42
Creatinine phosphokinase- MB (peak)[mg/dl]	263±201	273±183	0.84
Final İnfarct size(%)	20.0±12.6	27.1±15.2	0.062

BMI: body mass index; DM: diabetes mellitus; HbA1c: glycated hemoglobin; HDL: high-density lipoprotein; IQR: interquartile range; LDL: low-density lipoprotein; STEMI: ST-segment elevation myocardial infarction; HT: Hypertension; HL: Hyperlipidemia.

size was 20 ± 12% in the insulin infusion group and 27 ± 15% in the standard care group (p = 0.06).

In the univariate linear regression analysis, anterior location of the infarct, symptom duration, and mean 24-hour glucose level were found to be predictors of the final infarct size (beta [β] 8.74, p = 0.022; β 0.027, p = 0.033; β 0.174, p = 0.014, respectively). Partial effect plot of 24-hour blood glucose and final infarct size is shown in Figure 2. In the multivariate linear regression analysis adjusted for age, gender, symptom duration, infarct location, admission glucose levels, 24-hour glucose levels, HbA1c levels, and glucose-lowering modality, only mean 24-hour glucose level independently predicted the final infarct size (Table 2).

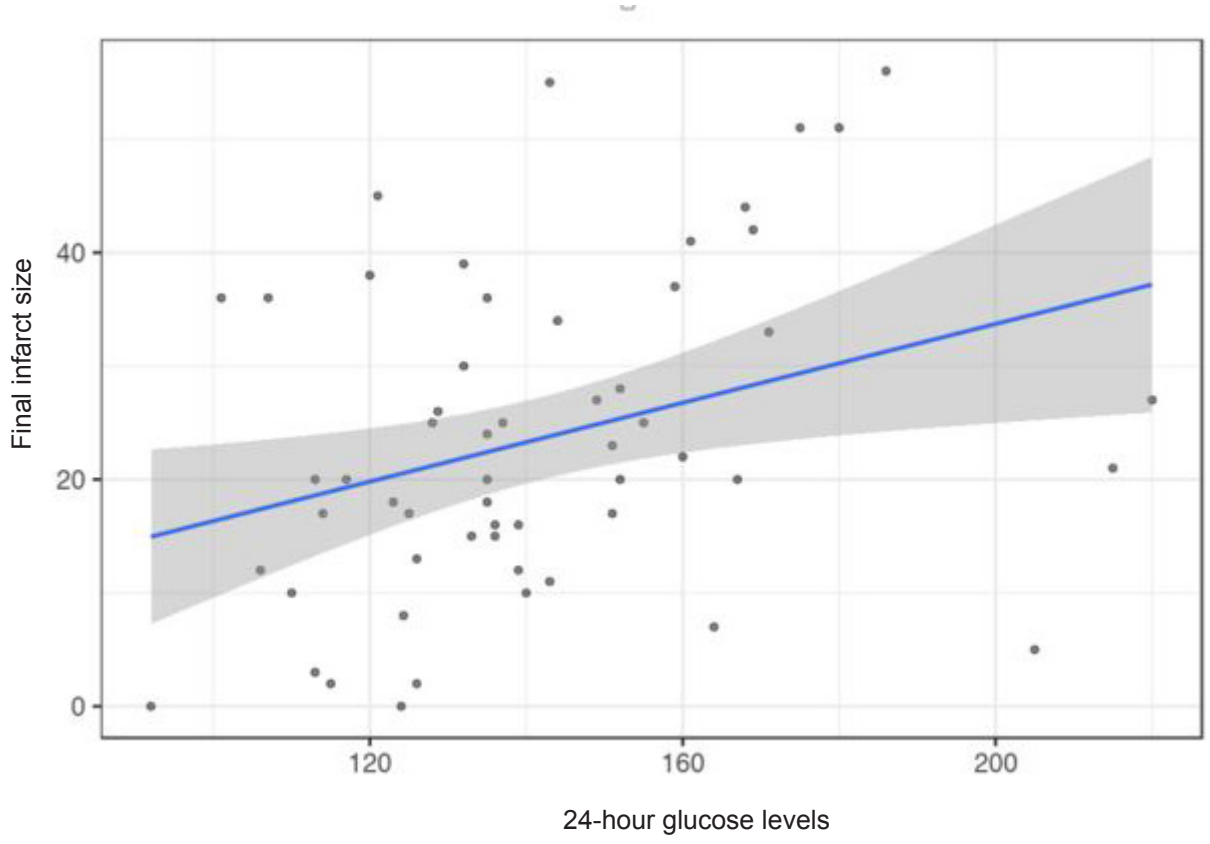

Figure 2 - Partial effect plot of 24-hour blood glucose and final infarct size.

Table 2 – Univariate and multivariate regression coefficients for predictors included in the model

	Univariate beta coefficient	Univariate p-value	Multivariate beta coefficient	Standard error	Multivariate p-value
Female gender	4.447	0.343	4.49	5.32	0.404
Age	0.251	0.124	0.12	0.194	0.527
Glucose-1	-0.03	0.933	-0.092	0.070	0.193
Glucose-24	0.174	0.014	0.290	0.125	0.026
HbA1c	0.260	0.806	-0.266	1.321	0.841
İnsulin infusion	-7.107	0.062	-2.867	4.846	0.558
Anterior location	8.74	0.022	4.246	4.608	0.363
Symptom duration	0.027	0.033	0.027	0.028	0.347

Glucose-1: admission glucose; Glucose-24: mean 24-hour glucose.

Relative effect of each predictor in the model is shown in Figure 3.

Discussion

The main finding of our study is the association of mean 24-hour glucose levels with a small infarct size in STEMI patients. Tight glucose control with insulin infusion did not reduce final infarct size when compared to standard glucose control regimen. Additionally, tight glucose control with a target level between 80-140 mg/dL during the first 24 hours of STEMI was defined as safe and feasible in our study population.

To the best of our knowledge, this is the first study that investigated the relationship between

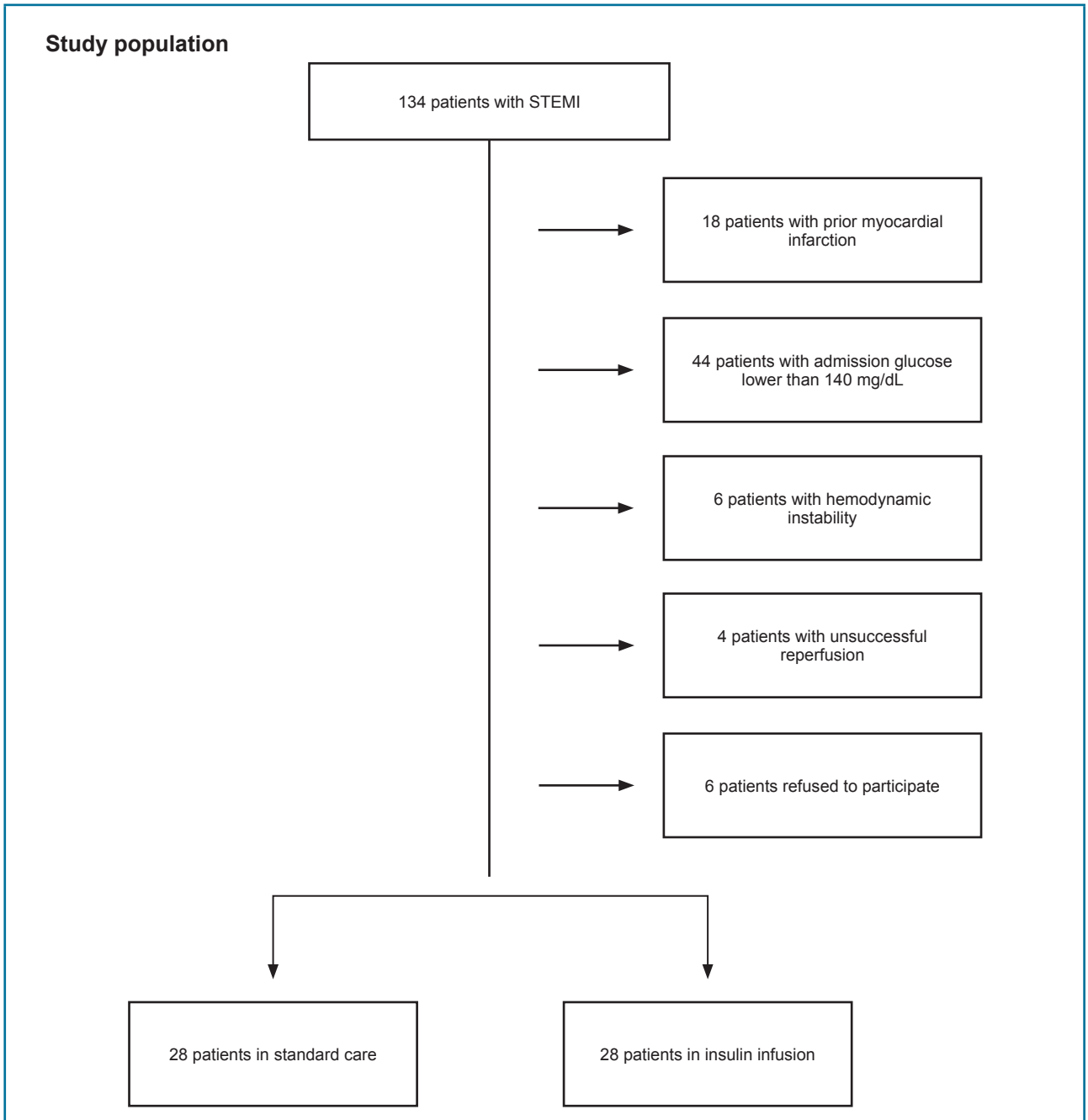

Figure 3 – STEMI: ST-segment elevation myocardial infarction.

tight glucose control with a target glucose level of 80-140 mg/dL and scintigraphic infarct size in STEMI patients. Stress-induced hyperglycemia is known to be related to longer hospital stays and increased mortality, especially in nondiabetic patients.[11] The American Heart Association reports that an admission glucose level higher than 140 mg/dL is considered hyperglycemia in ACS.[12] However, current STEMI guidelines recommend starting insulin therapy for glucose levels higher than 200 mg/dL.[6] Additionally, no detailed recommendations are provided by guidelines as to the modality of glucose level regulation to be used, whether insulin should be administered subcutaneously or via intravenous infusion. In most studies investigating the relationship between MI and glucose metabolism, a glucose-insulin-potassium (GIK) solution has been used.[13] The GIK infusion has in theory beneficial effects on the ischemic myocardium with the involvement of various mechanisms exhibiting a cardioprotective effect during the course of MI. Two of those mechanisms are noteworthy because one of them reduces free fatty acid (FFA) levels and the other one facilitates glycolysis. FFAs inhibit glycolysis, increase lactate levels, and facilitate the release of free hydrogen ions; thereby, they reduce contractility of the cardiac muscle, cause diastolic dysfunction, and lower the arrhythmia threshold.[14,15] Furthermore, insulin has anti-inflammatory, antioxidant, antiplatelet, and nitric oxide (NO)-mediated vasodilatation effects.[16,17]

In the DIGAMI-1 (Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction 1) study, patients were treated with glucose-insulin infusion during the first 24 hours of MI, and then subcutaneous insulin therapy was administered for the rest of the hospital stay. The mean glucose level was found to be lower in the infusion group, and the DIGAMI-1 study showed positive results with glucose-insulin therapy in a 1-year follow-up.[18] However, these findings were not confirmed in the DIGAMI-2 study because the study failed to achieve the target glucose levels.[19] In the HI-5 (Hyperglycemia: Intensive Insulin Infusion in Infarction) study on MI patients with admission glucose levels higher than 140 mg/dL, insulin-dextrose infusion therapy with target levels of 180 mg/dL was compared to placebo. However, the study failed to achieve the target levels and concluded that infusion therapy did not show any beneficial effects. A subgroup analysis of the study reported that patients with a mean 24-hour glucose level of less than 144 mg/dL (8 mmol/L) had lower mortality.[20] The CREATE-ECLA (Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation-Estudios Cardiologicos Latinoamerica) trial is the largest-scale study within this context and reported neutral results for the GIK infusion therapy in STEMI patients.[21] However, the study reported that the mean 24-hour glucose level was higher in the GIK arm compared to usual care alone (155 mg/dL vs 135 mg/dL, respectively). A subanalysis of the CREATE-ECLA study found that during the first 24 hours of MI, every 10 mg/dL elevation in glucose levels caused an additional 8% rise in mortality. Investigators of the CREATE-ECLA study concluded that there is a need to ascertain whether lowering the serum glucose levels with a modified regimen will affect clinical outcomes. An overall evaluation of the study results regarding the effect of glucose-insulin or GIK infusion on MI patients reveals that these treatment modalities have neutral or harmful impacts on mortality. However, the subgroup analysis demonstrated reduced mortality when the target glucose levels were achieved with treatment. In the BIOMArCS-2 (Biomarker Study to Identify the Acute Risk of a Coronary Syndrome 2) study, the effect of intensive insulin therapy on enzymatic and scintigraphic infarct size in ACS patients was investigated.[22] However, intensive insulin therapy failed to reduce both the enzymatic and scintigraphic infarct sizes in that study. Regarding the limitations of the BIOMArCS-2 study, the patient population consisted of both STEMI and non-STEMI patients, patients with a history of previous MI were included, and scintigraphy was performed 6 weeks after the index event. In our study, patients with a history of previous MI were meticulously defined and excluded. Furthermore, patients failing to achieve successful reperfusion were excluded in order to minimize the factors that could potentially affect the final infarct size.

Infarct location is a major factor that affects final infarct size. In our study, infarct location predicted final infarct size in univariate linear regression analysis. However, in multivariate analysis, infarct location failed to predict final infarct size. This could be explained by the small sample size of the study. In addition, all participants achieved early reperfusion successfully, which may have reduced the effect of location on final infarct size.

Our results demonstrated that reduced blood glucose levels during the first 24 hours of STEMI was related to smaller infarct size. This finding is compatible with reports of increased mortality with elevated mean 24-hour glucose levels in STEMI patients. Conversely, it is a matter of debate whether lowering glucose levels to less than 140 mg/dL is safe and would increase mortality. The insulin infusion protocol we used in our study has been demonstrated to be safe for avoiding hypoglycemia. The final infarct size was not different between the two groups (20.0% vs 27%, p = 0.06). We believe that this lack of statistical significance was associated with a tendency for higher admission glucose levels in the insulin infusion group and an aggressive subcutaneous insulin treatment in the comparator group, rather than occurring as a usual consequence of patient selection and treatment bias. The insulin infusion protocol achieved the target blood glucose levels in 20 out of 28 patients (71%) (mean: 80-140 mg/dL). Of the remaining 8 patients, 6 had admission glucose levels higher than 250 mg/dL. It could be argued that the protocol is not successful at achieving the target levels when the admission glucose levels are higher than 250 mg/dL. In two tests, the blood glucose levels were lower than 60 mg/dL, but symptomatic hypoglycemia was not observed in any patients. The mean number of blood glucose measurements in 24 hours was 12 and the mean insulin infusion rate was 1:35/hour. This treatment protocol seems to be safe for avoiding hypoglycemia and appropriate for the treatment of MI patients; however, its effectiveness will be reduced if the baseline glucose level is higher than 250 mg/dL.

Study limitations

This study has several limitations. It is a single-center study, there is no blinding, and the study population consists of relatively low-risk patients. Therefore, the results may not be generalized to all MI patients. Lack of angiographic data is another limitation. To detect myocardial salvage index is a more powerful outcome than final infarct size in the studies investigating the effect of a new treatment modality in STEMI patients. Therefore, lack of data regarding myocardium at risk limited the results of this study. The participation of a small number of patients in the study limited the analytical power.

Conclusion

Tight glycemic control with continuous insulin infusion is not associated with smaller infarct size when compared to standard care in STEMI patients. Conversely, glycemic control in the first 24 hours of STEMI may reduce the final infarct size irrespective of the regimen used for controlling blood glucose levels. A target blood glucose level between 80-140 mg/dL can be achieved by using the Yale University insulin infusion protocol safely in MI patients with admission glucose levels higher than 140 mg/dL.

Author contributions

Conception and design of the research: Gulsen K, Okcun B, Ersanli MK. Acquisition of data: Gulsen K, Ayca B. The authors thank Ali Karagoz for the statistical analysis. Writing of the manuscript: Gulsen K. Critical revision of the manuscript for intellectual content: Baskurt M, Okcun B.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Istanbul University Cerrahpasa School of Medicine under the protocol number 13728/2009. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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EDITORIAL

After a STEMI, is Less Sugar more Protective to Myocardium?

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Editorial referring to the article: Does Tight Glucose Control During the First 24 hours of Hospitalization Reduce Scintigraphic Infarct Size in STEMI Patients?

The infarct size reduction in acute myocardial infarction (AMI) has been studied for more than 50 years. Animal experiments were conducted in the 1970s, followed by the first clinical studies to reduce infarct size (IS), with fibrinolytic agents or with mechanical coronary angioplasty (PTCA). The clinical experience of coronary reperfusion indicated that left ventricle function was not normalized in 30% of the patients, and despite unblocking the epicardial vessel, demonstrated hemodynamically, there was no equivalent in myocardial perfusion. New concepts emerged such as reperfusion injury, microvascular dysfunction, "no-reflow" phenomenon, and stunned and hibernating myocardium, which became the focus of basic research and clinical investigation. To improve characterization, different technologies were used, such as contrast echocardiography, isotopic studies, including positron emission tomography, and magnetic resonance.[1]

Cardioprotection (CP) aims to reduce IS and improve clinical outcomes. The translation of CP from preclinical and promising proof-of-concept studies to clinical benefit (CB) for patients has been quite unsatisfactory. Almost all these studies that did not translate into CB had infarct size reduction as the primary endpoint and used protocols selected to achieve IS reduction.[2]

In 2001, a pioneering randomized clinical trial (RCT) conducted in Leuven, Belgium, found clear benefits in treating hyperglycemia, supporting a potential causal relationship between hyperglycemia and outcomes. The researchers studied 1548 critically ill patients admitted to a predominantly surgical intensive care unit (ICU), maintaining healthy fasting blood glucose concentrations (80-110 mg/dL), which led to a reduction in morbimortality, compared with tolerance to hyperglycemia up to the renal threshold (215 mg/dL).[3]

Later, the Leuven's research group confirmed the clinical benefit in critically ill adults admitted to a clinical ICU (n = 1200) and severely ill children (n = 700). [4,5] Subsequent mechanistic studies attributed the benefit obtained by rigid glucose control to a protection against glucose toxicity and not to glucose-independent insulin effects.[6,7]

Despite the promising effects of rigid glucose control in the first controlled studies, the benefit was not confirmed in subsequent multicenter studies and the NICE-SUGAR study found potential damage.[7-10] The increased risk of mortality in NICE-SUGAR was subsequently attributed to increased incidence of hypoglycemia.[11] This discrepancy can be explained by methodological differences between trials, and not by a different combination of cases.

Hyperglycemia (HGL) in the setting of myocardial revascularization (MR) is associated with increased adverse effects in patients with and without diabetes. Data suggest that acute HGL peri-procedure causes increased inflammation, platelet activity, endothelial dysfunction, and is associated with plaque instability and IS. While peri-procedure glycemia is an independent predictor of adverse effects in patients undergoing MR, treatment strategies remain uncertain.[12]

It is also known that cardioprotective actions of ischemic postconditioning (PCISQ) against ischemia/reperfusion injury (I/LR) are abolished in diabetic hearts. Several drugs used for treating diabetes have recently shown a reduction in difficult cardiovascular outcomes. Animal studies have sought to investigate the combined effect of PCISQ and these drugs on myocardial function and IS.[13]

Keywords

ST Elevation Myocardial Infarction; Fibrinolytic Agents; Angioplasty; Percutaneous Coronary Intervention; Myocardial Reperfusion; Ventricular Dysfunction Left; Myocardial Stunning; Diagnostic, Imaging.

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The scintigraphy image with a single photon emission computed tomography (SPECT) technique with sestamibi-99mTc (technetium) is based on the integration of myocardial perfusion and myocyte integrity. Sestamibi is distributed in the myocardium in proportion to blood flow [14] and cardiac uptake is dependent on a normal mitochondrial function.[15]

In the early 2000s Gibbons et al.[16] had already demonstrated in 2 publications with a wide literature review that SPECT imaging with sestamibi-99mTc was the best available tool to evaluate IS and with potential to serve as a surrogate outcome to discover advantages of new therapies that could be equivalent to those existing in relation to early mortality,[16] as well as to evaluate possible incremental benefits in multicenter studies.[17]

In 2011 Gibbons,[18] in an excellent review article, highlighted that SPECT with sestamibi-99mTc had multiple evidences that validated its clinical usefulness, being used as surrogate outcome in several randomized trials, and in some of them, both early and later imaging were used to evaluate myocardium at risk and myocardial salvage. The author recognized that despite its limitations, SPECT is a well-validated measure.[18]

In this edition of the IJCS, the authors Gulsen et al.[19] integrating this knowledge sought to investigate whether rigid glycemic control in the first 24 hours after AMI with ST elevation (STEMI) may have a cardioprotective role using IS through SPECT as an outcome, searching for a possible incremental benefit of this strategy, as already largely supported in the literature, and should be congratulated by this design based on robust literature, both for the intervention tested and the method used as a surrogate outcome to evaluate the response. The limitations of the single-center study stand out and, in relation to the evaluation of the benefits of a new therapeutic approach, despite the technical and logistical difficulties, the importance of determining myocardium at risk and the effectively spared seem relevant for the analysis of the results, whether positive or negative.

Despite promising experimental studies and proof-of-concept clinical studies such as these, interventions seeking to limit IS failed to improve clinical outcomes in STEMI. Although IS alone has prognostic value, Bochaton et al.,[20] demonstrated that other variables in STEMI treated with angioplasty may be associated with clinical outcomes, regardless of IS. Among these variables are risk factors, comorbidities, post-treatment variables, and simultaneous treatments.[20]

Therefore, CP should not only focus on the reduction of IS, but also on several factors that should contribute to clinical outcomes in the short and long term.[2] In this context, studies such as this seek to shed light on new approaches to known factors, in the treatment of

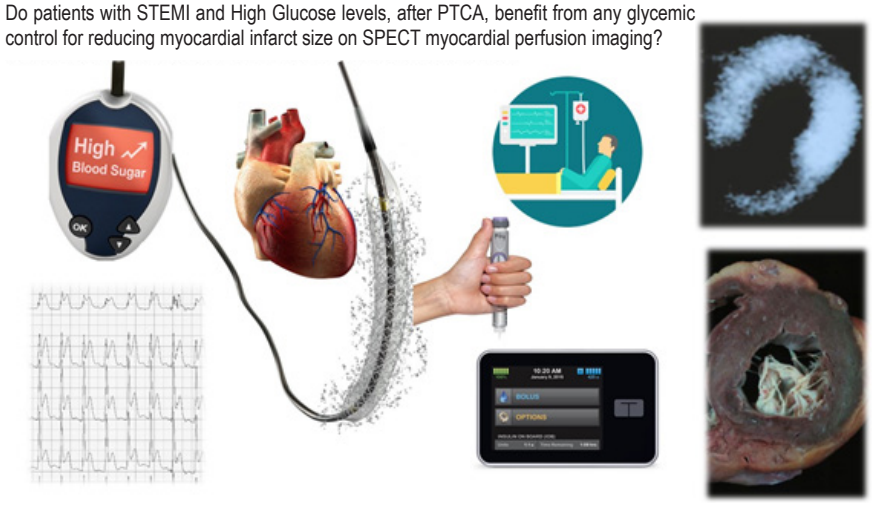

Figure 1 – The image illustrates the idea of high glucose levels as a risk factor that could implicate In the outcomes of STEMI patients and when controlled immediately after the PTCA could reduce the infarct size evaluated by myocardial perfusion spect, as surrogate outcome. STEMI ST Elevation Myocardial Infarction PTCA Percutaneous Transluminal Coronary Angioplasty.

AMI, such as glycemic levels, trying to answer whether after STEMI, less sugar means more protection for the myocardium, aiming to improve outcomes of this pathology that brings such a high cost for the patient and society. However, strict glucose control remains highly debated, which leads to wide variations in practice[21] and leaves us a reflection, paraphrasing Alan Turing, British scientist considered the father of computing: "We can only see a little of the future, but it is enough to realize that there is much to do".

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International Journal of Cardiovascular Sciences. 2020; 33(5):509-515

ORIGINAL ARTICLE

Association between Mean Platelet Volume-to-Lymphocyte Ratio and the Presence of Apical Mural Thrombus in Post-Myocardial Infarction Patients

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Abstract

Background: Left ventricular apical thrombus (AT) is generally associated with ischemic and non-ischemic cardiomyopathies. The thrombo-inflammatory process plays an important role in the pathophysiology of acute coronary syndromes and post-myocardial thromboembolic complications. Mean platelet volume (MPV) has been linked to poor prognosis following myocardial infarction. Recently, platelet-to-lymphocyte ratio (PLR) has emerged as a new marker of worse outcomes linking inflammation and thrombosis.

Objective: We aimed to investigate the prognostic significance of the marker – mean platelet volume to lymphocyte ratio (MPVLR) in patients with AT.

Methods: Fifty-six patients with left ventricular AT after an anterior myocardial infarction and 51 patients without left ventricular AT after an anterior myocardial infarction were enrolled in this study retrospectively. Admission MPVLR was compared between the two groups. Logistic regression analysis was carried out to identify whether MPVLR is an independent predictor of AT. The receiver operating curve (ROC) analysis was used to show the optimal cut-off for MPVLR to predict AT. P values less than 0.05 were considered statistically significant.

Results: Age, gender, frequency of diabetes mellitus, hypertension and atrial fibrillation, and ejection fraction values did not differ between the groups. MPVLR was higher in patients with AT than patients without AT (7.91±2.5 vs 5.1±2.1, p<0.001). ROC analysis revealed moderate diagnostic value in predicting the presence of AT with a MPVLR cut-off > 4.75 (82.1% sensivity and 70.2% specifity (area under the curve=0.811, 95% confidence interval [CI]: 0.731-0.891, p<0.001). MPVLR was found to be an independent risk factor for the formation of AT (B:0.441, p.0.001).

Conclusion: MPVLR is a simple, cheap and easily accessible test that can predict left ventricular AT formation. (Int J Cardiovasc Sci. 2020; 33(5):509-515)

Keywords: Myocardial Infarction; Cardiomyopathies; Thrombosis/complications; Lymphocyte Ratio; Cardiac Mass.

Introduction

One of the major complications of myocardial infarction (MI) is left ventricular apical thrombus (AT) formation, which may favor blood stasis, increased coagulability and endothelial injury.[1] Its incidence has reported to range between 30-40% in postmortem studies.[2,3] Left ventricular AT usually occurs in the presence of left ventricular aneurysm or apical akinesia after large anterior MI. Additionally, hypercoagulable or inflammatory states might accelerate thrombus formation.[4,5]

Platelet-to-lymphocyte ratio (PLR) has been suggested as an important and cheap prognostic factor in coronary heart disease.[6] It is an inflammatory marker derived from complete blood count and has been studied in various cancers,[7] chronic renal failures,[8] and coronary artery disease.[9]

Platelet size has been reported to reflect platelet activity. Larger size platelets are metabolically and enzymatically more active.[10] Mean platelet volume (MPV) is an indirect marker of platelet activity and that is readily available in clinical settings and has

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been linked to poor prognosis following ST-elevation myocardial infarction (STEMI).[11]

In view of the fact that platelet size reflects platelet activity more accurately than platelet count itself, the notion of replacing platelet count with MPV in the PLR to form mean platelet volume-to-lymphocyte ratio (MPVLR) seems plausible. In our study we aimed to evaluate whether MPVLR has a predictive value for the development of AT after myocardial infarction.

Material and methods

A total of 107 patients with anterior myocardial infarction were included. Fifty-six patients with AT, 51 control subjects without AT, matched by age, sex and ejection fraction were enrolled in this study retrospectively. Data regarding individual patients were retrospectively collected from patient files. Exclusion criteria were presence of infection, cancer, nonischemic cardiomyopathy, hematological disorders, and current therapy with corticosteroid, non-steroidal anti-inflammatory drugs or oral anticoagulants. Blood samples were drawn from a large antecubital vein into Vacuntainer tubes (Becton Dickinson, Rutherford, New Jersey) for determination of biochemical and hemostatic parameters (Symex K-1000, Kobe, Japan) at admission. All routine biochemical tests were performed using an auto-analyzer (Roche Diagnostic Modular Systems, Tokyo, Japan). PLR was defined as the absolute platelet count in the peripheral blood divided by the total lymphocyte count, and MPVLR was calculated as the ratio of MPV to lymphocyte count.

All patients underwent 2D echocardiography four weeks after anterior myocardial infarction. Two-dimensional echocardiography was performed with a 3.5 MHz transducer (IE33, Philips Medical Systems, Andover, Massachusets). Simpson's method was used to assess the left ventricular ejection fraction in two-dimensional echocardiographic apical four-chamber view, as recommended by the American Society of Echocardiography guidelines.[12] All images were stored and evaluated by independent cardiologist who were blinded to patients' data.

Statistical analysis

All analyses were performed using SPSS for Windows version 18.0 (SPSS, Chicago, Illinois). Quantitative data are presented as means ± standard deviation (SD) for parametric variables or medians with interquartile ranges (lower and upper quartiles) for nonparametric variables.

The Kolmogorov-Smirnov test was used to examine the normality of data distribution. Student's unpaired t-test was used to compare normally distributed data between the two groups and the Mann-Whitney U test was used for non-normally distributed data. The Pearson chi-square test was used for analysis of categorical variables. Logistic regression analysis was performed for parameters related to the presence of thrombus. P-values less than 0.05 were considered statistically significant. Receiver-operating characteristic (ROC) curves were estimated for MPVLR (and PLR for comparison). ROC analysis was used to determine the cut-off values of MPVLR in predicting thrombus formation. Ertem et al.,[13] previously demonstrated the relationship between apical mural thrombus and neutrophil-to-lymphocyte ratio in 55 patients with apical mural thrombus. In our study, we enrolled 56 patients with apical mural thrombus. According to power analysis, the power level of our study is 0.84.

Results

A total of 107 patients with anterior myocardial infarction were included in the study. The mean age of the study population was 60.7±7 years. Baseline demographic, clinical and echocardiographic features are summarized in Table 1. Presence of diabetes mellitus, hypertension, atrial fibrillation did not differ between patients with AT and without AT. Body mass index and rate of smoking were lower in patients with AT than without AT. Echocardiographic parameters (left ventricular ejection fraction, left atrium diameter) were not significantly different between the two groups as shown in Table 1. Medications were similar in both groups. MPV was higher in patients with AT than patients without AT (9.71±1.09 vs 8.84±0.61fL, p<0.001). Lymphocyte count was lower in patients with AT than patients without AT (1.37±0.48 vs 2.0±0.77 $10^3/mm^3$, p<0.001). While PLR did not differ between the two groups (p=0.068), MPVLR was higher in patients with AT than patients without AT (7.91±2.5 vs 5.1±2.1, p<0.001). The ROC analysis yielded a cut-off value of 4.75 for the MPVLR to predict AT, with a sensitivity of 82.1% and specificity of 70.2% (Area under the curve=0.811, 95% confidence interval [CI]:0.731-0.891, p<0.001) (Figure 1).

Table 1 – Demographical, echocardiographic and biochemical characteristics of study subjects and controls

Variables	Thrombus (+) patients (n:56)	Thrombus (-) patients (n:51)	p value
Gender (female) (n, %)	17(30%)	8(15%)	0.048
Age (years±SD)	65.3 ± 7.1	56 ± 7.9	0.001
Diabetes mellitus (n,%)	31(55%)	18(35%)	0.38
Hypertension (n,%)	33(58%)	29(56%)	0.831
Body mass index, kg/m²	25.7 ± 2.2	27.4 ± 2.7	0.001
Coronary heart disease (n,%)	51(91%)	49(96%)	0.298
Percutaneous coronary intervention (n,%)	53(94%)	49(96%)	0.727
Coronary artery bypass grafting (n,%)	4(7%)	2(3%)	0.472
Stroke (n,%)	6(10%)	2(3%)	0.184
Atrial fibrillation (n,%)	3(5%)	1(2%)	0.360
Heart failure (n,%)	56(100%)	51(100%)	1
Current smokers (n,%)	28(50%)	38(74%)	0.009
ACE blockers (n,%)	53(94%)	49(96%)	0.727
Aldosterone antagonists (n,%)	52(92%)	47(92%)	0.891
Betablockers (n,%)	56	51	1
Aspirin (n,%)	50(89%)	45(88%)	0.864
Clopidogrel (n,%)	48(85%)	44(86%)	0.934
Anticoagulants (n,%)	6(10%)	2(3%)	0.184
Statins (n,%)	56	51	1

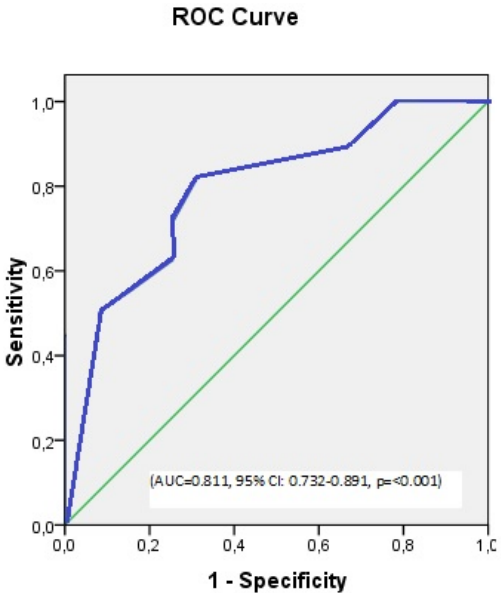

Figure 1 – Receiver operating characteristic curve for mean platelet-to- lymphocyte ratio for predicting apical mural thrombus

According to the cut-off > 4.75 for MPVLR, patients were divided into two groups; patients with a MPVLR > 4.75 were older, had a higher prevalence of female gender, and a lower frequency of smoking compared with the MPVLR ≤ 4.75 group (Table 2).

In multivariate logistic regression analysis, MPVLR (odds ratio [OR]: 1.406, 95% CI: 1.156-1.711, P ¼.0.001), MPV (OR: 2.293, 95% CI: 1.306-4.028, P ¼ .004), and smoking ((OR: 2.388, 95% CI: 0.886-6.434, P ¼ .020) were independent predictors of AT (Table 3).

Table 2 – Demographical, echocardiographic and biochemical characteristics of study subjects and controls according to mean platelet volume to lymphocyte ratio (MPVLR) cut-off value

Variables	MPVLR ≤ 4.75 (n:45)	MPVLR > 4.75 (n:62)	p-value
Gender (female) (n, %)	6 (15%)	20 (32%)	0.023
Age (years ± SD)	57.3 ± 8.9	60.1 ± 7.6	< 0.001
Diabetes mellitus (n,%)	26(55%)	23(35%)	0.378
Hypertension (n,%)	23(58%)	39(56%)	0.415
Body mass index, kg/m²	27.4±2.6	26.4±2.4	0.04
Percutaneous coronary intervention (n,%)	43(94%)	59(96%)	0.727
Coronary artery bypass grafting (n,%)	2(7%)	4(3%)	0.472
Stroke (n,%)	5(11%)	3(5%)	0.047
Atrial fibrillation (n,%)	0(0%)	4(6%)	0.084
Heart failure (n,%)	56(100%)	51(100%)	1
Current smokers (n,%)	34(75%)	32(51%)	0.012
ACE blockers (n,%)	42(94%)	60(96%)	0.407
Aldosterone antagonists (n,%)	41(92%)	58(92%)	0.638
Betablockers (n,%)	45(100%)	62(100%)	1
Aspirin (n,%)	41(89%)	54(88%)	0.518
Clopidogrel (n,%)	41(85%)	51(86%)	0.199
Anticoagulants (n,%)	1(10%)	7(03%)	0.080
Statin (n,%)	45(100%)	62(100%)	1
Diuretics (loop diuretic) (n,%)	42(92%)	58(94%)	0.969
Glucose (mg/dl±SD)	134 ± 61	156 ± 71	0.037
Creatinine (mg/dl±SD)	1.08 ± 0.21	1.09 ± 0.19	0.788
Total cholesterol (mg/dl±SD)	270 ± 58	290 ± 71	0.241
LDL cholesterol (mg/dl±SD)	139 ± 21	141 ± 26	0,535
HDL cholesterol (mg/dl±SD)	32 ± 8	34 ± 6	0.685
Triglyceride (mg/dl±SD)	208 ± 63	225 ± 67	0.102
Hemoglobin (g/l±SD)	11.7 ± 1.3	11.8 ± 1.7	0.681
White blood cell (10^3/μL±SD)	11.4 ± 3.9	10.19 ± 3.6	0.79
Platelet (10^3/mm³±SD)	208 ± 77	194 ± 71	0.356
Lymphocyte count, (/mm³)	2.2 ± 0.5	1.2 ± 0.4	< 0.001
Left ventricular ejection fraction, (%±SD)	31 ± 5	29 ± 5	0.082

ACE: angiotensin converting enzyme; LDL: low-density lipoprotein, HDL: high-density lipoprotein

Table 3 – Univariate and multivariate predictors of apical mural thrombus

Variables	Univariate		Multivariate	
	r	p	B	p
Age	0.166	0.087	-0,028	0.782
Sex	0.192	0.048	-0.056	0.584
Current smoker	-0.252	0.009	-0.195	0.020
Body mass index	-0.322	0.001	-0.136	0.102
Diabetes mellitus	0.201	0.038	0.121	0.553
Ejection fraction	-0.176	0.070	-0.050	0.585
Glucose	0.241	0.012	0.010	0.960
Platelet count	-0.198	0.041	-0.290	0.213
Lymphocyte count	-0.431	< 0.001	-0.301	0.179
Platelet-to-lymphocyte ratio	0.177	0.068	0.230	0.452
Neutrophil-to-lymphocyte ratio	0.408	< 0.001	0.210	0.068
Mean platelet volume	0.440	< 0.001	0.350	0.004
Mean platelet volume-to- lymphocyte ratio	0.501	< 0.001	0.441	0.001

Discussion

In this study, we showed that MPVLR was significantly higher in patients with AT after anterior myocardial infarction than without AT. To the best of our knowledge, this is the first study to determine the clinical utility of MPVLR in predicting AT after a myocardial infarction.

Left ventricular AT formation is known to occur in patients with acute anterior MI and dilated cardiomyopathy as a result of low flow and inflammatory states.[3]. AT can also be found in patients with severe congestive heart failure.[14,15] Reportedly, the incidence of LV apical thrombi was approximately 60% in patients with acute anterior MI particularly in the pre-thrombolytic era.[16,17] The formation of an LV apical thrombus was associated with reduced LVEF (≤35%) and presence of apical aneurysms.[18] Recently, percutaneous coronary intervention has replaced thrombolytic therapy and caused a decrease in the incidence of LV apical thrombi. A study by Choi et al.,[19] showed an incidence of LV apical thrombi of 3.3% (34 of 1,045) in patients with acute anterior MI.[19]

Besides the low LVEF, inflammatory states play an important role in thrombotic process. Erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), PLR and neutrophil-to-lymphocyte ratio (NLR) have been studied in a large number of epidemiological studies as indicators of systemic inflammation.[20,21] Lymphocytes are known to play a crucial role for a complete inflammatory response, and reduced lymphocyte counts induced by apoptosis may increase inflammatory damage.[22,23] PLR has been reported to reflect hyperactive inflammatory pathways.[6] High platelet counts reflect underlying inflammation, because many inflammatory mediators stimulate megakaryocyte proliferation and lead to relative thrombocytosis.[6] Higher cytokine levels may lead to the production of large size platelets in the bone marrow.[24] The platelet size shows platelet activity more accurately than the platelet count.[25] MPVLR, which was calculated using MPV instead of platelet count in PLR, was claimed to be a more plausible index of platelet activity.[25] Several studies have shown that a high MPV is associated with cardiovascular events.[26, 27] The mechanism mediating the relationship between high MPV and cardiovascular disease is not obvious. One of the reasons for increased number of larger platelets is cytokines released from ischemic tissues.[28] On the other hand, lymphocytes are involved the mechanisms of cell death caused by inflammation.[29]

Some studies have claimed that lymphocyte-mediated apoptosis is the most important type of cell death in ischemic myocardial tissue.[30] Increased physiologic stress can cause the release of cortisol and catecholamines during acute coronary syndrome.[31] In this situation, redistribution of lymphocytes to lymphatic organs results in apoptosis, which leads to lymphopenia,[32] and lower lymphocyte count.

In previous studies, researchers showed that higher PLR levels were associated with adverse events in various cardiovascular diseases.[29, 30, 33] Ertem et al.,[13] reported that PLR-like inflammatory marker, NLR, was associated with AT. Studies evaluating MPVLR in cardiac conditions are limited. Hudzik et al.,[34] reported that MPVLR was associated with high coronary thrombus burden and late mortality in STEMI patients. MPVLR was also found to be higher in patients with poor coronary collaterals.[35] In the present study, we found that MPVLR was strongly associated with AT. In response to increased inflammatory and thrombotic status, both higher MPV levels and lower lymphocyte counts may be associated with newly developed AT after a myocardial infarction. Taken together, the MPVLR is a simple and readily available biomarker that combines the predictive risk of MPV and lymphocyte counts into a single risk factor. According to our data, we suggest that the MPVLR is a better predictor than NLR, MPV, and PLR for AT.

Study limitation

The limitations of this study are that this is a single center study, with a small cohort and retrospective design, which may affect the strength of the results. Platelet count would be better assessed with peripheral blood smear, but peripheral blood smear samples were not available in this study population. Additionally, MPVLR was measure only on admission; it would be worthy to see whether follow-up measurements of MPVLR could have prognostic value. Finally, antiplatelet drugs and statins may affect MPV and lymphocyte count.[36] However, to the authors' knowledge, this is the first study in the literature to show an association between MPVLR and AT. It is believed that further studies are needed to confirm our findings.

Conclusions

MPVLR is an easily calculated and efficient index that can be considered a powerful and independent predictor of AT in anterior MI patients. The authors suggest that it can be a useful adjunct to standard tests in the diagnosis of AT.

Author contributions

Conception and design of the research: Koseoglu C. Analysis and interpretation of the data: Kurmus O. Statistical analysis: Koseoglu C. Writing of the manuscript: Koseoglu C. Critical revision of the manuscript for intellectual content: Kurmus O.

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No potential conflict of interest relevant to this article was reported.

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This article does not contain any studies with human participants or animals performed by any of the authors.

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EDITORIAL

Association between the Average Ratio of Platelet Volume and the Presence of Mural Thrombus in Post-Myocardial Infarction

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Editorial referring to the article: Association between Mean Platelet Volume-to-Lymphocyte Ratio and the Presence of Apical Mural Thrombus in Post-Myocardial Infarction Patients

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Cardiovascular disease is a serious public health problem, responsible for 31% of all deaths worldwide. Population growth, urbanization and the lack of proper policies to control modifiable risk factors lead to an increased number in cases.[1] Associated with this, we have new factors such as stress, pollution, income, unemployment, among others, which, associated with classical factors, increase the speed of atherosclerosis development. Acute ischemic syndromes are some of the worst consequences of the evolution of atherosclerosis, with mortality rates varying according to the type of infarction, place of care and the healthcare resources available.

Among the types of infarction, those with ST segment elevation (STEMI), particularly in the anterior wall, present peculiarities in their natural history, and may lead to complications, such as sudden death, heart failure and embolic events, usually due to the formation of apical thrombus (AT) in the left ventricle.

The pathophysiology of AT formation has been studied for decades and we do not have laboratory elements to determine the patients that may have this condition. Complications due to the presence of AT are serious, with systemic embolization to different territories and the possibility of complications, death and permanent sequelae.[2]

Detection of AT formation after STEMI is essential and its presence indicates treatments that aim to reduce the probability of embolization. Many of these thrombi develop at different times and, therefore, are not diagnosed, greatly increasing the risk of complications for these patients.

The study of platelet aggregation and coagulation cascade, which are more active during and after acute coronary syndrome, points to this possibility, but we do not have any elements that may signal this condition.[3]

Literature data show that increased platelet volume (MPV) makes them more active from a metabolic and enzymatic point of view and the platelet-to-lymphocyte ratio (PLR) is known as an inflammatory marker that has been widely studied in other diseases, such as cancer, chronic kidney disease and coronary artery disease.

In a very elegant way, a study was designed using these two variables, called MPVLR, and their association with AT formation. The findings showed that MPVLR was significantly increased in patients with thrombus in the left ventricle after myocardial infarction, compared with patients with no thrombus, with 82.1% sensitivity and 70.2% specificity in the ROC analysis, representing a predictor of AT formation.[4]

This is the first study that determined the use of MPVLR as a predictor of thrombus formation in the left ventricle after acute myocardial infarction in the anterior wall, through an easy-to-apply methodology and the findings seem to be a predictor of the possibility of AT development.[4]

There are study limitations due to the small number of study participants, because it is retrospective, conducted in a single center and with limitations where the authors recognize that the platelet counting methodology should be improved, in addition to further MPVLR testing at other times during the infarction, mainly to assess the

Keywords

Cardiovascular Diseases/prevention and control; Public Health Program;Risk Factors; Stress; Atherosclerosis; Mortality; ST Elevation Myocardial Infarction; Thrombosis.

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maintenance of results and interference of drugs used in these patients, such as antiplatelet agents, statins, and others that may alter the MPV.

A great step has been taken towards a large multicenter study that may confirm these initial data and thereby determine the possibility of developing AT after STEMI in the anterior wall, and it may be studied in other cardiac diseases with potential for embolization.

The detection of this possibility and early and effective treatment may change the natural history of the disease, protecting patients from serious complications, reducing mortality due to the evolution of these diseases.

We have seen a steady growth in cardiovascular mortality over the past few decades. Technological and drug-related advances, capacity-building at the services and adherence to treatment have greatly helped reducing mortality.

Prevention of cardiovascular diseases on all stages of human life through the control of risk factors still needs greater adherence and better results, negatively impacting the reduction of development and complications, such as acute ischemic syndromes.[1]

The use of MPVLR may be useful at first to prevent embolic complications in acute coronary syndromes.

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REVIEW ARTICLE

Inflammation in Cardiovascular Disease: From Basic Concepts to Clinical Application

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Abstract

Although low-density lipoprotein cholesterol is central to the development and progression of atherosclerosis, the role of inflammation in the atherosclerotic process is becoming better understood and appreciated. Chronic inflammatory conditions such as rheumatoid arthritis, lupus, psoriasis, HIV infection, and inflammatory bowel disease have all been shown to be associated with an increased blood levels of inflammatory biomarkers and increased risk of cardiovascular events. Evidence from observational studies suggests that anti-inflammatory therapy decreases this risk in these conditions. Clinical trials of anti-inflammatory drugs in patients with coronary disease have yielded mixed results. Drugs that have failed in recent trials include the P38 MAP kinase inhibitor losmapimod, the phospholipase A2 inhibitors darapladib and varespladib, and methotrexate. Canakinumab, an interleukin-1β inhibitor, reduced cardiovascular events in patients with coronary disease in the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS). Canakinumab increased the rate of fatal infections in CANTOS and is very expensive; it is thus unlikely to be widely used for risk reduction in cardiology. On the other hand, colchicine is a safe and inexpensive anti-inflammatory drug. In the Colchicine Cardiovascular Outcomes Trial (COLCOT), where patients within 30 days of a myocardial infarction were randomized to low-dose colchicine or placebo and followed for a median of almost 2 years, colchicine treatment was associated with a 23% reduction (p=0.02) in cardiovascular events. Newer studies with anti-inflammatory drugs have the potential to improve outcomes of patients with atherosclerosis, just as low-density lipoprotein cholesterol-lowering drugs have done over the past two decades.

Keywords

Lipoproteins,LDL, Atherosclerosis; Cardiovascular Diseases; Inflammation; Arthritis, Rheumatoid; Coronary Disease; Anti-Inflammatory Agents/therapeutic use; Colchicine/therapeutic use; Canakinumab/therapeutic use; Risk Factors.

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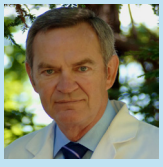
Introduction

Atherosclerosis is a slowly progressive condition that eventually affects perfusion of various organs, most importantly the heart and brain. The classical risk factors that accelerate atherosclerosis include diabetes, hypertension, smoking, and hyperlipidemia, which are in turn influenced by genetic factors, diet and physical activity levels. Interactions among these factors are complex, and the pathogenesis of atherosclerosis is still incompletely understood.

Nevertheless, the central role of low-density lipoprotein cholesterol (LDL-C) has been clearly established, as detailed in a recent consensus statement from the European Atherosclerosis Society.[1]

A key feature of early atherosclerosis is the uptake of LDL-C particles by the arterial wall, where LDL-C is oxidized and stimulates an inflammatory response.[1] Inflammation thus becomes a powerful contributor to the progression of atherosclerosis. While the centrality of LDL-C to the development of atherosclerosis has long



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been recognized, and LDL-C lowering has been a goal of therapy, the role of inflammation has been a focus of attention only more recently.

This review addresses two aspects of inflammation and cardiovascular (CV) disease. In the first section we review the body of evidence showing that chronic inflammatory diseases are associated with an increased risk of CV events, and that anti-inflammatory therapy reduces this risk. In the second section we summarize the clinical trials that assessed the effects of anti-inflammatory treatments on CV events in patients without underlying inflammatory conditions.

Inflammatory Conditions with Increased Cardiovascular Risk

Rheumatoid Arthritis

Some of the inflammatory conditions associated with increased risk of CV events and supporting studies[2-6] are listed in Table 1. The link between rheumatoid arthritis (RA) and increased CV risk is particularly clear. In a meta-analysis[2] including eight studies and a total of 788 patients with RA and 1,641 controls, the presence and severity of coronary artery disease (CAD) was assessed with coronary computed tomography angiography (CCTA). Compared with controls, there was an increased risk of CAD (relative risk [RR] = 1.26, 95% confidence interval [CI] 1.04-1.52), and a higher prevalence of a coronary calcium score >100 and multivessel CAD. RA disease activity was linked to high-risk (non-calcified or mixed) coronary plaques. Methotrexate treatment was associated with an absence of CAD.

Other studies have shown that the presence of RA increases the incidence of coronary and cerebrovascular events. In a report from the Taiwan National Health Insurance Research Database, 10,568 patients with RA were compared to 42,272 controls matched for age, sex, urbanization and income.[7] During a six-year follow-up, an increased risk was seen for ischemic stroke (HR 3.48, 95% CI 2.16-5.61), coronary heart disease (HR 2.77, 95% CI 2.32-3.32), atrial fibrillation (HR 2.90, 95% CI 1.17-7.20), and heart failure (HR 2.88, 95% CI 2.01-4.14).

Not only are CV events more likely in patients with RA, they are more severe. In a matched cohort study from Sweden, RA subjects more frequently presented with sudden cardiac death and ST-segment elevation myocardial infarctions (STEMI),[8] and had higher levels of troponin and more in-hospital complications compared with controls. The seven-day mortality after acute coronary syndrome (ACS) was also higher in RA patients compared to controls: HR 1.65 (95% CI 1.32-2.08).

As summarized by Klingenberg and Lüscher,[9] circulating T cells of patients with ACS and of patients with RA are characterized by clonal restriction, with increased $CD4+CD28^{null}$ T cells. Clonal restriction indicates a reduced repertoire of antigens recognized by the T cell receptor complex and reveals similar autoimmune responses against specific antigens in ACS and RA.

An army of cytokines, including TNF-α, IL-1β, IL-6, and IL-17, contribute to the inflammatory joint damage in RA and are current or potential targets of therapy.[10] Some of these inflammatory mediators have been implicated in the pathogenesis of ACS, including TNF-α.

Table 1 – Chronic inflammatory conditions that increase the risk of cardiovascular events

Condition	Type of Study	Study Endpoint	Number of Patients	RR/HR (95% CI)
Rheumatoid arthritis[2]	Meta-analysis 8 studies	Coronary Ca^+ Score	785 pts 1641 controls	1.26 (1.04-1.52)
Lupus[3]	Meta-analysis 9 studies	Incident CAD	3320 pts	3.19 (2.15-5.35)
Psoriasis[4]	Prospective cohort	Myocardial infarction	130,976 pts 556,995 controls	1.11 (1.07-1.17)* 1.43 (1.18-1.72)^
HIV[5]	Meta-analysis 80 studies	Incident CVD	793,635 pts	2.16 (1.68-2.77)
Inflammatory Bowel Disease[6]	Meta-analysis 6 studies	Incident IHD	123,907 pts	1.18 (1.08-1.31)

** hazard ratio for mild psoriasis vs controls; ^ hazard ratio for severe psoriasis vs controls*

TNF-α antagonists are now widely used in the treatment of RA, and have been shown to have a beneficial effect on cardiac risk factors,[11] and on surrogate markers of atherosclerosis such as endothelial function[12] and carotid intima-media thickness.[13]

Based on the aforementioned data, one might expect that TNF-α inhibition would reduce CV events in patients with RA. This was in fact demonstrated among 10,156 RA patients enrolled in the Consortium of Rheumatology Researchers of North America RA registry (CORRONA).[14] Patients were treated with TNF-α antagonists, methotrexate, or non-biological disease-modifying antirheumatic drugs (DMARDs). During a median follow-up of 22.9 months, 88 CV events occurred. Using a TNF-α antagonist reduced the adjusted risk of a CV event (HR 0.39, 95% CI 0.19-0.82) compared with users of DMARDs, while methotrexate was not associated with an adjusted reduced risk.

Although all studies examining this issue do not yield concordant results, findings from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis recently confirmed the benefit just described in the North American registry. A total of 14,258 patients were analyzed, 11,200 receiving TNF-α inhibitors and 3,058 receiving DMARDs.[15] There were 58 verified first MIs during a median follow-up of 3.5 years in the DMARD cohort and 194 MIs during a median follow-up of 5.3 years in the TNF-α inhibitor cohort. The risk of myocardial infarction (MI) in the TNF-α inhibitor cohort was 0.61 (95% CI 0.41-0.89) compared with the DMARD cohort.

To summarize for RA, the risk of CV events is increased, which is likely related to inflammation, and is reduced by anti-inflammatory treatment.

Systemic Lupus Erythematosus

The prevalence of lupus is much lower than that of RA, and thus the relationship between lupus and CV events has not been as well documented. In a meta-analysis of nine studies (eight cohort and one case-control), including 3,320 lupus patients, the RR of CAD compared to controls was 3.39, 95% CI 2.15-5.35.[16] This meta-analysis, however, has limitations; for example, most of the included studies did not account for treatment, and a common treatment for lupus, glucocorticoids, can by itself increase the risk of CV events.

Lupus patients at highest risk for CV events are those with lupus nephritis. Atherosclerotic plaques in the carotid and femoral arteries have been reported to be more common in patients with lupus compared to controls, with the excess risk comparable to that seen in RA or in diabetes.[17] Endothelial dysfunction is a common feature of lupus, even in mild cases and early in the disease.[18] This has been attributed to a variety of mechanisms including impaired clearance of apoptotic cells, oxidative stress, circulating autoantibodies, different subtypes of T lymphocytes, and a cascade of cytokines.[18]

A distinct subset of lupus proinflammatory neutrophils, termed low-density granulocytes (LDGs), appear to play a key role in enhancing CV risk in lupus. In a recent study, lupus subjects and healthy controls underwent 18F-fluorodeoxyglucose–PET/CT imaging to measure vascular inflammation, a mechanism of arterial dysfunction, and CCTA to determine plaque burden; LDGs were quantified by flow cytometry and cholesterol efflux capacity was also measured.[19] Vascular inflammation, arterial stiffness, and noncalcified plaque burden were all increased in lupus patients compared to controls, even after adjustment for traditional risk factors. In lupus subjects noncalcified plaque burden was directly associated with LDGs and negatively associated with cholesterol efflux capacity in fully adjusted models.[19] These associations suggest that LDGs may contribute to vascular damage and unstable coronary plaque in the setting of lupus.

Psoriasis

In a cohort study from the United Kingdom with 130,976 psoriasis patients and 556,995 controls, 13,625 MIs were documented during a mean follow-up of 5.4 years.[4] Risk of MI was elevated in subjects with psoriasis and was highly dependent on age and severity of psoriasis (Figure 1). For example, for a 30-year-old patient with mild or severe psoriasis, the adjusted RR of having a MI was 1.29 (95% CI, 1.14-1.46) and 3.10 (95% CI, 1.98-4.86), respectively. For a 60-year-old patient with mild or severe psoriasis, the adjusted RR of having a MI is 1.08 (95% CI, 1.03-1.13) and 1.36 (95% CI, 1.13-1.64), respectively.[4]

In a more recent study, subjects with psoriasis were shown to have more noncalcified coronary plaque and more high-risk plaques by CCTA compared to healthy volunteers.[20] Moreover, improvement in skin disease severity after one year was associated both with a reduction in circulating levels of proinflammatory cytokines such as TNF-α and IL-1β, and with improvement in total coronary plaque burden and noncalcified plaque,

Int J Cardiovasc Sci. 2020; 33(5):518-527
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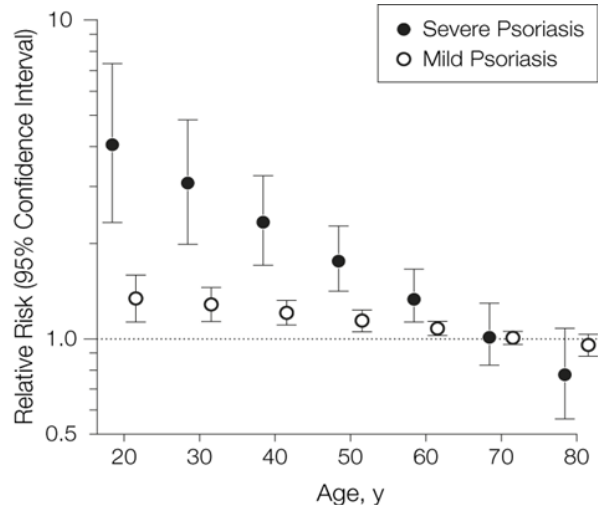

Figure 1 – Adjusted relative risk of myocardial infarction in patients with psoriasis based on age and disease severity. Adjusted relative risk is depicted on a log scale (y axis). From reference #4.

unexplained by traditional risk factors.[20] Thus, control of peripheral inflammation appeared to have a salutary effect on coronary disease. These findings raise the question: would anti-inflammatory therapy in psoriasis reduce the risk of CV events?

The answer to this question seems to be yes. A Danish cohort study of 6,902 patients with severe psoriasis showed that relative to other therapies, methotrexate (HR 0.53, 95% CI 0.34-0.83) and TNF-α inhibitors (HR 0.46; 95% CI 0.22-0.98) were associated with reduced risk of the composite CV endpoint.[21]

HIV

In a recent meta-analysis including 80 studies of 793,635 people living with HIV and a total follow-up of 3.5 million person-years, the RR for CV disease was 2.16 (95% CI, 1.68-2.77) compared with individuals without HIV.[5] As shown in Figure 2, this risk is similar to the risk of hypertension, diabetes, lipids and smoking.[22,23]

Several factors increase the risk for CV disease in persons living with HIV in addition to inflammation.[24] Smoking is more prevalent in subjects with HIV in many countries. Antiretroviral treatment may increase the risk of CV events directly or by inducing or worsening lipid abnormalities, most frequently hypertriglyceridemia.[25] Improvements in antiretroviral therapy in recent years has led to better control of infection; the HIV population is aging, and thus at higher CV risk.

The mechanisms leading to HIV atherosclerosis are complex and poorly understood. Even when HIV infection is controlled, low-level transcription of HIV genes continues and HIV-encoded proteins induce inflammation and endothelial dysfunction.[24] Second, immune abnormalities persist in successfully treated subjects, and these abnormalities are predictive of CV events.[24] For example, one such abnormality, the CD4:CD8 ratio, is a marker of immunosenescence. Third, co-infection with cytomegalovirus has been linked to an increased CV risk through different potential mechanisms.[24] CMV-specific T cell responses correlate with increased carotid intima-media thickness,[25] a surrogate marker of increased CV risk. Fourth, an early feature of HIV infection is impairment of the gut barrier, such that microbial products leak through the intestinal barrier and cause immune activation, a process termed microbial translocation.[24] Markers of microbial translocation, specifically plasma levels of soluble CD14 and lipopolysaccharide, predict progression and mortality of HIV disease, and are associated with higher levels of the inflammatory markers TNF-α and IL-6.

All the aforementioned mechanisms increase inflammation. High plasma levels of inflammatory and coagulation markers, such as C-reactive protein (CRP), IL-6 and d-dimer, strongly predict CV events and all-cause mortality in subjects with HIV infection.[24] These relationships suggest that anti-inflammatory treatment might reduce the risk of CV events in persons with HIV infection.[26] Although this hypothesis has not yet been tested in a randomized clinical trial, a small pilot study of canakinumab, a monoclonal antibody targeting IL-1β, showed a significant reduction of plasma IL-6 and CRP levels.[27] This was paralleled by reductions in leukopoietic activity, monocyte cytokine production, and arterial inflammation as assessed by FDG-PET CT.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD), comprising Crohn's disease and ulcerative colitis, is a risk factor for both stroke and coronary disease. In a meta-analysis of five studies reporting 2,424 cerebrovascular events in 98,240 IBD patients, IBD conferred an increased risk (adjusted OR, 1.18, 95% CI 1.09-1.27).[6] Similarly, the risk of a coronary event was increased across six studies reporting 6,478 ischemic heart disease events in 123,907 patients with IBD (adjusted OR 1.18, 95% CI 1.08-1.31).[6] For both cerebrovascular and ischemic heart disease endpoints, the increased risk was present for both

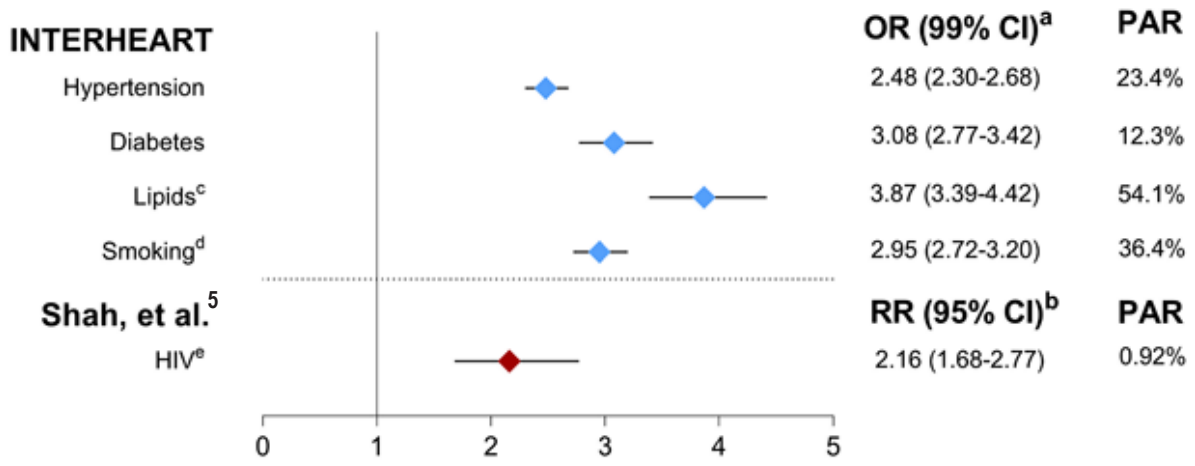

Figure 2 – Cardiovascular risk of HIV compared with traditional risk factors. The odds ratios for hypertension, diabetes, lipids and smoking are taken from the INTERHEART study[23] and the relative risk for HIV from Shah et al.[5] Odds ratios are not directly comparable to relative risk and should be adjusted downward slightly for comparison.
a risk of acute MI, adjusted for age, sex, and smoking.
b risk of ASCVD (CVD, stroke, or MI).
c high ApoB/ApoA1 ratio.
d OR (99% CI) for current smoking; PAR for any smoking.
e PAR for 2015 using prevalence data for HIV for the 15- to 49-year-old group. Apo indicates apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; HIV, human immunodeficiency virus; MI, myocardial infarction; OR, odds ratio; PAR, population attributable risk; and RR, risk ratio. From reference #22.

Crohn's disease and ulcerative colitis, and appeared to be greater in women than in men.

In a Danish registry-based study IBD patients had an increased risk of MI during flares (RR 1.49, 95% CI 1.16-1.93), and during persistent activity (RR 2.05, 95% CI:1.58-2.65), but no increased risk during remission (RR 1.01, 95% CI 0.89-1.15).[28] Studies reporting surrogate endpoints such as carotid intima-media thickness or arterial stiffness in IBD patients are sparse or inconclusive.[29]

In contrast to some of the other inflammatory conditions already discussed, the effect of anti-inflammatory therapy on CV events in IBD has not been well documented. A common treatment for IBD, 5-aminosalicylic acid (5-ASA), which might possess aspirin-like anti-platelet properties, has been reported to be associated with a reduced risk of CV events in IBD patients.[30] In the same study a trend toward fewer CV events among IBD patients treated with TNF-α inhibitors was also seen, but the authors cautioned that this relationship may have been underestimated due to confounding by indication, because sicker patients were more likely to be treated with this drug.

Anti-inflammatory Drugs That Reduce CV Events

As discussed in the preceding section, a wide range of chronic inflammatory diseases are associated with an increased risk of CV events. The evidence is strong for some of these conditions that anti-inflammatory therapy reduces CV risk; for others, the evidence is weaker. However, even the strong evidence is drawn mainly from observational studies and is thus subject to bias.

These data form a basis for consideration of the role of anti-inflammatory therapy for the prevention of CV events in subjects without concurrent inflammatory conditions. Table 2 lists some of the anti-inflammatory drugs that have been tested to date in clinical trials.[31-37] Older failed trials with the P38 MAP kinase inhibitor losmapimod[31] and the phospholipase A2 inhibitors darapladib[32,33] and varespladib[34] will not be discussed further, except to note that these drugs reduced markers of inflammation and inhibited biomarkers that were predictive of CV events. The results of trials with statins, methotrexate, canakinumab and colchicine will be discussed in the remainder of this article.

Statins

The reduction in CV events with statin treatment is proportional to the amount of LDL-C reduction; specifically, each mmol/L (38.6 mg/dl) reduction in LDL-C is expected to produce a 22% reduction in CV events, slightly less during the first year, and slightly more thereafter.[38] In addition to LDL-C lowering, statins exert anti-inflammatory effects through a wide variety of mechanisms. Statins reduce inflammatory markers including C-reactive protein CRP, cytokines (IL-1β, IL-6, IL-8, TNF-α), and adhesion molecules (P-selectin, ICAM-1).[39] They reduce T cell activity and monocyte activation and increase nitric oxide levels.[39] These anti-inflammatory effects may contribute to event reduction, despite the close relationship between LDL-C reduction and event reduction. PCSK9 inhibitors lack some of the anti-inflammatory properties of statins, and this has been suggested as an explanation for why they do not reduce CV events as much as expected, based on their degree of LDL-C lowering.[40]

In the JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), healthy subjects with LDL-C levels below 130 mg/dl and CRP levels of 2 mg/L or higher were randomized to rosuvastatin 20 mg/day or placebo and followed for a median of 1.9 years.[41] The primary endpoint, a composite of MI, stroke, arterial revascularization, hospitalization for unstable angina, and CV death was reduced in the active treatment group (HR 0.56, 95% CI 0.49-0.69). Thus, targeting subjects with evidence of inflammation without hyperlipidemia markedly reduced CV events.

In patients with ACS, levels of inflammatory markers are high, and are reduced more rapidly and to lower levels by potent statins compared to placebo.[42] Statins reduce CV events early post-ACS, and this event reduction has been attributed more to a decline in inflammatory markers than to a decline in LDL-C levels.[43] Although the anti-inflammatory effects of statins cannot be disentangled from their cholesterol-lowering effects, it is reasonable to assume that part of the benefit of this class of drugs is related to their effect on inflammation.

Methotrexate

Methotrexate is a folic acid antagonist with broad anti-inflammatory effects. As previously noted, methotrexate use was associated with a reduction in CV events by nearly half in a large Danish series of patients with severe psoriasis.[21] In a cohort study of patients with RA, where information about CV events was obtained by questionnaire, prolonged methotrexate use was associated with a 15% reduction in CV morbidity.[44] Similarly, a 21% reduction in CV events was reported with methotrexate treatment in a meta-analysis of patients with various rheumatologic diseases.[45] Based upon this body of evidence, a trial of methotrexate to prevent CV events in patients with coronary disease seemed promising.

The Cardiovascular Inflammation Reduction Trial (CIRT) randomized 4,786 patients with previous MI or multivessel coronary disease who also had type 2 diabetes or metabolic syndrome, to low-dose methotrexate or placebo.[35] The trial was terminated by the Data and Safety Monitoring Board after a median follow-up of 2.3 years because it had crossed the prespecified boundary for futility and because methotrexate did not lower IL-1β, IL-6, or CRP

Table 2 – Anti-inflammatory drugs for the prevention of cardiovascular events

Drug	Mechanism of Action	Clinical Trial	Result
Losmapimod	P38 MAP kinase inhibitor	LATITUDE-TIMI 60[31]	No benefit
Darapladib	Lipoprotein-associated phospholipase A2 inhibitor	SOLID-TIMI 52[32] STABILITY[33]	No benefit
Varespladib	Secretory phospholipase A2 inhibitor	VISTA-16[34]	Stopped early for probable harm
Methotrexate	Folic acid antagonist	CIRT[35]	Stopped early for futility
Canakinumab	IL-1β inhibitor	CANTOS[36]	15% reduction at higher doses (p=0.007)
Colchicine	inhibition of NLRP3 inflammasome	COLCOT[37]	23% reduction in primary endpoint (p=0.02

levels compared to placebo. No reduction in CV events was seen with methotrexate. Thus, the CIRT failed to reproduce, in patients with coronary disease, positive results with anti-inflammatory drugs reported in non-randomized studies on patients with chronic inflammatory conditions. Baseline CRP levels were not elevated in CIRT patients, and as pointed out by the authors, this may have accounted for both the lack of CRP lowering and the lack of clinical benefit with methotrexate.

Canakinumab

Anakinra is a humanized monoclonal antibody that decreases signaling via both IL-1α and IL-1β.[46] It is used to treat RA and has been shown in pilot studies to reduce CRP and IL-6 after MI, as well as improve other surrogate measures.[46] A limitation of anakinra is that it affects IL-1α and IL-1β, thereby interfering with immune function. Canakinumab, another humanized monoclonal antibody, neutralizes IL-1β specifically, and thus has the potential to favorably affect atherosclerosis without affecting immune function.[46] In a pilot study of 556 patients with diabetes, canakinumab reduced CRP, fibrinogen, and IL-6 with no negative effects on serum lipids.[47]

The Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) randomized 10,061 patients with previous MI and a high-sensitivity CRP level of ≥2 mg/L to placebo or to one of three doses of canakinumab (50 mg, 150 mg, or 300 mg, administered subcutaneously every three months).[36] The primary efficacy end point was nonfatal MI, nonfatal stroke, or CV death. More than 90% of study patients took statins and median LDL-C levels at baseline were 82 mg/dl with no change during follow-up. Compared to placebo, CRP levels were reduced by 26%, 37% and 41% with increasing doses of canakinumab ($p<0.001$ for all).

At a median follow-up of 3.7 years, the HR was, in the 50-mg group, 0.93 (95% CI 0.80-1.07, p=0.30), in the 150-mg group 0.85 (95% CI 0.74-0.98, p=0.021), and in the 300-mg group 0.86 (95% CI, 0.75-0.99; p=0.031). The 150-mg dose, but not the other doses, met the prespecified threshold for statistical significance adjusted for multiple comparisons. Canakinumab was associated with a higher incidence of fatal infection compared to placebo and there was no significant difference in all-cause mortality for all canakinumab doses versus placebo. These results demonstrate that targeting the IL-1β pathway with canakinumab reduced CV events among post-MI patients with elevated CRP levels.

Outcomes in CANTOS were related to on-treatment CRP levels. Trial participants allocated to canakinumab who achieved a CRP concentration of <2 mg/L had a 25% reduction in major adverse CV events (adjusted HR 0.75, 95% CI 0.66-0.85), whereas no significant benefit was observed among those with an on-treatment CRP concentration of ≥2 mg/L (adjusted HR 0.90, 95% CI 0.79-102, p=0.11).[48]

The effects of canakinumab on IL-6 and IL-18, and the prognostic value of these interleukins were assessed in a subset of CANTOS patients who had these measurements at baseline and at three months of follow-up.[49] The reductions in IL-6 at three months were 24.8%, 36.3%, and 43.2% for the 50, 150, and 300 mg doses of canakinumab, but there was no change in IL-18 levels. Nevertheless, both on-treatment IL-6 and IL-18 levels were predictive of prognosis. For example, for major adverse cardiac events, each tertile increase in IL-18 was associated with a 15% increase in risk (95% CI 3-29%, p=0.016), and each tertile increase in IL-6 was associated with a 42% increase in risk (95% CI 26-59%, p<0.0001). These findings suggest that IL-6 and IL-18 are still useful biomarkers to predict risk in canakinumab-treated patients, but more importantly, that an inhibitor of IL-18 might also reduce risk.

Colchicine

Colchicine is one of the most ancient of all drugs, so that its safety and side effect profile are well established. However, its anti-inflammatory effects are complex and under ongoing investigation. Colchicine has anti-mitotic activity and inhibits neutrophil migration.[50] In gout, urate crystals activate the NLRP3 inflammasome and colchicine inhibits it.[51] Multiple mechanisms have been described through which colchicine inhibits the NLRP3 inflammasome[50] and these mechanisms are active not only against urate crystals in gouty joints but also against cholesterol crystals in atherosclerotic coronary arteries. In a study where inflammatory markers were simultaneously measured in the coronary sinus and aorta in patients with ACS, trans-coronary gradients of IL-1β, IL-6 and IL-18 were observed, and were reduced by colchicine pretreatment.[52] Thus, coronary production of the inflammasome-specific IL-1β and IL-18, and the more downstream IL-6, were blocked by colchicine in ACS.

In a retrospective cross-sectional study of 1,288 patients with gout, the prevalence of MI was 1.2% in colchicine users and 2.6% in non-users (p=0.03).[53] In a small (n=59) randomized trial, pre-operative colchicine administration significantly reduced peak troponin and creatine kinase-MB levels after coronary bypass surgery.[54] In a pilot study of 151 patients randomized to colchicine or placebo for 5 days after

ST-elevation MI, infarct size as assessed by area under the creatine-kinase-MB curve and by MRI in a substudy of 60 patients was significantly reduced in the colchicine group.[55]

The Low-Dose Colchicine (LoDoCo) trial randomized 532 patients with stable coronary disease to colchicine 0.5 mg/day or no colchicine and followed them for a median of 36 months.[56] The primary outcome, a composite of ACS, out-of-hospital cardiac arrest, or non-cardioembolic ischemic stroke, occurred in 15 of 282 colchicine patients (5.3%) and in 40 of 250 (16.0%) of those who did not (HR 0.33, 95% CI 0.18-0.59). Such a large treatment effect is likely to be a consequence of the small number of outcome events, and an exaggeration of any benefit of the drug. In the absence of placebo treatment in the control group, the adverse effect rate cannot be accurately ascertained; however, 32 patients (11%) assigned to colchicine discontinued the drug within 30 days due to intestinal intolerance.

The Colchicine Cardiovascular Outcomes Trial (COLCOT) randomized 4,745 within 30 days of MI to colchicine 0.6 mg/day or to placebo.[37] The primary efficacy endpoint was a composite of CV death, resuscitated cardiac arrest, MI, stroke, and urgent hospitalization for angina leading to coronary revascularization. Patients were followed for a median of 22.6 months. The primary endpoint occurred in 5.5% of colchicine patients and 7.1% of placebo patients (HR 0.77, 95% CI 0.61-0.96, p=0.02). Figure 3 depicts the Kaplan-Meier curves for the primary outcome. Although COLCOT was underpowered to demonstrate a significant reduction in individual components of the composite endpoint, stroke and urgent hospitalization for angina leading to coronary revascularization were reduced by large, statistically significant margins, while the reductions for CV death and MI were much less impressive.

The incidence of diarrhea in COLCOT was not significantly higher in the colchicine group (9.7% versus 8.9%, p=0.35); however, pneumonia occurred more often in colchicine-treated patients (0.9% versus 0.4%, p=0.03). Although this difference may be only a chance finding, pneumonia has been reported more frequently in colchicine users in a large database study from Taiwan.[57]

Other randomized trials of colchicine in different populations of coronary patients are either complete or in their later stages. The COLCHICINE-PCI trial randomized 714 patients to 1.2 mg of colchicine or placebo two hours before percutaneous coronary intervention.[58] The primary outcome of PCI-related myocardial injury was seen in 57.3% of colchicine-treated and 64.2% of placebo-treated subjects (p=0.19), and there was no difference in CV event rates at 30 days.[58] The Low-Dose Colchicine 2 trial (LODOCO2) randomized 5,322 patients with stable CAD who tolerated 0.5 mg of colchicine for one month to colchicine or placebo.[59] This trial is event-driven and is nearing completion. CLEAR-SYNERGY is a randomized two-by-two factorial design trial comparing colchicine 0.5 mg BID, spironolactone 25 mg/day, and corresponding placebos in 4,000 STEMI patients receiving a SYNERGY stent (ClinicalTrials.gov NCT03048825). The estimated completion date for this trial is December 2021.

Future Directions

Targeted anti-inflammatory drugs are not yet part of the treatment guidelines for patients with atherosclerosis, but it is possible to imagine a future where is the case.[60,61] In addition to canakinumab, other IL-1β inhibitors including anakinra, gevokizumab, and rilonacept, and the IL-6 inhibitors tocilizumab, sarilumab, sirukimab, and olokizumab, as well as IL-18 inhibitors may one day become part of our therapeutic arsenal alongside more familiar drugs such as statins.

Author contributions

Conception and design of the research: Waters DD. Acquisition of data: Waters DD. Analysis and interpretation of the data: Waters DD. Statistical analysis: Waters DD. Writing of the manuscript: Waters DD. Critical revision of the manuscript for intellectual content: Waters DD. Supervision / as the major investigador: Waters DD.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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REVIEW ARTICLE

The Gut Brain-Axis in Neurological Diseases

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Abstract

Recent evidence suggests that dysfunction of the gut-brain axis may be an important factor contributing to many diseases of the nervous system. Increased gut permeability associated with chronic gastrointestinal dysfunction, as well as changes in the composition of the gut microbiota could contribute to exposure of the enteric and central nervous system to pathogens and its metabolites, including endotoxins and pro-inflammatory cytokines. As a consequence, dysfunction of the host's immune system could contribute to an abnormal immunological response leading to auto-immune conditions, such as multiple sclerosis. So far, gut dysbiosis has been reported in association with Parkinson's disease, Alzheimer's disease, multiple sclerosis, neurodevelopmental and neuropsychiatric conditions, and cerebrovascular disease. These findings suggest that the possibility of targeting the gut microbiota could become a future therapeutic option to treat these conditions. However, before this knowledge can be useful in the clinical setting, more data is needed to establish clear causal relationships between dysfunction of the gut-brain axis and neurological diseases.

Introduction

Hundreds of millions of years of co-evolution have resulted in a complex symbiotic relationship between multicellular life and bacteria. While it is very likely that more aggressive interactions predominated in the early days, survival in the long run demanded a more harmonic relationship. For modern humans, the benefits of this relationship are evident when the digestive tract is considered. Commensal bacteria, which colonize the human gut shortly after birth, acquire nutrients from their hosts. In exchange, they assist the digestive process and the production of metabolites that contribute to the host's survival. The collective of host-associated microbes is denominated microbiota, and its genomic constitution, microbiome.[1]

The enteric nervous system consists of approximately 200 million neurons that control the function of the entire digestive tract. It is composed of an intrinsic network of nervous fibers and ganglia, the myenteric and submucosal plexus. The myenteric plexus controls mainly the motility of the digestive tract (peristalsis) and is located deeply between the longitudinal and circular layers of the entire digestive tract. It is composed mainly of a network of ganglia linked by unmyelinated fibers connected to the vagus nerve and sympathetic ganglia. The submucosal plexus (Meissner plexus) is located more superficially and closer to the intestinal lumen from the stomach to the colon. It is composed mainly by nervous fibers and ganglia, and controls the mucosal secretions, vascular flow and absorption.[2]

The gut-brain axis is an information exchange platform which allows two-way communication between the gut and the host nervous system. Information can be exchanged via neural network, hormones and the immune system.[3] Disruption of the delicate balance between host and gut bacteria could be a contributing factor behind many diseases. Following publications that have reported changes in the composition of the gut microbiome, in association with many digestive and non-digestive conditions, research interest in the gut-brain axis has significantly increased making it a research hot topic. This review will explore the physiology and pathophysiology of the gut-brain axis and its role in neurological diseases.

Keywords

Gastrointestinal Tract; Brain; Nervous System; Microbiome Gastrointestinal/complications; Neurobehavioral Manifestations.

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Pathophysiology

Normal functioning of the gut-brain axis

The intestinal epithelial barrier relies on tight junctions between cells to keep its integrity and to separate the external (the gut microbiota) from the internal environment (the gut immune and nervous systems). The composition of the gut microbiota is regulated by both extrinsic factors, such as diet, lifestyle and early microbiota exposure; and intrinsic factors, such as genetic background, metabolism, and activity of the host's hormonal and immune systems.[4]

One of the most studied extrinsic factors that is able to alter the gut microbiota composition is diet. Dietary fibers are degraded by commensal bacteria in the gut and lead to the production of short-chain fatty acids (SCFA), which are beneficial to the brain. On the other hand, epidemiological studies have reported a positive correlation between increased risk of cognitive decline and consumption of high-saturated-fat food, high intake of animal protein and refined sugars.[5] The Mediterranean diet, known for its association with longevity, is also able to influence the composition of the gut microbiome, resulting in higher levels of fecal SCFA and predominance of *Prevotella* and *Firmicutes* species, a composition that appears to be more favorable to the host.[6] SCFAs are important bacterial metabolites that can reduce inflammatory response and promote CNS plasticity. A diet high in fructose has been associated with an exacerbated inflammatory response in the hippocampus, which could be a consequence of changes in the gut bacteria.[7]

Patients with refractory epilepsy can benefit from a ketogenic diet. Olson et al[8] have studied how this type of diet can influence the gut microbiota. Higher levels of hippocampal GABA have been reported alongside an increase in *Akkermansia* and *Parabacteroides* species. This change appears to confer seizure protection, as it does not occur if germ-free mice were fed with a ketogenic diet.[8]

The vagus nerve is an important gut-brain axis pathway that allows for direct connection between these two organs. By controlling gut motility and secretion, the vagus nerve is able to change the gut environment and to control the enteric immune system response with a direct consequence to the gut microbiota. Conversely, gut bacteria produce metabolites that are able to influence both the enteric and the central nervous system and to affect the production of neurotransmitters, such as gamma-aminobutyric acid (GABA), acetylcholine and the serotonin precursor tryptophan.[1] Commensal gut bacteria are also capable of producing important nutrients, such as choline and SCFA, as well as the hormones ghrelin and leptin. They are also able to alter brain function through changes in the expression of CNS receptors.[9] Animal research using murine models have highlighted the importance of the gut bacteria, not only for preserving the health of the brain, but also for contributing to its normal development. Collins et al.,[10] have reported a decrease in nerve density, a decrease in neuronal density in ganglia, and an increase in the prevalence of nitrergic neurons in the myenteric plexus of the jejunum and ileum of germ-free mice, highlighting the importance of the gut microbiota in the normal development of the enteric nervous system.[10] Worse cognition and increased stress response have been reported in germ-free mice, a different behavioral phenotype compared to control animals.[11] The gut microbiota can also affect brain circuits responsible for motor and behavioral control.[12] Increased microbiota diversity has been associated with improved structural organization of the hippocampus, hypothalamus and caudate nucleus.[13]

Dysfunction of the gut-brain axis

A complex immune interplay is in place allowing the gut microbiota to co-exist peacefully with the host's cells. The gut immune system needs to be finely tuned to maintain its vital defensive function in the presence of commensal bacteria. Diverse pathological forces could break this delicate and complex relationship resulting in diseases.

The composition of the gut microbiota appears to be an important factor contributing to diseases. An unbalanced composition of the gut microbiota, known as dysbiosis, has been implicated not only in diseases of the gut, but also in pathologies of distant organs/systems. The immune system can be affected by dysbiosis in many ways. Activation of T-cells by changes in gut microbiota has been associated with auto-immune uveitis[14] and could have a role in other auto-immune conditions. Furthermore, systemic levels of pro-inflammatory cytokines can be affected by commensal gut bacteria and could be implicated in different conditions. Lastly, allergies have also been associated with changes in the composition of the gut microbiota.[15]

Another possible factor connecting dysbiosis to diseases is an increase in gut permeability ('leaky gut'), caused by local pathological processes. This could allow gut bacteria and/or its metabolites to reach the host's circulatory system and the brain (provided they are capable of crossing the blood-brain barrier), interfering with the normal functioning of distant structures. Furthermore, absence of normal gut microbiota in mice has been associated with increased permeability of the blood-brain-barrier, which can be reduced by exposure to pathogen-free microbiota.[16]

It is likely that, in many conditions, both gut dysbiosis and a leaky gut are required to cause diseases, as seen in patients with hepatic encephalopathy. As a consequence of increased permeability of the gut wall in the context of hepatic dysfunction, plasma levels of cytokines and bacterial endotoxins increase, leading to cognitive dysfunction. Gut dysbiosis appears to be an important pathophysiological phenomenon as well. Not only a predominance of *Alcaligenaceae* and *Porphyromonadaceae* has been reported in these patients, but it has also been correlated with cognitive dysfunction.[3]

Neurological conditions

This section focuses on the latest advances on the influence of the gut-brain axis in neurological disease. A summary is presented in Table 1.

Neuropsychiatric symptoms and neurodevelopmental conditions

Inducing gut dysbiosis by antibiotic use in animal models, researchers have reported that anxiety and other cognitive abilities, such as motor control, memory and learning can be influenced by gut bacteria. The ability of commensal bacteria to influence the stress response by modulating the activity of the hypothalamic-pituitary axis, and to produce neurotransmitters and neuromodulating substances is a possible explanation for the reported association between gut microbiota dysbiosis and stress and depression. Dysbiosis could also explain the higher prevalence of psychiatric comorbidities in individuals with inflammatory bowel diseases and irritable bowel syndrome.[17]

Research interest in the connection between gut bacteria and neurodevelopmental disorders, such as autism, followed the initial reports on the importance of the gut microbiome for the normal development of the central nervous system. A different composition of the gut microbiota has been reported in animal models of autism spectrum disorders. Children with autism appear to have a distinct composition of the gut microbiota, with lower levels of *Bifidobacterium*, *Firmicutes*, *Bacteroidetes*, *Akkermansia* and higher levels of *Lactobacillus*, *Clostridium*, *Suterella* and *Bacteroidetes*.[4]

A specific bacterial metabolite, propionic acid, appears to be important to the development of autism spectrum disorders in animal models. Intraventricular

Table 1 – Dysfunction of the gut-brain axis in neurological diseases

Condition	Dysbiosis	Bacterial metabolites/ endotoxins	Leaky gut	Inflammation	Immune dysfunction
Autism spectrum disorders	X	X			
Amyotrophic lateral sclerosis	X	X	X		
Parkinson's disease	X	X	X	X	X
Alzheimer's disease	X	X		X	
Multiple system atrophy	X	X	X	X	
Multiple sclerosis	X	X	X		X
Cerebrovascular disease	X	X			

Different mechanisms leading to dysfunction of the gut-brain axis, which have been reported in association with neurological conditions.

injection of this substance has been reported to induce autism-like behaviour. Furthermore, treatment with *Bacteroidis fragilis*, can reduce the levels of propionic acid and improve behavioral symptoms.[18]

Neurodegenerative diseases

The pathophysiological processes driving many neurodegenerative conditions and leading to neuronal death remain elusive. Such processes are varied and complex and beyond the scope of this review. However, shared pathophysiological features of neurodegeneration, such as aggregation of misfolded proteins and inflammation have recently been studied from the perspective of the gut-brain axis.

Parkinson's disease

Parkinson's disease (PD) appears to be the consequence of a complex interplay between environmental and genetic factors associated with age-related neuronal loss. These factors, either isolated or in combination, lead to dysfunction of diverse neuronal structures/systems and, consequently, to neuronal death.[19] In PD, insoluble forms of alpha-synuclein (a synaptic protein found in healthy neurons) aggregate and accumulate in neurons, resulting in damage to critical cell processes such as mitochondrial activity and axonal flux. Alpha-synuclein is one of the main components of Lewy bodies, inclusions routinely found in patients with idiopathic PD.

Clinical data, showing that digestive symptoms are ubiquitous in PD, and anatomopathological studies confirming deposition of alpha-synuclein in the enteric nervous system suggest that the gut may play an important role in the pathophysiology of PD. PD can affect all levels of the digestive tract, and gastrointestinal symptoms are well known nonmotor symptoms of the disease. Constipation, specifically, is the most frequent nonmotor symptom, affecting 50 to 80% of patients. Not only it can manifest early in the disease course, but it can also precede motor symptoms by many years, which is why it is considered one of the prodromal symptoms of PD.[20]

Lewy pathology (alpha-synuclein aggregates, Lewy neurites and Lewy bodies) is found in the myenteric, submucosal plexus and mucosal fibers of patients with PD in territories innervated by the vagus nerve. The finding that Lewy bodies are also present in the dorsal nucleus of the vagus[21] led to the theory that molecular changes in alpha-synuclein initially occur in the gut and spread to vulnerable areas of the CNS, via retrograde axonal and transneural transport.[20] This theory is compatible with Braak's model of PD progression, according to which the disease enters the CNS via the olfactory or the vagus nerve.[22] The finding by Svensson et al. that patients submitted to truncal vagotomy earlier in life are less likely to develop PD supports this theory.[23]

In PD, there is increased permeability of the intestinal barrier, which could be the consequence of chronic gastrointestinal dysfunction. A leaky gut results in exposure of enteric neurons to bacterial endotoxins and local inflammation. Local aggregation of alpha-synuclein could occur as a consequence of exposure to yet unknown environmental factors associated with alpha-synuclein pathology.[24]

There is evidence to support an immune role for alpha-synuclein, such as expression of this protein in the human gut after viral infections, the ability to attract macrophages and stimulate dendritic cells, and the increased propensity of alpha-synuclein knockout mice to develop infections. Considering this putative role in immunity, alpha-synuclein could also accumulate in the enteric nervous system due to production rates far greater than the clearance rate in the presence of chronic gastrointestinal infection and inflammation.[25] However, the presence of gut microbiota may be required for the aggregation and spread of alpha-synuclein. In an alpha-synuclein overexpression mice model, germ-free animals show reduced alpha-synuclein pathology. Reduced pathology has also been achieved by treatment with antibiotics.[26]

Further exploring the relationship between the gut microbiome and PD, Scheperjans et al.,[27] reported a reduction in *Prevotellaceae* species compared with the controls, and a correlation between an excess of *Enterobacteriaceae* species and the severity of postural instability and gait dysfunction.[27] Other researchers have reported a higher prevalence of bacterial species associated with bacterial lipopolysaccharides and inflammation in PD patients and a decrease in species associated with a reduced inflammatory response.[4] Intestinal inflammation in PD can also be influenced by bacterial metabolites, such as SCFA. Lower fecal SCFA levels have been reported in PD patients, who also exhibited increased levels of intestinal inflammation.[28]

Considering the heterogeneous findings reported in the literature on the composition of the gut microbiota in PD, consistent data were reported for abundance of *Verrucomicrobiaceae* and *Akkermansia* and for decreased *Prevotellaceae*, whereas inconsistent findings were reported for *Lactobacillaceae* and *Bacteroidetes*.[29]

Specific compositions of the gut microbiota have also been studied in atypical parkinsonism. Barichella et al.,[30] compared 193 PD patients with 113 healthy controls, 22 progressive supranuclear palsy and 22 multiple system atrophy (MSA) patients. The only consistent finding between PD and healthy controls was abundance of *Lachnospiraceae*. A clinical profile of worse cognitive impairment, gait dysfunction and postural instability was associated with decreased *Lachnospiraceae* and increased *Lactobacillaceae* and *Christensenellaceae*. MSA patients had similar PD profiles, with the exception of a reduction in *Prevotellaceae* and no decrease in *Lachnospiraceae*, whereas PSP *Lactobacillaceae* were similar, and *Streptococcaceae* were reduced.[30]

Similarly to what has been reported in PD, a small study of six MSA patients showed dysfunction of the intestinal barrier and signs of intestinal inflammation associated to bacterial endotoxins. Furthermore, there was abundance of Bacteroidetes and Proteobacteria (pro-inflammatory bacteria) and a reduction in butyrate-producing bacteria (anti-inflammatory).[31]

Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative condition and one of the main public health issues worldwide due to ageing of the population and the lack of a curative treatment. Its pathological signature is the deposition of neurofibrillary tau tangles and amyloid-β plaques in specific areas of the central nervous system.

The formation of amyloid plaques could be influenced by gut bacteria. Amyloid metabolites can be produced by the intestinal microbiota, which could contribute to inflammation and increase vascular permeability, resulting in amyloidogenesis.[32] Furthermore, bacterial endotoxins are also able to increase the formation of amyloid plaques by influencing amyloid-β peptide fibrillogenesis.[33]

An additional piece of the puzzle comes from studies showing that individuals with AD infected by *H.pylori* have a more severe AD phenotype compared to non-infected controls.[34] Furthermore, eradication of *H.pylori* appears to improve cognitive function.[35] A possible explanation has been given by Wang and colleagues who have demonstrated that *H.pylori* can contribute to neurodegeneration by inducing tau hyperphosphorylation.[36]

A peripheral inflammatory state has been described in individuals with cognitive impairment in the context of amyloidosis. Gut microbiota could play an important role in this phenomenon, since it has been associated with an increase in pro-inflammatory bacterial species, such as *Escherichia* and *Shigella*, and a decrease in anti-inflammatory species of bacteria, such as *E.rectale*.[37] The role of the gut microbiome in AD is strengthened by studies showing cognitive function improvement through the use of probiotics, both in animal models and in patients with the disease.[4]

Multiple sclerosis

The availability of an animal model of multiple sclerosis (MS) and a surge in research interest in this condition, associated with the development of novel immunomodulatory treatments, have led many authors to study the influence of the gut-brain axis in the development of MS.

As stated previously, auto-immune diseases could be triggered by activation of T-cells by gut commensal bacteria, a phenomenon that has been shown to occur in an animal model of relapsing-remitting MS. The importance of gut bacteria in activating T-cells is highlighted by the finding that germ-free mice do not develop encephalomyelitis, unless they receive fecal transplant.[38]

This abnormal immune response appears to be modulated by bacterial metabolites. In the same animal model, long-chain fatty acids are associated with exacerbation of the disease, whereas SCFA improves symptoms.[39] Tryptophan is a precursor of serotonin and its levels can be regulated by the gut microbiota. This substance appears to be beneficial to a mouse model of MS,[4] probably as a consequence of its ability to control microglial activation and reduce inflammation in the CNS .[40]

The role of the gut microbiota in the development of multiple sclerosis is also supported by studies with human subjects. Similar to other conditions, increased gut permeability has been reported in individuals with MS. While there is still no specific gut microbiota composition associated with MS, similarities with

non-neurological auto-immune pathologies and inflammatory bowel disease have been reported, such as an increase in *Archea* and reduction in *Clostridium* and *Bacteroidete*.[1]

Cerebrovascular disease

Cerebrovascular disease is an important cause of morbidity and mortality worldwide. Commensal gut bacteria could be connected to the development of stroke by diverse factors. Diet contributes to atherosclerosis and other risk factors of cerebrovascular disease, such as arterial hypertension, dyslipidemia and diabetes. It can also have a direct effect on the composition of the gut microbiota, making any correlations between dysbiosis and atherosclerosis susceptible to many confounding factors. However, recent research suggests that the gut microbiota may have a more direct role to play in atherosclerosis and cerebrovascular disease.

Trimethylamine n-oxide (TMAO) is a metabolite produced by gut bacteria from dietary choline and is extensively found in body tissues and fluids. It has been implicated in both cardiovascular and cerebrovascular diseases. In a large prospective study involving more than 4,000 people, plasma levels of TMAO were correlated with cardiovascular events. The importance of gut bacteria in producing TMAO was highlighted by the fact that treatment with antibiotics reduced its levels.[41] Furthermore, individuals with stroke and transient ischemic attack have lower levels of TMAO compared to individuals with asymptomatic atherosclerosis.[42]

Animal models show that supplementation of phosphatidylcholine metabolites (including TMAO and choline) can increase the expression of macrophage receptors associated with atherosclerosis. This effect appears to require the presence of gut bacteria. In germ-free mice, choline supplementation is not associated with an increase in atherosclerosis and leads to a reduction in aortic plaque size.[43,44] These findings need to be interpreted with caution since both choline and TMAO can be influenced by diet, and gut microbiota has so far been associated with both protective and harmful effects in the origin and course of atherosclerosis.[11]

Normal microbiota appears to be important for recovery following vascular lesions. Depletion of microbiota by broad spectrum antibiotics after occlusion of the middle cerebral artery results in decreased survival in an animal model.[45] Furthermore, stroke outcomes can be improved by fecal transplant.[46] Treatment with *C butyricum* decreases neuronal injury and improves cognitive function in brain injury induced by ischemia/reperfusion after bilateral carotid common artery occlusion.[47]

Dysbiosis has been shown to occur after stroke and influence its outcome by negatively affecting the size of the lesion and contributing to inflammation. Reduced diversity and abundance of *Bacteroidetes* have been reported after stroke (46). Stroke and transient ischemic attack patients have been reported to harbor more opportunistic pathogens, such as *Enterobacter*, *Megasphaera*, *Oscillibacter*, and *Desulfovibrio*, and fewer commensal or beneficial genera, including *Bacteroides*, *Prevotella*, and *Faecalibacterium*.[42] Furthermore, an abundance of *Peptococcaceae* and *Prevotellaceace* has been correlated with stroke severity.[48]

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis is a neurodegenerative condition which affects primarily the motor neuron. It is an aggressive condition that commonly leads to death a few years after diagnosis. Changes of the gut-brain axis have also been reported in animal models of this condition, such as dysfunction of the gut epithelium and of the gut immune system, and a reduction in the prevalence of bacterial species that produce butyrate.[49] Interestingly, butyrate supplementation can increase survival in the same animal model.[50]

Conclusions

The gut-brain axis is an exciting research topic, which has received a great deal of attention from the scientific community in recent years. However, the role of the gut-brain axis in the development of neurological diseases is far from established. Evidence that the gut microbiota and its metabolites interfere with the host's immune and endocrine systems, affecting neurological function and its vasculature, derives mainly from studies showing correlations, not causality.[4] More prospective studies are needed to demonstrate a causal relationship. When studying neurodegenerative conditions with disease progression spanning several years, one also needs to consider that changes in microbiota occur much faster, complicating even more the interpretation of causality. Another important issue is that the majority of studies published so far have used animal models, limiting extrapolation of their findings to humans.

Furthermore, it is also important to consider the many confounding factors associated with human fecal experiments that are likely to contribute to the heterogeneity of findings, such as diet, demographic, clinical and socioeconomic factors, as well as sample collection, laboratory procedures and genetic sequencing techniques. Ideally, control populations should be selected with a similar risk profile. For example, using controls from households could help minimize dietary variations.[29]

The potential benefits that could derive from research on the gut-brain axis in neurological disease are the identification of biomarkers of neurodegeneration and the development of novel treatments, such as the use of probiotics and fecal transplant. However, there is still no good quality evidence to support clinical use. Administration of the probiotics *Lactobacillus* and *Bifidobacterium* to PD patients can improve constipation, but it does not affect other symptoms of the disease.[51] More data is needed, particularly after reports of worse outcomes with the use of probiotics in immunocompromised patients and in individuals with pancreatitis.[11]

Considering the influence of the gut microbiota in several modifiable risk factors of cerebrovascular disease and its influence in post stroke complications, in theory many benefits could derive from targeting the gut microbiota. More data is needed to address the feasibility of targeting the gut microbiota by using antibiotics, probiotics or fecal transplant .[11]

Despite recent advances in our understanding of the gut-brain axis, more data is needed to address if this knowledge can be useful in the clinical setting. Future research needs to establish more clear causal relationships between the gut bacteria and different neurological conditions and whether targeting the microbiota is a safe and beneficial therapeutic option.

Author contributions

Conception and design of the research: Barbosa PM, Barbosa ER. Acquisition of data: Barbosa PM, Barbosa ER. Writing of the manuscript: Barbosa PM, Barbosa ER. Critical revision of the manuscript for intellectual content: Barbosa ER.

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Ethics approval and consent to participate

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REVIEW ARTICLE

Transcatheter Aortic Valve Implantation: Where are we in 2020?

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Abstract

Aortic stenosis is an insidious disease of rapid progression after the onset of symptoms. Aortic valve replacement surgery is a well-established therapy that reduces symptoms and increases survival rates. However, the procedure may be associated with high operative mortality rates and promote comorbidity. Depending on the local reality, the prevalence of patients considered inoperable (due to medical comorbidities and age) may achieve 30%. For these patients, transcatheter aortic valve implantation (TAVI) was initially indicated; over time, the method has advanced technologically and been simplified, and become an alternative therapy for patients at low and intermediate surgical risk also, and considered one of the major advances of modern medicine.

Introduction

Aortic stenosis is an insidious disease with a long latency period. It has a rapid progression after the onset of symptoms, resulting in a high mortality rate (approximately 50% in the first two years) in untreated asymptomatic patients,[1-3] in whom sudden death is common. Duration of asymptomatic stage is variable. The prevalence of aortic stenosis is increasing due to population aging and is considered the most common valve disease requiring intervention.[4]

Valve replacement surgery for treatment of aortic stenosis reduces symptoms and increases survival rates.[5-7] In general, surgical mortality is 1-3% in individuals younger than 70 years and 408% in the elderly. Despite the higher risk, age alone cannot be considered an absolute contraindication, since favorable outcomes have been reported even in patients aged 80 or older.[8-10]

In clinical practice, surgical treatment is not indicated for nearly 30% of patients (this can vary from one region to another) due to high-risk medical conditions.[11-14] Some of these include advanced age, female sex, functional class, surgical emergency, ventricular dysfunction, pulmonary hypertension, previous cardiac surgery, and coronary artery disease. In these cases, a less invasive procedure – transcatheter aortic valve implantation (TAVI) – may be indicated.

TAVI was first performed in 2002 by Professor Alain Cribier, who showed that it was possible to repair severe aortic stenosis by TAVI in a critically-ill patient.[15] With global dissemination and accumulated experience, technological advances in TAVI have been made; the technique has been simplified and become a low-risk therapeutic option for patients at intermediate surgical risk. In the last 15 years, more than 350,000 procedures have been performed in approximately 70 countries.[16] medicine.

Indications

Based on recent studies, indications for TAVI now encompass all risk groups. Clinical benefits of TAVI was initially shown in patients with severe calcific aortic stenosis, advanced age and high surgical risk (The Society

Keywords

Aortic Valve Stenosis; Percutaneous Aortic Valve Replacement; Aged; Risk Factors; Morbidity; Mortality.

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of Thoracic Surgeons, STS > 10%, Euroscore > 4%). The most relevant studies have shown that TAVI is not inferior to heart valve replacement surgery in terms of one-year follow-up mortality in high-risk patients. In addition, compared to standard therapy, it would be necessary to treat five patients to prevent one death in one-year period.[17,18]

TAVI has also become a therapeutic option to treat patients with STS-defined intermediate risk since publication of the PARTNER2[19] and SURTAVI[20] clinical trials.

In 2020, with publication of the PARTNER3[21] and EVOLUT LOW RISK[22] clinical trials, TAVI has been recognized as one the main revolutionary therapies of contemporary medicine and become indicated for low-risk patients also (STS<4%). The PARTNER3 study, conducted in 71 centers with patients with mean age of 73 years and STS 1.9%, showed the superiority of TAVI for the primary composite endpoint (death, stroke and rehospitalization) in one-year follow-up. The secondary endpoints showed a lower incidence of new atrial fibrillation within 30 days, lower hospitalization rates and more effective control of heart failure-related symptoms (according to the KCCQ score and the 6-minute walk test). The EVOLUT LOW RISK,[22] conducted on patients at same age range, analyzed the composite endpoint of death and stroke in 24-month follow-up. The study showed lower incidence of debilitating stroke, acute renal failure, bleeding-related complications, and atrial fibrillation. On the other hand, the study showed higher incidence of moderate-to-severe aortic regurgitation and need for pacemaker implantation.

A study conducted by the FDA with 30 days of follow-up showed zero mortality in low-risk patients treated with TAVI, as well as a shorter length of hospital stay and lower incidence of atrial fibrillation, corroborating the safety of the therapy.[23] Clinical and echocardiographic results have been recently published in the five-year follow-up NOTION clinical trial. Despite its limitations, including the small number of participants, the study brings relevant results of a longer follow-up. The study concluded that there were no significant differences between the patients undergoing TAVR and patients undergoing surgical aortic valve replacement in all-cause mortality, stroke, or myocardial infarction.[24]

Calcification of tricuspid prosthetic valve is considered the most common cause of aortic stenosis, as shown in Figure 1. This entity is no longer considered "degenerative" because of its complex and highly regulated pathophysiological basis, marked by an active and highly regulated process. It involves mechanisms that may occur simultaneously and contribute to disease development, including chronic inflammation, lipoprotein deposition, activation of the renin-angiotensin system, osteoblastic transformation of valvular interstitial cells and active calcification.[25-28]

The incidence of bicuspid aortic valve stenosis is higher in young than in older subjects. Individuals older than 80 years account for approximately 20% of surgeries.[29] Some anatomical features of this condition, such as the oval-shaped annulus, and uneven calcification and size of the leaflets, may lead to less predictable outcomes of the TAVI. However, a recent meta-analysis with 13 observational studies including data of 758 patients with bicuspid valves showed a successful rate of 95% of the procedure.[30,31] Early events rates, including all-cause mortality, stroke, life-threatening bleeding, vascular complications and valve dysfunction, were not different between patients with bicuspid and tricuspid valves. Also, no difference was found in the rate of annular rupture between the groups. However, a higher need for pacemaker implantation was observed and the combined incidence of moderate-to-severe paravalvular regurgitation was 12.2%.[30]

Valve-in-valve (ViV) TAVI has emerged as a novel, less invasive approach for bioprosthetic aortic valve degeneration treatment. The use of the MEDTRONIC (CoreValve, Evolute R and Evolut Pro) and EDWARDS (SAPIEN XT and SAPIEN 3) valves have been approved for high-risk patients. Recently, results of the PARTNER 2 ViV registry[33] of a study on the safety and effectiveness of self-expanding TAVI[34] have been published. The first study reported 30-day and one-year mortality rates at one year of 2.7% and 12.4%, respectively, and in the second, these rates were of 2.2% and 14.6%, respectively. Moderate or severe aortic regurgitation occurred in 3.5% of the patients. Factors significantly associated with higher residual aortic gradients were surgical valve size, stenosis as modality of surgical valve failure, and presence of surgical valve prosthesis-patient mismatch.[33,34]

A recent review of five meta-analyses[35-39] comparing ViV TAVI to the new surgical procedure showed similar mortality rates (in-hospital, 30-day and one-year mortality) between the groups, even considering that patients that underwent ViV TAVI were at higher surgical risk. Thirty-day mortality of ViV TAVI reported in these meta-analyses was not different than that reported in the VIVID registry,[40] with a non-significant tendency toward a higher rate in the VIVI-registry (7.6% vs. 4.4%, p>0.05).

The experience has shown that complications of ViV TAVI can be prevented. Patients with small surgical bioprostheses

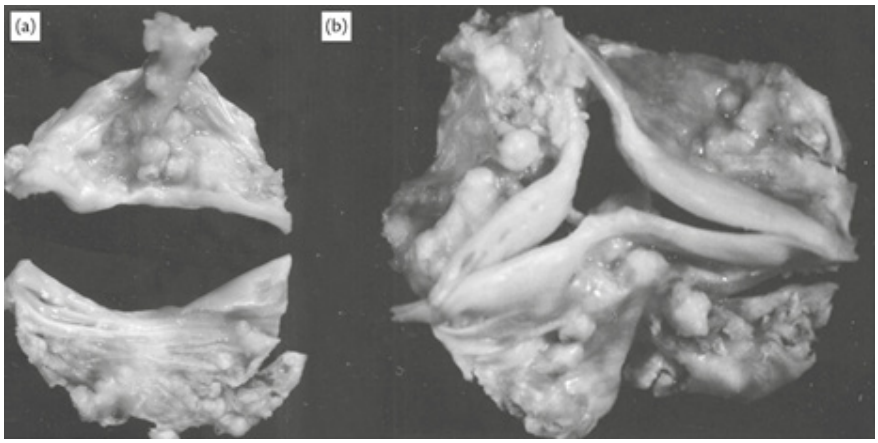

Figure 1 – Calcified bicuspid (A) and tricspid (B)aortic valve[32]

represent a particular challenge, as they seem to show higher residual gradient and higher late mortality than patients undergoing ViV TAVI. Supra-annular bioprosthetic valves and a high implant could mitigate this complication.[41] More recently, some researches have described a technique involving bioprosthetic valve fracture with a high-pressure balloon to facilitate ViV TAVI. The strategy seemed to facilitate the expansion of the transcatheter valve, with reduction of residual transvalvular pressure gradients.[42]

Clinical Indication

According to recent guidelines, TAVI is indicated for symptomatic patients with an average gradient greater than or equal to 4m/s. For patients with low gradient and low flow, valve area smaller than or equal to 1cm^2, and reduced ejection fraction, the indication continues for those with preserved flow reserve (which can be analyzed by dobutamine stress echocardiogram). For patients with preserved ejection fraction and no flow reserve, the severity of stenosis can be estimated by calculation of calcium score by computed tomography.[43]

Immediate and Late Results

After successful valve replacement surgery, the symptoms and quality of life generally improve, although with a longer recovery time as compared with TAVI. Operatory mortality rates vary from 1 to 8%, and long-term survival is comparable to that in the general elderly population of same age.[8-10] Younger subjects have shown substantial improvement with valve replacement surgery compared with conservative medical therapy, with low survival rates though. Risk factors for late mortality include age, comorbidities, severe symptoms, left ventricular dysfunction, ventricular arrythmias and untreated coronary artery disease.[44,45]

For those cases with well-defined indications, TAVI has been shown as a feasible procedure. Constant improvement in early mortality and complication rates has been shown with accumulated experience, improved pre-procedural image processing and better techniques regarding respective valves and delivery systems. While 30-day mortality rates varied from 5% to 15% in the first reports,[17,46-48] more recent studies using late-degeneration devices have shown a decrease by 1-2% in these rates, varying from 5% to 7%.[49,50]

With respect to long term survival, studies have reported a one-year survival rate of 60-85% in patients at high risk, greatly depending on the severity of comorbidities,[17,18,46,48,51-53] reaching 95% in patients at intermediate risk. Although improvement of health and quality of life at one year after TAVI is comparable to that seen in open surgeries, it emerges faster in case of TAVI, due to its less invasive nature.[45,52] Long-term durability of these procedures has been carefully studied, although no difference has been reported in five-year outcomes between transcatheter and surgical bioprosthetic aortic valves.[54,55]

Table 1 summarizes the main outcomes of TAVI of clinical trials. Overall and individual analyses showed that vascular complication rates, need for pacemaker implantation, and paravalvular regurgitation rates were higher in TAVI than conventional open surgery.[20,56] On the other hand, severe bleeding, acute renal injury and new-onset atrial fibrillation were significantly more frequent in open surgery than TAVI, and no statistically significant difference was seen in cerebrovascular event rates.[19,56]

Table 1 – Outcomes of transcatheter aortic-valve implantation obtained from clinical trials

	Partner A	Partner B	Partner 2	Core Valve	SURTAVI	Partner 3	ELR*
N	348	179	1011	394	879	1000	1403
Age	83.6	83.1	81.5	83.2	79.9	73.3	74
Female (%)	42.2	54.2	45.8	46.4	42.2	32.5	36
STS risk-score (%)	11.8	11.6	5.8 +- 2.1	7.3 +- 3	4.4 +- 1.5	1.9	1.9
Prosthesis	SAPIENTM	SAPIENTM	SAPIENTM XT	Core Valve TM	Core Valve TM (16% Evolut R TM)	SAPIENTM3	Core ValveTM Evolut RTM . Evolut PROTM
30-day mortality (%)	3.4	5	3.9	3.3	2.2	0.4	0.5
30-day stroke (%)	3.8	6.7	5.5	4.9	3.4	0.6	2.1
Moderate-to-severe regurgitation (%)	13.1	15	3.7	10	5.3	0.6	4.3
Pacemaker (%)	4.4	3.4	8.5	19.8	25.9	7.3	19.4
Vascular event (%)	11	16.2	7.9	5.9	6	2.8	3.8
Major bleeding (%)	9.3	16.8	10.4	28.1	12.2	7.7	3.2
Acute renal injury (%)	2.9	1.1	1.3	6	1.7	0.4	0.9
New-onset AF (%)	8.6	0.6	9.1	11.7	12.9	7.0	9.8
One-year mortality (%)	24.3	30.7	12.3	14.2	6.7	1.1	2.4
Two-year mortality (%)	33.9	43.3	16.7	22.2	11.4		
Five-year mortality (%)	67.8	61.8	-	-			

**ELR=Evolut Low Risk Trial; STS: Society of Thoracic Surgery; AF: atrial fibrillation*

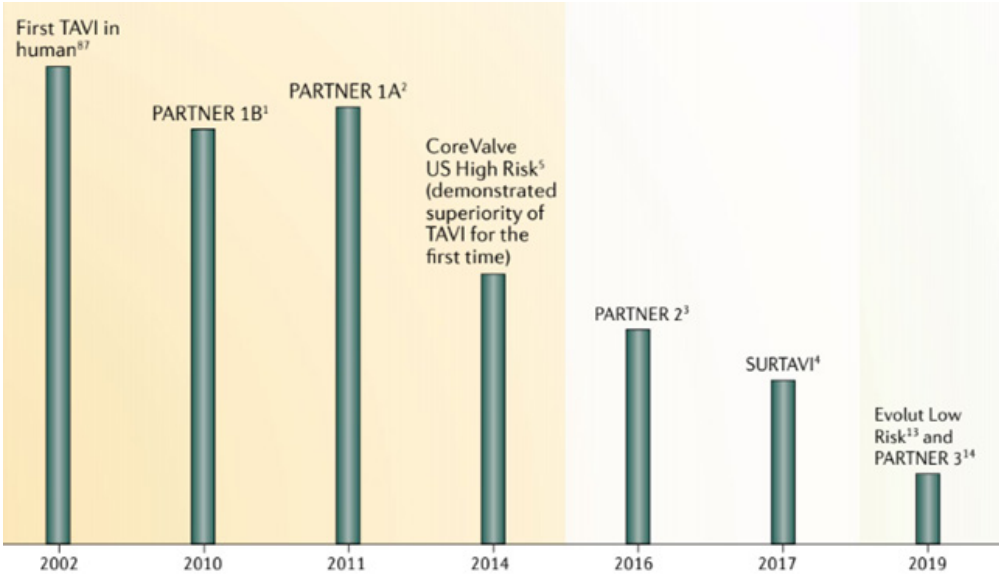

Figure 2 – Chronological sequence of published clinical trials[57]

The decision towards a therapy is made based on clinical, anatomical, and technical aspects that may be considered alone or in combination. Some conditions, such as previous cardiac surgeries, restricted mobility, frailty, chest irradiation sequelae, porcelain aorta, chest deformity, marked scoliosis, and obesity favor the choice of TAVI. On the other hand, open surgery is the preferred procedures in case of unfavorable access for TAVI, suspected endocarditis, short distance between coronary ostia and annulus, ascending aorta aneurysm, aortic or left ventricular thrombus, other valvular dysfunction, coronary artery disease and need for bypass revascularization, and septal hypertrophy.

Procedure

In the periprocedural period, some aspects should be considered without compromising patient's safety. The procedure may be performed in a cath lab instead of a hybrid room. If performed via a transfemoral approach, the presence of a cardiac surgeon is not obligatory, but the professional should be involved in the process and be available in case of complications. The staff should include at least two surgeons, one nurse and one X-ray technician. The presence of an echocardiographist, anaesthesiologist, cardiac surgeon, vascular surgeon and perfusionist in the catheterization laboratory is not an absolute requirement, but they should be involved in selected and more complex cases or in those at the initial phase of the learning curve.[58]

The first implants were conducted via an antegrade transseptal approach. Over the years, this approach has been abandoned in favor of the transfemoral approach, which is the method of choice, in addition to alternative routes (transapical, trans-aortic, trans-subclavian, transcarotid). An accurate analysis, guided by computed tomography coronary angiography, is essential for the selection of the access route, considering vessel anatomy, the profile and size of the device.[59]

Immediately after the procedure, all patients should be monitored in the hybrid operating room for at least 10-15 minutes, with special attention to hemodynamics and cardiac rhythm. Then, the patients should be transferred to a coronary care unit or to a cardiac telemetry unit, according to local protocols. Patients' clinical status, especially concerning the procedural outcomes, echocardiogram, and laboratory results, should be carefully evaluated. Mobilization should be prescribed a few hour later, in the absence of vascular access problems (e.g. hematoma or bleeding) and removal of temporary pacemaker. Patients without complications (or those whose complications were successfully managed) can be discharged on the next day.[58]

The efforts to accelerate recovery and mobilization require shorter hospitalization time and minimize unnecessary use of resources. Hospital discharge within 24-72 hours after the procedure seemed not to affect the safety of the procedure, as reported in previous studies.[60-62] A clinical protocol of early discharge tested at low-, medium-, and high-volume TAVI centers showed excellent safety and efficacy outcomes.[63] The most common problems involved in a prolonged hospitalization include conduction disturbances, bleeding and acute renal injury. Monitoring of atrioventricular block is by far the most important measure.

The cost-benefit relationship of the minimalist approach in TAVI has not been well defined. In a small U.S. series of 142 patients (n=70 undergoing minimalistic transfemoral TAVI and n=72 undergoing standard transfemoral TAVI), it was demonstrated that that the minimalistic strategy decreased the cost of TAVI (USD 2,869 estimate) and could be used frequently to prevent costs associated with hybrid operating rooms and anesthesia.[64]

Although TAVI is a complex procedure, important advances toward its simplification have been made. In many centers, the minimalist approach has been routinely performed and shown to be as safe and effective as the standard approach.

Complications

Despite technical advances in the development of implantation techniques and devices, in addition to more possible procedures and indications, potential complications may occur and do require consideration and prevention. The first complications of TAVI were peri and post-procedural neurological, conduction disturbances, and events vascular complications, peri neurological events, and perivalvular regurgitation.[15,16] More recently, despite their low incidence, increasing interest has been devoted to aortic rupture and coronary occlusion due to their potential and severe impact.[34,65] However, other concerns have concomitantly emerged regarding durability and risk of thrombosis, since procedures have been performed in younger and at lower-risk patients.[66-68]

Therefore, the fact that TAVI is indicated for younger patients today make mandatory the recognition and

monitoring of possible complications related to durability of the procedure, since these patients have higher life expectancy, and calcium metabolism that accelerates leaf calcification compared with those patients for whom TAVI was first indicated. Failure of the procedure may be related to deterioration (consequent to calcification, pannus or thrombus formation) or intraprosthetic regurgitation (e.g. reduced leaflet mobility and endocarditis).[69]

No significant increase in average gradient or structural valve deterioration was reported in the five-year follow-up in the PARTNER study. Results of follow-up of up to five years have also been described in other three studies,[70-72] two of them did not raise important issues regarding durability, with stable transprosthetic pressure gradient over time and dysfunction rates of 3.4% and 4.2%, respectively, based on different definitions.

With respect to late durability, some studies have presented data from 7-8 year-follow-up using a SAPIEN (Edwards Lifesciences) or a CoreValve device. Three different studies conducted in one center reported stable transprosthetic gradient over time, and severe prosthetic dysfunction rates of 2.4%, 3.2% and 3,6%.[73-75] Holy et al.,[76] evaluated long-term results of 152 consecutive patients undergoing TAVI with the self-expanding CoreValve between 2001 and 2011.[76] Echocardiographic follow-up at 6.3±1.0 years (5.0-8.9 years) was 88% complete (60 out of 68 survivors beyond five years). No evidence of structural valve deterioration was reported, and five patients (3.3%) had undergone redo TAVI or surgery due to paravalvular leakage. Deutsch et al. reported an overall crude cumulative incidence of structural valve deterioration of 14.9% (CoreValve 11.8% vs. SAPIEN 22.6%; p=0.01) at seven years.[77]

Vascular complications such as bleeding, need for transfusion and hemodynamic instability were initially identified as major limitations of TAVI. However, with improvement of the devices and in patient selection, and accumulated experience, these complications have become rarer. Today, the mean complications are minor bleeding and direct damage such as dissection and occlusion of the vessel.[78]

Cerebrovascular events are associated with high morbidity and mortality. A meta-analysis of 64 studies involving 72,318 patients found an incidence of cerebrovascular events of 3.3% within 30 days post-TAVI.[79] Nearly half of the events occurred 24 hours following the procedure and the others attributed to catheter manipulation via aortic valve, balloon dilatation and prosthesis release. Neurological events clinically manifest as focal signs or even silent ischemia, detected by brain magnetic resonance imaging.[16,80] More recent studies have reported a favorable trend of decrease in the incidence of events to nearly 1.2% at one year, particularly with improvement of devices and growing experience.[21] In addition, protective devices have been developed to filter or deflect debris from cerebral vasculature.

The most common conduction disturbances are left bundle branch block and total atrioventricular block.[81] Efforts have been made to prevent these complications, as they are associated with lower recovery of left ventricular function, greater need for pacemaker and rehospitalizations, and longer hospital stay. The assessment of valvular anatomy and selection of the most appropriate prosthesis not always minimize these effects.

Paravalvular leak may occur and has been more commonly associated with TAVI and standard surgery.[16,82] The incidence of moderate-to-severe leakage in first generation devices were reported in 12-21% of the cases.[82] This deserves special attention and prevention, due to its relationship with high morbidity and mortality.[83] The three mechanisms involved are incomplete apposition of TAVI to the valve annulus because of severe calcification, undersizing and poor positioning of the prosthesis. In more recent series, the incidence of leakage significantly decreased, as mentioned previously. This is explained by a more precise evaluation of the valve annulus before surgery, by computed tomography angiography, ability to recapture, reposition and finely adjust the valve. Other improvements include sealing skirts or an additional external sealing layer to fill the gaps between the transcatheter prosthesis and the aortic annulus.[84]

Thrombosis of bioprostheses can occur by two different mechanisms: first, as symptomatic, obstructive valve thrombosis, with increased transvalvular gradient and reduced effectiveness of the orifice measured by echocardiography. This is a rare event, reported in approximately 0.5% of the patients undergoing TAVI.[85,86] Second, as asymptomatic, subclinical valve thrombosis, with thickening and reduced motion of prosthetic valve leaflets detected by computed tomography, with normal transvalvular gradients at transthoracic echocardiography. This has been more commonly reported patients treated via a percutaneous approach., with an incidence varying form 5% to 40% in patients with TAVI.[86] The RESOLVE and SAVORY,[68] an observational study on subclinical leaflet thrombosis has reported an incidence of 4% of

Table 2 – Composite endpoints defined by the VARC2[88]

Device success
Absence of periprocedural mortality AND
Correct anatomical positioning AND
Intended performance of the prosthesis (no prosthesis-patient mismatch and mean aortic valve gradient<20 mm Hg or peak velocity<3 m/s, and no moderate-to-severe aortic valve regurgitation)
Early safety
All-cause mortality
Stroke
Major bleeding
Acute kidney injury
Coronary artery obstruction requiring intervention
Major vascular complication
Valve-related dysfunction requiring repeat procedure (BAV, TAVI, SAVR)
Clinical efficacy
All-cause mortality
Stroke
Requiring hospitalizations for valve dysfunction or heart failure-related symptoms
NYHA class III or IV
Valve dysfunction (mean aortic valve gradient ≥ 20 mm Hg, EOA ≤ 0.9–1.1 cm2 and/or DVI<0. 35 m/s, and/or moderate-to-severe valve regurgitation)
Long-term safety
Structural valve deterioration
Valve dysfunction (mean aortic valve gradient ≥20 mm Hg, EOA ≤0.9-1.1 cm2 and/or DVI<0.35 m/s, and/or moderate-to-severe valve regurgitation
Requiring repeat procedure (TAVI or SAVR)
Prosthetic valve endocarditis
Prosthetic valve thrombosis
Thromboembolic events (e.g., stroke)
Bleeding, unless clearly unrelated to valve therapy (eg, trauma)

BAV: Balloon aortic valvuloplasty; TAVI: transcatheter aortic valve implantation; SAVR: surgical aortic valve replacement

this event in 138 patients undergoing standard surgery and 13% in 752 patients undergoing TAVI. Subclinical leaflet thrombosis was also less frequent in patients receiving anticoagulants, compared with those in double antiplatelet therapy (4% vs. 15%; p< 0.0001).[68] An incomplete frame expansion of TAVI, as well its metallic nature seem to be two of the main risk factors for subclinical thrombosis.[84]

Endocarditis, although less common after valve replacement surgery (0.5-3.1%;[58] 1-6%[84,87]), can be a severe complication. In a recent multicenter registry, including 250 post-TAVI patients, in-hospital mortality was 36% and two-year mortality 66.7%. [61] Younger age, male sex, family history of diabetes mellitus, and moderate-to-severe residual aortic regurgitation were significantly associated with increased risk of infectious endocarditis.[61] The most common causative agents of prosthetic valve endocarditis were Staphylococci (31.5%), Enterococcus (20%) and Streptococcus (14%).[87]

Although the possibility of late failure of transcatheter aortic valve replacement is regarded as a major concern, preliminary observations revealed that, in contrast to reoperation following the conventional surgical procedure, which is technically challenging with a significant risk of morbidity and mortality, the redo TAVI seems to be safe and effective.[62]

In summary, understanding the complications is extremely important for the planning of the procedure. The association of these complications with patients' profile has become more and more important, since, as evidence has shown, indication of TAVI has been expanded for younger and at lower-risk patients.

With the aim of defining endpoints that reflect clinical efficacy of the device and patients' safety, the Valve Academic Research Consortium (VARC) consensus was created in 2011. One year later,

the document was updated, with the objective to broaden the understanding of risk stratification of the patient and selection of the cases, and to revise the endpoints for the development of clinical trials. Thus, the so-called VARC-2 recommends the inclusion of a time-related valve safety, which combines valve dysfunction, endocarditis, and thrombotic complications. Table 2 describes the composite endpoints defined in this document.[88]

Antithrombotic Therapy

Current guidelines are based mainly on specialists' opinions and recommend double antiplatelet therapy in the first six months, followed by low dose aspiring throughout life. For patients with atrial fibrillation (AF), the use of vitamin k antagonists is recommended.[89,90]

AF is a predictor of stroke and systemic embolism and can be found in up to one third of patients with indications for TAVI. Due to the need for anticoagulation, patients undergoing TAVI are at increased risk for hemorrhagic events after the procedure and during follow-up.[91] In case of hemorrhagic complications in patients with concomitant AF, mortality at one year after TAVI increases to 50%.[92] Therefore, evaluation of the ideal antithrombotic therapy in this population should be carefully considered.

The use of novel oral anticoagulants (NOACs) in patients undergoing TAVI, without formal indication for anticoagulant therapy is still under investigation. In the recent GALILEO study,[93] the use of rivaroxaban at a dose of 10 mg daily (combined with aspirin at a dose of 75 to 100 mg) was tested in 1,644 after successful TAVI. A higher incidence of death, thromboembolic complications and life-threatening bleeding was observed in the rivaroxaban group compared with the antiplatelet group. Additional studies evaluating the effects of other NOAC are ongoing, including the ATLANTIS and the ENVISAGE-TAVI AF, and their results are expected to be published soon.

Guidelines

According to the American Heart Association (AHA), American College of Cardiology (ACC) and Society of Thoracic Surgery (STS), indications for TAVI have changed to high-risk patients (class I; level of evidence A) and as alternative therapy for patients at intermediate risk (class IIa; level of evidence B).[94] European guidelines have followed the same trend, corroborating the indication for patients at intermediate or high surgical risk (STS score or EuroSCORE > 4%) and mainly for elderly, inoperable patients (class I; level of evidence B).[43]

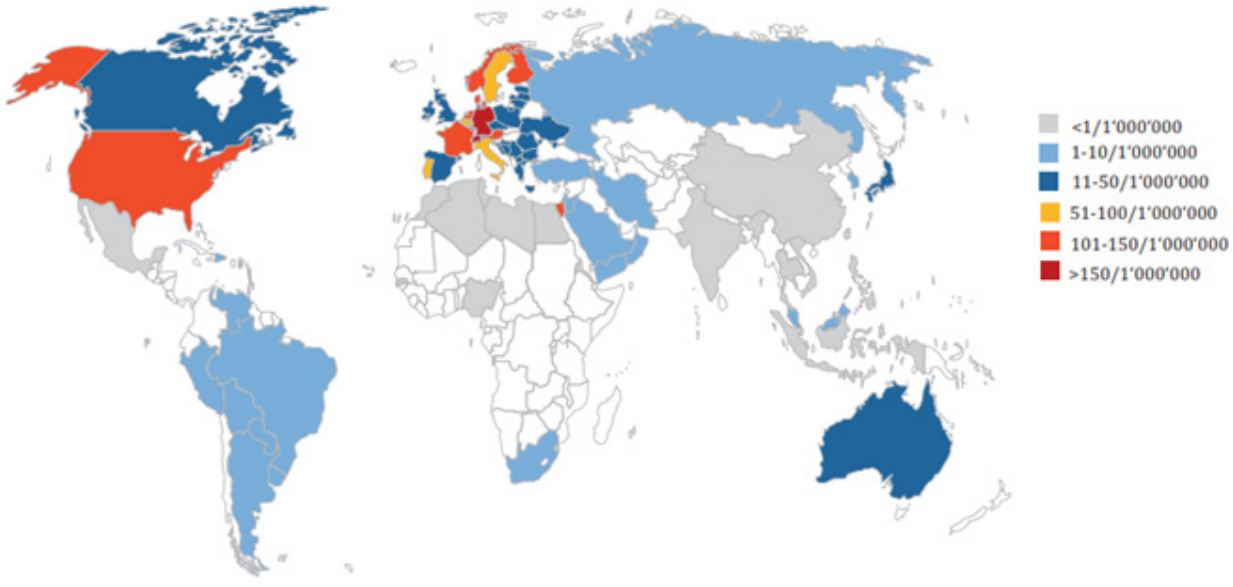

Figure 3 – Geographic dispersion of transcatheter aortic-valve implantation in the world. The legend indicates the number of procedures per 1,000,000 inhabitants.[95]

Future Perspectives

Today, the greatest challenges are related to TAVI durability, and several limitations prevent a more robust evaluation. First, TAVI is a relatively young technology, since its use started to expand only after the procedure received the CE mark in 2007 and was approved by the US Food and Drug Administration in 2011. This means that there may be few data available on valve durability during periods longer than 10 years. Second, currently available data from five-year follow-up studies a related to first generation devices, implanted by relative inexperienced operators, with higher rates of improper positioning of the valve and size-related problems. Finally, the main limitation of durability over time is older age of patients, multiple comorbidities and the high risk due to lower life expectancy, and consequently a small number of patients (generally less than 50% of initial population) in the long-term follow-up.

Another important issue is the optimization of antithrombotic therapy after device implantation. As previously mentioned, ongoing studies are expected to be published soon, and can modify or not currently established practices.

Aortic Regurgitation

Data are still limited for analysis of safety and efficacy of TAVI in patients with pure aortic regurgitation. Its application, even in those at high surgical risk is off-label. Most devices that have been approved worldwide are for the treatment of aortic stenosis.

The prevalence of aortic regurgitation increases with age and affects nearly 13% of patients with native left-sided valvular heart disease. The symptoms tended to disappear late in the course of the disease with the onset of left ventricular dilatation and systolic dysfunction. Patients with ejection fraction lower than 30% have an annual mortality risk of 20%.[96]

Based on current European and North American guidelines, a surgical procedure should be considered for patients with moderate or severe symptomatic aortic regurgitation, and reduced left ventricular systolic function (<50%) or severe left ventricular dilatation (left ventricular end-systolic diameter > 50mm, left ventricular end-diastolic diameter > 65-70mm; or left ventricular end-systolic volume >45mL/m^2).[97,98] However, there is a high-risk subgroup of inoperable patients for whom TAVI should be considered.

The main challenge for TAVI procedure is the absence of annular and leaflet calcification, which is required for anchoring and stabilization of the device during its implantation. The lack of calcium, secondary increased systolic volume, and dilation of the aortic root are limitations for proper positioning of the prosthesis and predispose to moderate or severe embolization or regurgitation after the procedure (which are associated with worse clinical outcomes).[99] Migration of the valve may occur in the aorta or deeper in the left ventricle up to several hours post-implantation. Over-dimensioning of the valve has been proposed to reduce the risk of migration – an oversizing of 15-20% has been recommended - no greater than that, to avoid the risk of annular rupture and abnormalities in the conduction system.[100,101]

New generation devices, such as the CoreValve, Evolut R, ACURATE neo, Lotus and Sapien 3, have some resources that make them different from previous devices. Characteristics like ability of retrieval and repositioning in the case of self-expansible, and adaptative sealing skirt of the Sapien 3 and Lotus, enable a more controlled and predictable TAVI.[102,103] The authors reported the safety and early clinical efficacy of TAVI in 254 patients from 46 centers. The authors reported the device success, defined according to the VARC-2 criteria, of 67%.[104] Yoon et al.,[105] studied 331 patients from 40 centers, and reported a device success of 74.3%.[105]

Author Contributions

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Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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REVIEW ARTICLE

Translational Approach for Percutaneous Interventions for the Treatment of Cardiac Arrhythmias

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Abstract

New translational concepts on cellular and tissue substrate of cardiac arrhythmias have been responsible for the development of non-pharmacological interventions, with important achievements compared to the conventional approach with antiarrhythmic drugs. In addition, the increasing knowledge of anatomical and electrophysiological studies, sophisticated mapping methods, special catheters, and controlled clinical trials have favored the progression of ablation of tachyarrhythmias, particularly of ventricular tachyarrhythmias and atrial fibrillation.

Introduction

Cardiac arrhythmias and conduction disturbances occur in any region of the heart and are caused by critical changes in the electrical activity of myocytes.[1] Electrophysiological studies have been developed in the last fifty years, with translational clinical and experimental models, and favored the development of non-pharmacological interventions for the treatment of arrhythmias. Sophisticated mapping methods, special catheters, and new energy sources have introduced new techniques for ablation of ventricular tachyarrhythmias and atrial fibrillation (AF).

In the 1960s, since the introduction of direct current defibrillators by Lown, other contributions have provided support for the continued development of techniques for the percutaneous treatment of arrhythmias, including the recording of His bundle activity by Scherlag et al.,[2] the electrical stimulation of the heart by Wellens,[3] anatomical surgical ablation of the accessory tracts by Cobb et al.,[4] and, finally, the catheter-induced ablation with initial direct current by Scheinman et al.,[5]

During this same period, the Cardiac Arrhythmia Suppression Trial[6] demonstrated that flecainide and encainide, two potent antiarrhythmic drugs, suppressed ventricular arrhythmias but, paradoxically, increased death in patients, thereby changing completely the paradigm of antiarrhythmic drug therapy. Additionally, no effective drugs for atrial arrhythmias acting on specific channels such as the potassium channel, were available. Then, the introduction in the 1990s of radiofrequency-induced ablation techniques in the United States, Europe[7] and in Brazil[8] followed pathophysiological and translational concepts.

Biophysical Concepts

Catheter interventions to destroy the arrhythmogenic tissues have mostly used heating with direct current, microwave, ultrasound, laser, and radiofrequency. The most used form of energy has been radiofrequency, a form of alternating electric current of 500–1000 kHz. When unipolar energy is applied between the distal pole of the catheter and a surface, it affects the cell membrane, cytoskeleton, nucleus, and cellular metabolism, including the microvascular inflammatory response. After reaching a temperature of 50°C, well-defined and irreversible heating lesions develop because of the sarcolemma lesion and intracellular calcium overload. Temperature monitoring

Keywords

Arrhythmias, Cardiac/physiopathology; Catheter Ablation; Anti-Arrhythmia Agents; Cryosurgery/methods; Translational Medical Research; Atrioventricular Node; Echocardiography/methods; Tomography, X-Ray Computed/methods.

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prevents excessive heating at the catheter tip (which can also be avoided with the use of irrigated catheters), formation of blood clots, and increase in impedance.

Another thermal mechanism is cryoablation, in which pressurized liquid nitrogen is used to freeze and crystallize the structures in contact with a balloon catheter, reversibly (up to -40°C) or irreversibly (<-40°C) compromising the cardiac structures that are in direct contact with the freezing source. More recently, pulse field ablation, a unique investigational tissue-selective nonthermal cardiac ablation modality that creates nanopores with tissue electroporation, may change the future of ablation in the coming years.

Anatomical and Electrophysiological Concepts

Automatism

Myocyte depolarization is dependent on intracellular and extracellular ion concentrations and mediated mainly by the influx/efflux of sodium and potassium. This ion movement is controlled by multiple channels (Figure 1A) and normally, automatically depolarized. These automatic cells act in heart rate control, from structures hierarchically arranged preferably in the sinus node, atrioventricular node (AVN) and in the His-Purkinje (HP) system.

Through automatism or triggered activity (early or late depolarizations), there is an increased depolarization of cells, with faster rhythms in areas like sinus node, AV node and HP system, in the right heart (junction with the superior vena cava, terminal ridge, and right ventricular outflow tract [RVOT]) or in the left heart (pulmonary veins, left vena cava, left atrial appendage, left ventricular outflow tract [LVOT], and papillary muscles) (Figure 1B).

The ionic basis of late post-depolarization is related to the overload of calcium in the myoplasma and sarcoplasmic reticulum, and to the secondary release of the calcium ion after repolarization, especially in the presence of catecholamines or cyclic AMP. Generally, these are focal rhythms, and their early activation allows establishing the source focus and mapping for the arrhythmia ablation, if percutaneously accessible.

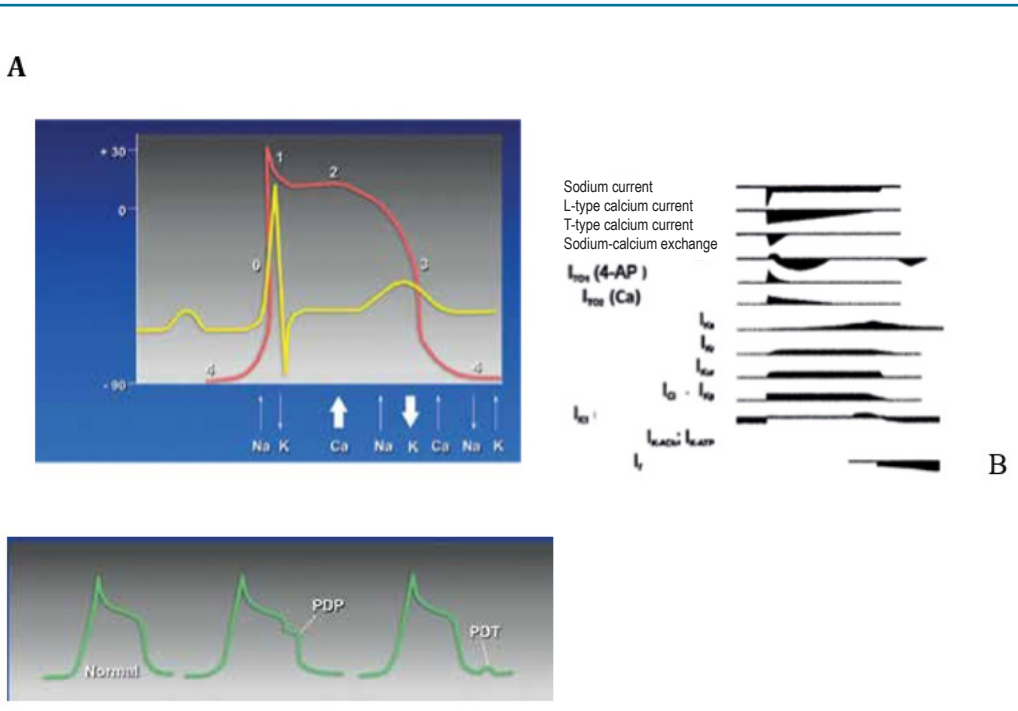

Figure 1 – (A) Ionic currents determining the action potential: inward currents are directed from outside to inside the cell; and outward currents come from within the cell and are directed to the extracellular environment; (B) Automatic cells, with oscillations in their action potential by early and late ionic fluxes PDP: early post-depolarizations, PDT: late post-depolarizations.

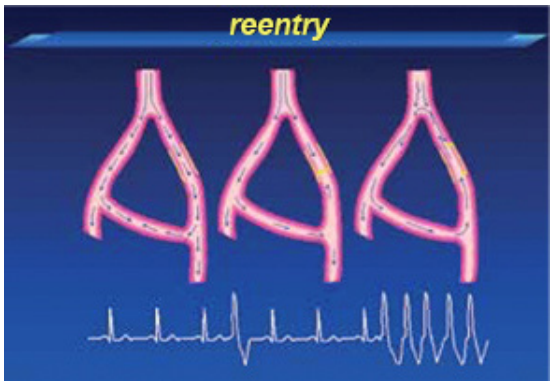

Figure 2 – (A) Tissue with a structural or functional change in conduction without impairing passage in the stimulus under normal conditions. (B) In the presence of an ectopia, there is a bidirectional block. (C) During a precocious ectopia, there is a unidirectional anterograde block and, due to the delayed conduction, there is time to enable retrograde activation and triggering of arrhythmia.

Reentry

In the presence of conduction abnormalities, the activated electric current flows through tissues with different conduction and refractory properties. Thus, it is possible that a stimulus conduction is perpetuated by its passage through an adjacent tissue that functions as a conduction circuit with heterogeneous refractory periods, unlike in normal tissue. This phenomenon (Figure 2) of reentry can be reproduced in the laboratory as nodal, atrioventricular (AV), and ventricular monomorphic tachyarrhythmias, which may be related to normal or pathological tissues, the latter being represented by scars in the atria and ventricles, due to ischemia or degenerative processes.

The most frequent sustained arrhythmias with reentrant mechanisms were the first to be treated with catheter ablation, notably nodal, AV and ventricular reentrant tachycardia, which will be described below. Subsequently, automatic arrhythmias were also managed using this technique.

Atrioventricular Nodal Reentrant Tachycardias (AVNRT)

The AV node is the natural filter to slow the conduction of the impulse through the atrioventricular junction, ensuring the physiological contractile sequence and protection of the ventricle from fast atrial rhythms such as AF. This slower conduction velocity is determined by the small diameters of the nodal myocytes, the interposition of connective tissue, and, mostly, by the failure of continuity determined by the connexins. Thus, optical, histological mapping, and immunological assays, along with action potential recording, can detect the coexistence of rapid (transitional tissue) and slow (lower nodal extensions) nodal pathways, marked by high and low expression of the connexins Cx40 and Cx43, respectively. In 20% of individuals, slower pathways (Figure 3) with a short refractory period are found in the vicinity of the AVN and may, in special circumstances, trigger AVNRT.

AVN reentry can occur because of functional differences in groups of cells that compose the AV node. There are some evidences of the presence of two major slow pathways participating in AVNRT: right inferior extensions (RIE) and left inferior extensions (LIE), both of which connecting the right atrium to the left atrium through the proximal coronary sinus (Figure 4). Both RIE and LIE can participate in AVNRT and serve as either the antegrade or retrograde limb of the reentrant circuit.

The positioning of catheters and ablation of the slow pathway of patients with AVNRT is generally simple, with a success rate of 95%; it consists of the radioscopic topographic localization (Figure 3D) and electrophysiological evaluation of the potential of the slow pathway for application of radiofrequency energy (30-50 W, 1 min, temperature 40-50°C). Complications are related to poor vascular access (1% of deep venous thrombosis) and proximity of the AVN (1% of total AV block), with a one-year recurrence of 5%.

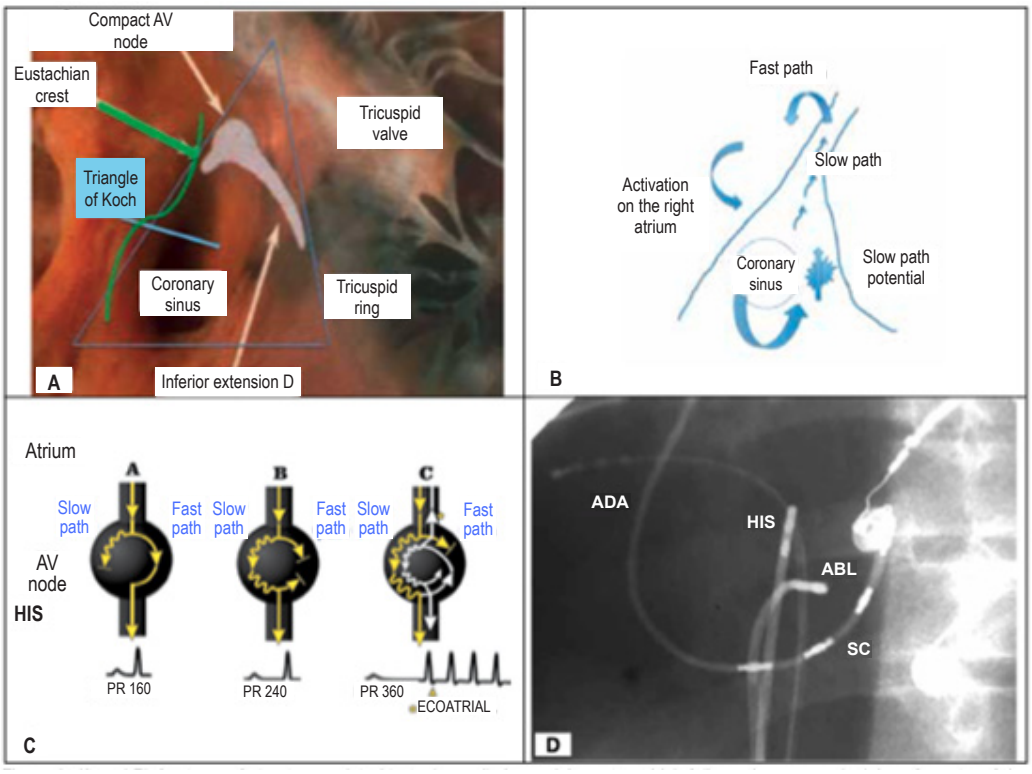

Figure 3 – (A and B) Anatomy of structures related to atrioventricular nodal reentry tachycardia, which follows the same principles of reentry of the electrocardiographic (C) identification of saltatory conduction through the atrioventricular node that precedes tachycardia. (D) Radiographic images of catheters used in the left anterior oblique projection and their positions.
AV: atrioventricular, HRA: high right atrium, H: His, CS: coronary sinus, ABL: ablation catheter. RIE: Right inferior extension, LIE: Left inferior extension. Modified from Inoue.[10]

Atrioventricular Reentrant Tachycardias (AVRT)

The accessory pathway consists of bundles of myocardial cells inserted freely along the mitral annulus (60%), tricuspid (15%), or the right or left septal side of these valves (25%). Rarely, the accessory pathways emerge directly from the atria (atriofascicular), AVN (nodofascicular, nodoventricular), or the His bundle (His-fascicular). They may be multiple (13% of the cases) and, in the presence of Ebstein's disease, accessory pathways are 4-fold more frequent (52%). They may also present decremental conduction such as in the Mahaim fibers, with anterograde conduction, behaving functionally as a duplicated His bundle in the lateral region of the tricuspid ring and inserted distally in the right HP system, near the apex of the right ventricle. Finally, there are also postero-septal fibers with exclusively retrograde decremental conduction, generating Coumel-type tachycardia that, because of its incessantness, can lead to the development of tachycardiomyopathy.

Radiological and electrophysiological techniques seek to define the insertion of pathways along the AV ring, with similar success and clinical outcome of ablation of accessory pathways to those of AVNRTs. There is a greater technical difficulty in the epicardial ablation of pathways, multiple pathways, or when the accessory pathways are associated with complex heart diseases.

Some muscle fibers that involve the coronary sinus and its tributary veins can function as a connecting muscle bridge between atria and ventricles. When there is a need for ablation in this location of limited blood flow, irrigation at the catheter tip is performed; in this way, the lesion will be formed without limiting the increase of impedance and temperature. The proximity of the arteries (mainly the posterior descending artery) with the branches of the venous sinus requires anatomical definition and special care during ablation.

Depending on the anatomical peculiarities of anomalous bundles, sheaths can be used to stabilize the mapping of larger rings such as the tricuspid, for the transeptal access in the left routes and pericardial access for epicardial routes.

Ventricular Reentrant Tachycardias

The scar substrate of sustained ventricular tachycardias (VTs) after myocardial infarction has provided a reproducible reentry model, intensely studied by contemporary electrophysiology. The scar region is composed not only of a dense scar but also of surrounding tissues with myocardial fibrils inserted into the scar, characterized by alterations in CX43, decreased intercellular coupling, slow conduction, and predisposition to reentrant VT. Adaptive changes in the sympathetic and parasympathetic nervous system with increased efferences and decreased neuronal afference of the infarcted area result in greater heterogeneity and multiplicity of the arrhythmogenic substrate circuits, identified by fractional potentials, late potentials, and abnormal localized ventricular activity (Figure 4).

Structural remodeling of the myocardium is associated with the appearance of myofibroblasts, fundamental cells, and the translational biological basis of the VT substrate. Recent animal studies showed that after 6 weeks of experimental infarction, the isthmus of the VT has a very high density of myofibroblasts (an increase of 5 times) and increased vascularity (an increase of 1.7 times) in the border of scars, due to the increase in cellular recruitment or by pro-angiogenic factors of these same myofibroblastic cells. There are also cell bridges between the myofibroblasts and the remaining cardiomyocytes, with organized heterogeneity at the edges of the scar and isolated by collagen septa, with altered tissue heterogeneity and resistance due to the non-uniform heterocellular coupling between the cardiomyocytes.[11] These experimental findings were based on the relationship between electrical heterogeneity and conduction abnormalities and the inducibility of ventricular arrhythmias.

The presence of a stable substrate, characterized by a scar with viable myocardial tissue in its interior, establishes the conditions for the reentry mechanism and, with it, the reproduction of human monomorphic ventricular tachycardia (VT) in the laboratory.

The possibility of mapping of sustained VTs (SVTs) by using electrophysiological techniques has defined locations, with a good correlation with surface electrocardiogram, offering the possibility of non-invasive diagnosis of their origin (Figure 5).

The substrate of SVTs consists of regions of abnormal myocardium where the ventricular muscle is replaced by fibrous tissue, creating regions of slow conduction and the occurrence of reentry, characterized regionally by low local electrical activity and segmental contraction deficit. The response of these regions to programmed electrical stimulation, allowing the reproduction in laboratory of clinical SVT in patients with previous myocardial infarction, has been one of the most important translational milestones for the understanding of the arrhythmogenic mechanisms of modern electrophysiology. Subsequently, the advent of radiofrequency as an energy source enhanced the accuracy of cardiac electrophysiological mapping techniques, increasing the knowledge of important pathophysiologic bases of arrhythmogenesis.

In these patients with heart disease and monomorphic SVTs, the more frequent presence of reentrant macro circuits facilitates the investigation of critical locations for the maintenance of these arrhythmias in the endocardium, epicardium, or intramural region of the ventricles. These circuits are usually made of scars with residual surviving myocytes, constituting true conducting channels (Figure 6). These channels, called isthmuses, are complex structures that form non-excitable anatomical (scar, valve annulus) or functional (blockage of conduction during tachycardia) barriers, that slow the conduction of the electric impulse, thereby preventing wave front penetration and perpetuation of SVTs.

In addition to characterization of the circuits, electrophysiological techniques have enabled the localization and non-pharmacological treatment of SVTs, which has advanced with electroanatomic mapping techniques, towards a more accurate localization of the arrhythmogenic circuits (Figure 7).

The propagation of the electrical impulse to ventricular endocardium is dependent of the high conduction velocity of the Purkinje system. When tachycardia originates from the epicardium, there is slow conduction, longer duration of the QRS complex , absence of initial R and presence of pseudo-delta waves with intrinsicoid deflection in the leads related to the origin of the VT (Figure 8).

It has been emphasized that epicardial ventricular tachycardia is more frequent in cardiomyopathies, mainly in chagasic cardiopathy, accounting for >50% of the cases.

Figure 4 – Surface lead (V6) and ablation catheter electrogram.Fragmented and late potentials in sinus rhythm of the arrythmogenic substrate in patients with sustained ventricular tachycardia, who underwent radiofrequency ablation.

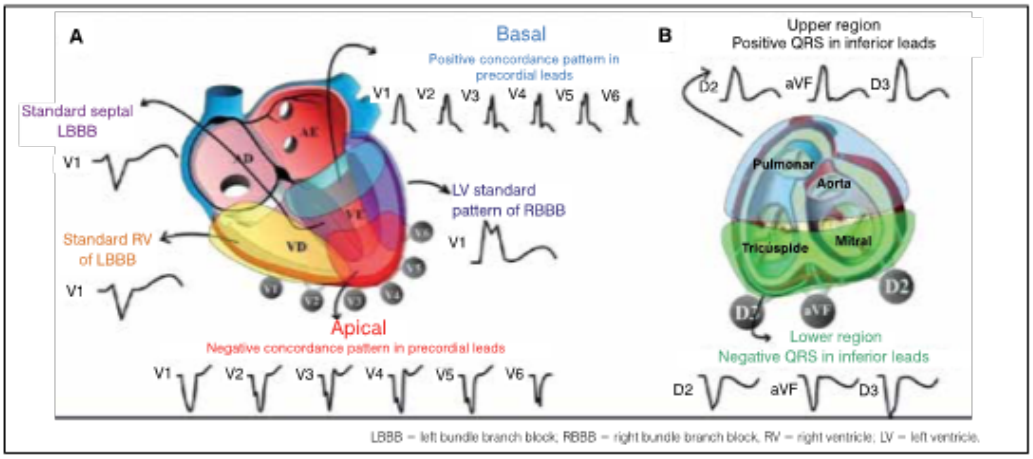

Figure 5 – (A) Sagittal and (B) transverse section of the heart. (A) Complete left bundle-branch block (LBBB) ventricular tachycardia suggests a RV (right ventricular) origin, comprising Right ventricular outflow tract tachycardia (RVOT) .The V3 and V4 leads can characterize the basal and apical left ventricular (LV) regions and, by the vectorial result in the electrocardigram, differentiate the basal (predominant R waves) from the apical (prdominant S waves) origins.

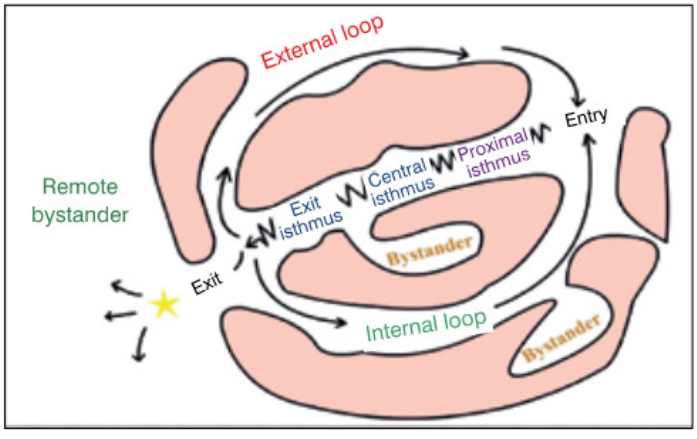

Figure 6 – Reentry models in a scheme represented by pink areas of non-conducting fibrosis, surrounded by viable muscle that allows the passage of the stimulus in the form of "8". "Bystander" areas do not actively participate in the circuit but can communicate with the external stimulus loop that will enter a central channel called "isthmus", a channel of viable tissue, surrounded by barriers of unexcitable tissue, wich aids in the stability and perpetuation of arrhythmia. This mechanism forms the basis for "reentry", a continuous and circular process of wavefront propagation, wich returns and reactivates its place of origin.

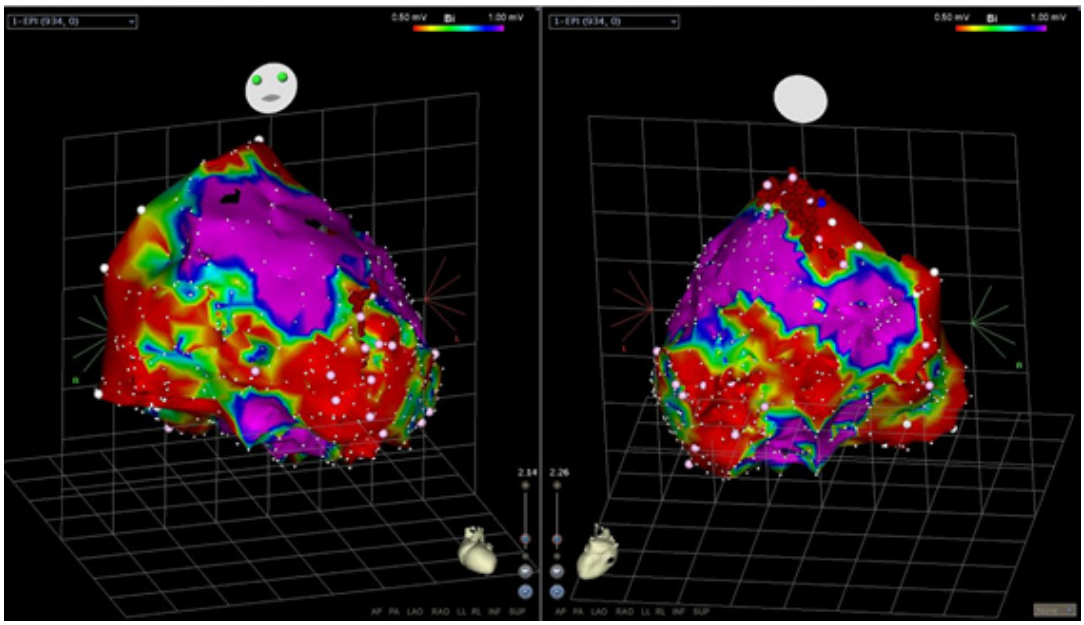

Figure 7 – Electroanatomic mapping of the heart in anterior and posterior views showing regions of low voltage (red), which, combined with conventional electrophysiological techniques, define the location for ablation (red points) in the left ventricular epicardium.

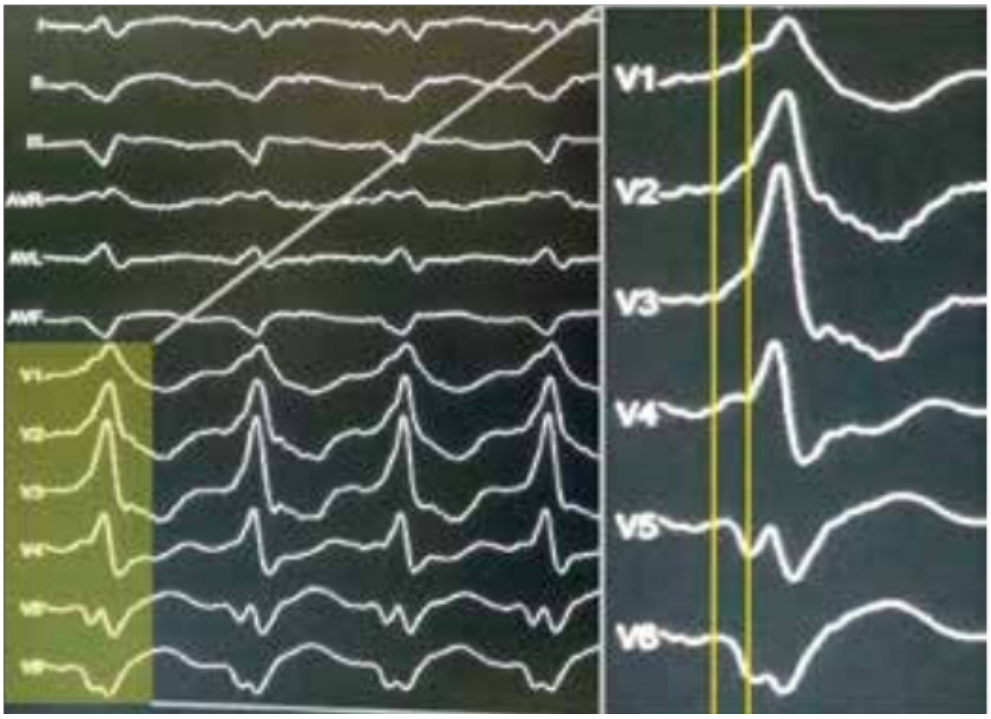

Figure 8 – Electrocardiogram of a patient with sustained ventricular tachycardia with an epicardial focus, showing the pseudo-delta waves (between yellow lines in precordial leads V1 to V6) originated by the slow conduction of epicardial activation

Ventricular Arrhythmias and The His Purkinje (HP) System

The HP system consists of specialized fibers insulated from the ventricular myocardium until their peripheral arborization into muscle. In the right ventricle, they present with a single branch and in the left ventricle with two interconnected fascicles, coordinating the electrical conduction from the AVN (atrioventricular node). The HP system has cellular, ionic, and electrophysiological structures that differ from the rest of the conduction system and may lead to ectopic beats or VTs that can be treated by conventional ablation techniques.

Arrhythmias arising from the HP system may explain sudden death and electrical storms in the normal heart. Ectopic activity triggered by the HP system may be found in patients with idiopathic ventricular fibrillation (VF). This information has given rise to the demand for techniques and strategies aiming the elimination of these foci. Opportunistic ablations[12] were indicated in cases where ectopic beats facilitate the mapping and ablation of VF, thereby controlling this delicate and catastrophic clinical situation (Figure 9).

Situations similar to an HP system ectopia were also recognized in cases of VF associated with the presence of moderator band of the right ventricle, long QT syndrome, and early repolarization syndrome.

Focal VTs

The mechanism of focal idiopathic monomorphic VTs may be secondary to automaticity, micro-reentry, or related to the activity of cyclic AMP.[4] Thus, stimulation of beta-adrenergic receptors by catecholamines results in the release of calcium from the sarcoplasmic reticulum and, subsequently, increase of intracellular calcium, delayed afterdepolarizations and triggering of the VTs. These VTs are more often located in the right ventricular outflow tract (RVOT) and the left ventricular outflow tract (LVOT).

RVOT VTs are the most common VTs and are more frequently located in the septum (mainly in the cusps, followed by the aortic mitral continuity) than in the free wall of the right ventricle.

RVOT is positioned to the left and anterior to the LVOT; the pulmonary valve is positioned superior to the aortic valve. A careful placement of electrodes on the anterior region of the thorax allows the electrocardiographic recording of precordial derivations and a differential diagnosis between RVOT VT and LVOT VT (Figure 10). The typical morphology of the QRS complex is a complete left bundle-branch block, with lower axis deviation. R wave transition in precordial derivations suggests left ventricular outflow when it occurs in V2, and occasionally in V3. Anatomical details are important for the success of the procedure, which has been around 90% in published series.[13]

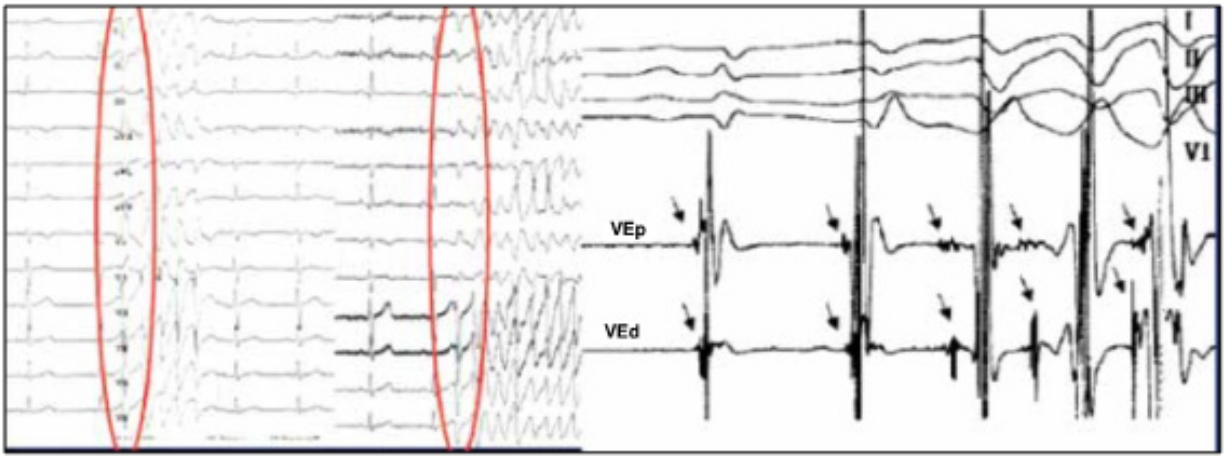

Figure 9 – EPatient with idiopathic ventricular fibrillation related to the His-Purkinje system. Left: Electrocardiogram showing that the morphology of the ventricular extrasystole that triggers polymorphic ventricular tachycardia (VT) is compatible to its origin in the His-Purkinje system of the posterior-inferior left ventricle. Right: Intracardiac signals, surface ECG leads I, II, III and VI, ablation proximal (LVp) and distal (LVd) indicating the potential and the probable region of slow conduction that gives rise to polymorphic VT.

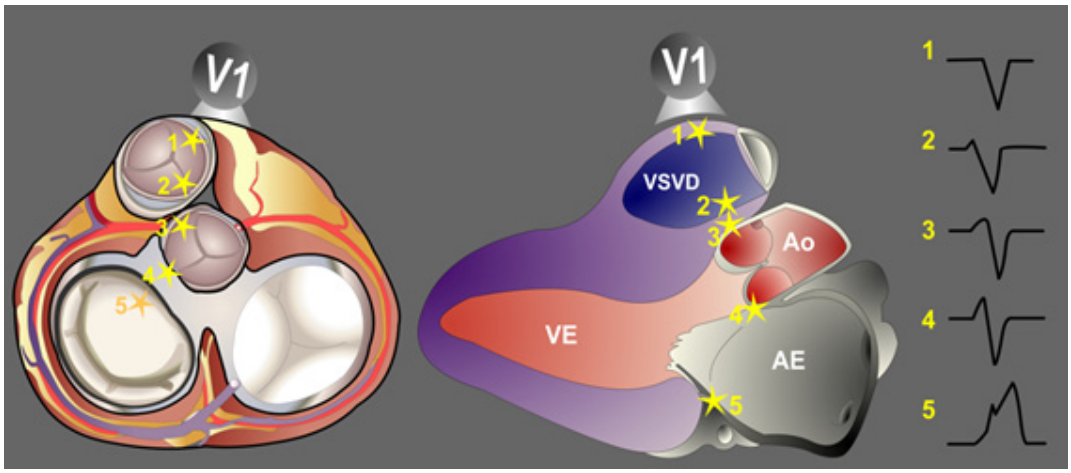

Figure 10 – Transversal and sagittal sections of the heart showing relations between the right ventricular outflow tract, aorta, left atrium, and left ventricle and the morphology of the QRS complex in lead V1, in five possibilities of the origin of ventricular tachycardia. Note the increase in R-wave amplitude when the origin of the ventricular tachycardia and ventricular extrasystoles are more posterior. Modified from Asirvatham.[14]

Imaging During VT Ablation

Imaging modalities for the investigation of patients with VT have expanded. Transthoracic Doppler echocardiography, a simple and routinely performed method, can analyze the thickening of the wall and infer the presence of scarring, although it has limitations in image definition in 10-15% of the cases.[15]

Most VT ablation techniques are related to electroanatomical systems (Carto, Biosense Webster Inc.; NAVX, St Jude Medical; Rhythmia Mapping, Boston Scientific Inc.). Although the big technological leap has allowed the examination of a virtual organ using a catheter, details of scars and myocardial thickness may be incorrectly estimated. The use of cardiac magnetic resonance (CMR) imaging allows endocardial, epicardial, or even intramural delineation of the scar, with a better planning for ablation strategy. Similarly, integration of CMR imaging with electroanatomical mapping (EAM) allows the identification of heterogeneous regions where transmural and scar borders frequently correspond to the isthmus of the reentrant circuits, which are potential targets of ablation.[16-18]

These advances in echocardiography, cardiac computed tomography with multiple detectors, CMR imaging, and EAM can provide integrated hybrid images, far beyond the simple measurement of ejection fraction, with further details of innervation, cardiac metabolism, scar architecture, and electrical activation. Also, these imaging methods have enabled the development of models for proof-of-concept studies to predict not only the arrhythmogenic substrate and characteristics of its circuits, but also future arrhythmic events.[19,20]

Translational Aspects of AF Ablation

It is estimated that 1-2% of the population has AF and, in selected cases, mainly after failure of pharmacological treatment, ablation may be indicated.[21] The perception of AF symptoms is very variable; AF is more frequently asymptomatic in men, in patients with older age, and in those with persistent AF. After ablation, many patients with AF become asymptomatic, hindering the effectiveness of the procedure.

AF Substrate

In addition to cardiomyocytes, vascular cells, nerve cells, and fibrous tissue are present in the atria and in the myocardial sleeves of pulmonary veins with the presence of P-cells, Purkinje cells and transitional cells, normally found in the atrioventricular and sinoatrial node, and in the bundle of His. One hypothesis is that spontaneous depolarization in P-cells may lead to electrical impulses that are propagated to the left atrium through Purkinje cells. Sudden change of fibers direction in pulmonary veins may induce decremental conduction. Therefore, combination of enhanced automaticity, triggered activity and microreentry are related to the mechanisms of pulmonary veins arrhythmogenesis.[22]

A few days after AF, atrial electrical remodeling, action potential shortening, and heterogeneity in refractoriness and conduction velocity occur, which favor the reentry mechanism. After months, interstitial fibrosis occurs, with induction of persistent AF, alteration of expression of ion channels, and suppression of activity of calcium and sodium currents (ICaL and INa and increment of IK1).

For decades, the conceptual mechanistic hypotheses of AF were (a) multiple reentrant waves, (b) automatic foci, and (c) single reentry with fibrillatory conduction. Recently, a series of sophisticated studies (in vitro and in vivo) involving computer simulations, surface mapping, and spherical catheters (basket) has indicated other possible mechanisms, such as automatic activities generating multiple wavefronts, with the presence of rotors or spiral waves, resulting in peripheral fragmentation of the electric activity fronts. Thus, current knowledge indicates that ectopic activities and reentrant phenomena, anchored in complex anatomical structures or atrial fibrotic regions, can generate and maintain AF. Over time, AF, initially related to triggers, becomes more dependent on substrate changes and structural remodeling related to its natural history.[22]

Isoproterenol, a beta-adrenergic agonist, increased the activity in pulmonary veins after infusion of the vessels, increasing production of EAD (early afterdepolarizations) from cardiomyocytes.[22] In contrast, infusion of phenylephrine, known to cause reflex vagal activation, reduced focal activity in the pulmonary veins . The extensive innervation of pulmonary veins by sympathetic and parasympathetic nerves and resulting autonomic tone may play a role in the generation of ectopic activity arising in the pulmonary veins.

The autonomic nervous system, comprised of extrinsic sympathetic and parasympathetic (brain neurons and medulla) and intrinsic (epicardial ganglion plexuses, predominantly parasympathetic) components. The density of nerve bundles is higher in the epicardial region of the antrum, 5 mm from the cavoatrial junction and pulmonary veins. This proximity between nerve structures and myocytes greatly favors local ectopic activity, sympathetic or parasympathetic stimulation with proarrhythmic action in the atrium, and, consequently, shortening of the refractory period and increased repolarization heterogeneity. Although parasympathetic activity is more related to the genesis of AF in patients without heart disease, and sympathetic activity in patients with heart disease, sympathovagal discharge is strongly pro-arrhythmogenic and pro-fibrillatory, often triggering paroxysms of atrial tachycardia and AF. Results of autonomic modulation as an adjunct therapeutic strategy in AF ablation are controversial; there have been favorable[23,24] and unfavorable results,[25,26] in addition to experimental evidence of increased induction of AF with partial vagal denervation. The possible dysfunction of the autonomic nervous system in AF seems to be complex, with individual variations and responses. Due to their localization, ganglionated plexi ablation often occurs during wide circumferential pulmonary vein ablation.

Translational Anatomical Basis For AF Ablation

One of the seminal observations of Haissaguerre et al.,[27] was the behavior of cardiomyocytes, which, when embedded in the pulmonary veins, favor the emergence of automatic foci and micro-reentry activities. Older anatomical studies[28] have shown that the muscle transition between the atria and the veins is geometrically favorable for electrical disturbances and is an important target for AF catheter ablation and mapping (Figure 11). Thus, the elimination of triggers and the arrhythmogenic substrate must be part of the therapeutic strategy for AF, by using catheter ablation that basically involves the confection of circumferential lesions around the right pulmonary veins and arteries, addressing the venoatrial junctions, which are critical locations for the genesis and maintenance of AF by its automatic capacity, micro-reentrant sites, and rich in ganglionic plexus.

Proof-of-concept studies have been consolidated in recent decades, and the role of pulmonary veins in the genesis of AF has been confirmed clinically and experimentally. The selective monitoring of veins (Figure 12) determining the culprit vein, venous tachycardia triggering AF, and the ability of the antral ablation, supported by sophisticated imaging systems, enabled the development of techniques that allow the elimination of clinically important AF in approximately 70–80% of patients.[29]

Non-pulmonary Vein Triggers

Supraventricular tachycardias (nodal reentrant tachycardias or AVRT) may be present in 4% of cases. High doses of isoproterenol (20–30 mcg/min) may reveal other triggering points to be addressed during AF ablation in up to 11% of cases. These are clustered in places which contain cardiomyocytes that can exhibit arrhythmogenic

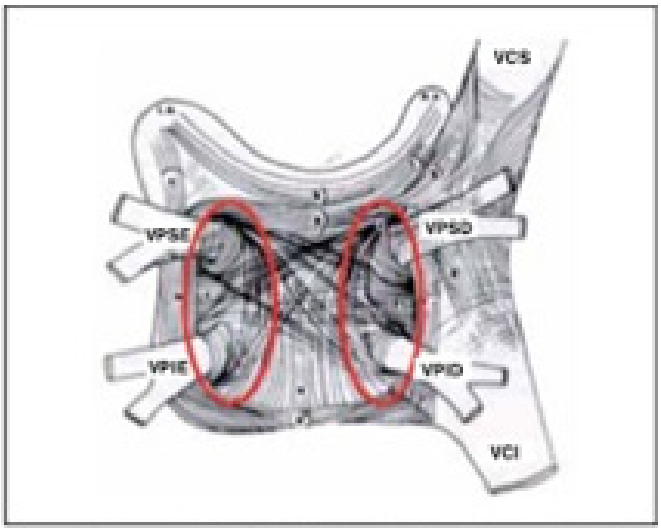

Figure 11 – Posterior view of the left atrium (red circle) showing that the complex mesh of muscle fibers is more entrapped in the pulmonary vein ostium, allowing anisotropic conduction and arrhythmogenic phenomena. Modified from Nathan et al.,[28]

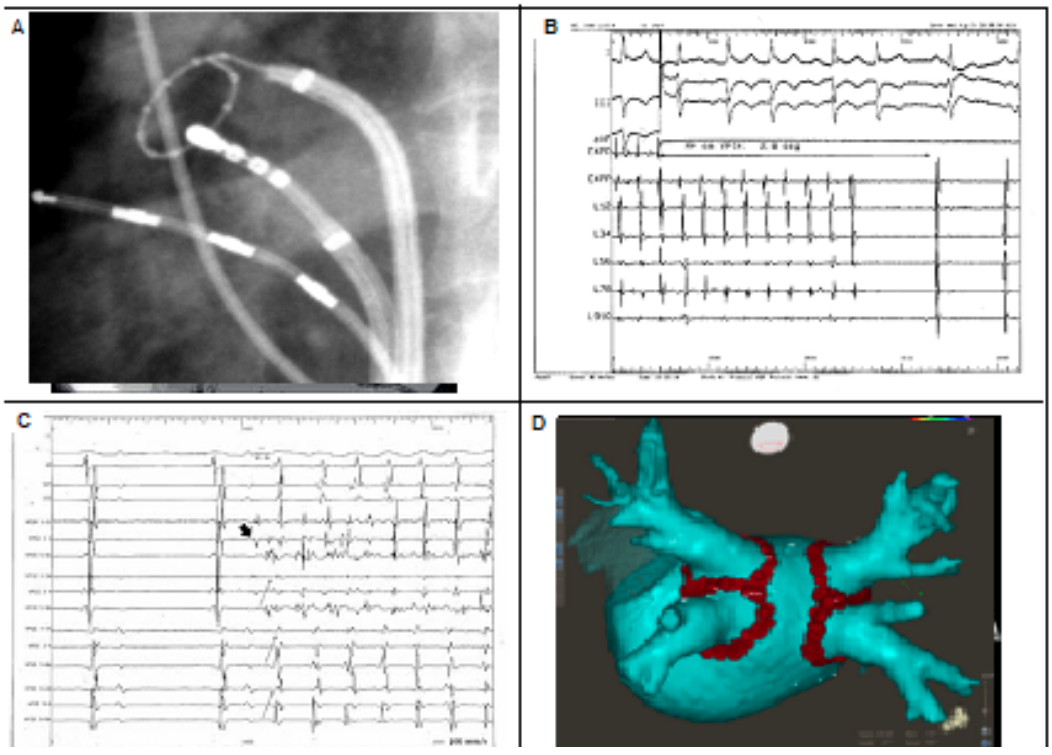

Figure 12 – Images of pulmonary vein ablation for treatment of atrial fibrillation (AF). (A) Posteroanterior radiograph showing the insertion of microcatheters into pulmonary veins to detect the culprit vein. (B) Induction of AF. (C) Resolution of tachycardia and AF control after application of radiofrequency in the left superior pulmonary vein (LPSV) in another patient. (D) Electroanatomic voltage map of the left atrium in anteroposterior view, projected on a 3D model, showing the area of antral ablation and isolation of the pulmonary veins (red dots).

activity: the inferior mitral annulus (MA), the posterior left atrium, the interatrial septum (fossa ovalis limbus), the crista terminalis (CT) and Eustachian ridge, the coronary sinus (CS), the superior vena cava (SVC), the LAA, and the ligament of Marshall (LOM). All these sites have been shown to contain cardiomyocytes that can exhibit arrhythmogenic activity (Figure 13). Enhanced automaticity, triggered activity and localized micro-reentrant circuits are the mechanisms involved in these sites.

Embryonic sinus venous tissue present in the SVC is capable of spontaneous firing. Histological studies have demonstrated the presence of pacemaker cells within the Eustachian ridge, which can be a source of abnormal automaticity. The left atrium wall should be considered as an extension of pulmonary veins with arrhythmogenic potential. The 3 to 5 cm muscular portion of the proximal CS may serve either as a trigger for AF or as a part of a reentrant circuit and, at the level of the valve of Vieussens, triggers from the LOM may be identified. Triggers from inferior vena cava are rare.

Complex Fractionated Electrograms, Fibrosis, Rotors, and Left Atrial Appendage

The success rate of ablation of paroxysmal AF (up to 80%) is not achieved in patients with persistent AF (>1 week) or long-standing (>1 year) persistent atrial fibrillation, probably because of other mechanisms involved.

The need for new percutaneous strategies for the treatment of more chronic cases led to the reproduction of the maze (labyrinthine) surgery , by creating linear lesions in the left atrial roof and in the mitral isthmus and ablation of complex fractionated electrograms. Also, ablation of rotors detected by phase map analysis for the has been suggested for the approach of AF as described in the CONFIRM (Conventional Ablation for Atrial Fibrillation with or without Focal Impulse and Rotor Modulation) study .[30]

Despite the physiopathological basis for persistent AF ablation, the first encouraging results[31,32] were not reproducible and not superior to the conventional, pulmonary vein isolation alone. Clinical and laboratory

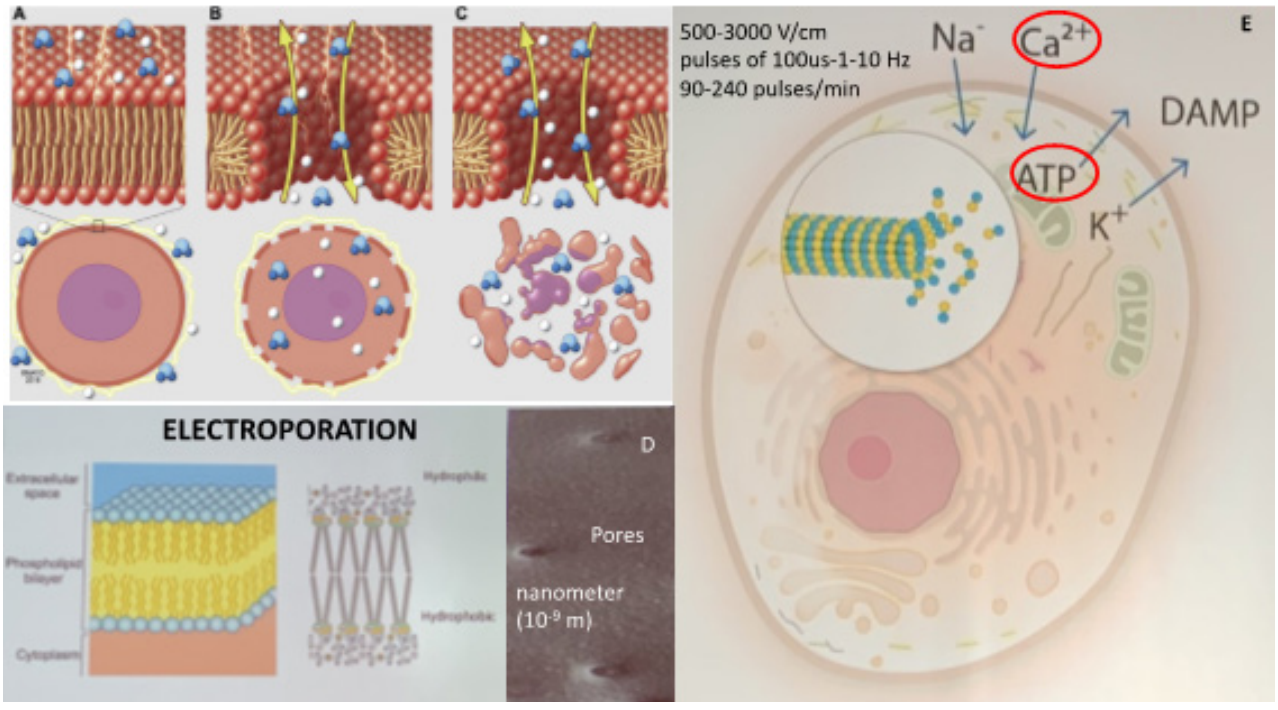

Figure 13 – Electroporation - modified from Maor.43 Formation of pores driven by local electric field gradient (from A to C), followed by water penetration in the bilayer interface, creating pores (D). Leakage of ions and osmotic balance, loss of cell homeostasis entrance of calcium and release of damage-associated molecular patterns (DAMP) with alteration of function and structure of membrane proteins (E)

observations now suggest that atrial signals that show complex activity (0.06–0.25 mV or <120 ms cycle), although represent passive electrical signals resulting from wave front collision, do not necessarily mean local intrinsic activity. No significant benefit was gained by the addition of ablation of these complex fractionated electrograms to the standard procedure, as described in the STAR AF II (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II)[33] and CHASE-AF (Randomized Catheter Ablation of Persist End Atrial Fibrillation Study) trial.[34]

The clinical impact of the approach of fibrosis as a substrate is not yet defined. The use of delayed-enhancement CMR to classify structural changes of the atrium by degrees of fibrosis (stages I–IV of Utah) is difficult to reproduce, and the electrophysiological approach of fibrosis (<0.5 mV [dense fibrosis] or 0.5–1.5 mV [moderate fibrosis]) has not shown consistent clinical results. Finally, ablation guided by the identification of atrial areas with rotational and fibrillatory activity and triggers of AF (rotors with >50 sustained rotations) in the CONFIRM[30] study, or by electrocardiographic imaging[34] and dominant frequency analysis,[35] were not reproducible and were not superior to isolation of the pulmonary veins.[36,37]

Perioperative Imaging in AF Ablation

The most used stroke risk score is CHA2DS- 2-VASc (C = heart failure, H = arterial hypertension, A = age >65 years, A2 = age >75 years, S = previous vascular accident, V = vascular disease, S = women). Thrombogenesis in non-valvular AF, mediated mainly by the left atrial appendage, presents a risk of <0.3% when CHA2DS2-VASc is 0 and> 5% when CHA2DS2-VASc is ≥2. Patients with a score of ≥2 receive oral anticoagulation that usually is not uninterrupted during ablation. In these patients, preoperative transesophageal echocardiography is always performed to rule out the presence of thrombus. In addition to the ability to detect thrombi, computed tomographic angiography and intracardiac ultrasound provide important images that may be useful during the procedure, either for image coupling or for intracardiac echocardiography monitoring of atrial structures and catheters, providing higher safety to the procedure.

Although patients with CHA2DS2-VASc ≥2 still require anticoagulation after AF ablation, some studies have suggested that suspension of oral anticoagulation may be considered after successful AF ablation, when the meticulous monitoring demonstrates the absence of these arrhythmias.[39] Studies in progress such as the EAST (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial, ClinicalTrials.gov identifier NCT01288352), the CABANA (Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial, NCT00911508), and the OCEAN (Optimal Anticoagulation for Higher Risk Patients Post-catheter Ablation for Atrial Fibrillation, NCT02168829) may provide more consistent data for this approach.

The presence of silent cerebral microembolism in patients with AF ablation can be detected very accurately by diffusion magnetic resonance imaging (with or without fluid-attenuated inversion recovery) 30 min after ablation and, depending on the ablation systems used, can be detected in up to 50% of the cases. These worrying findings that require more meticulous and prolonged monitoring may also be present in other invasive procedures such as coronary angiography, stenting of carotid arteries, and insertion of valve prostheses. Fortunately, most studies have shown a regression without glial sequelae, with complete normalization of imaging examinations at 3 months,[40] with no solid data of declining of neurocognitive functions[41] in the populations studied.

New frontiers of AF ablation – the pulsed-field ablation

Two other important modalities of ablation use radiofrequency and cryothermal energy; these are thermal energy sources and both rely on time-dependent conductive heating/cooling, ablating all tissue types indiscriminately, with similar clinical results.[38] The dependence on contact and also the heat-sink effect caused by blood flow impairs lesion formation that can explain the high recurrence of arrhythmia. The desirable improvement of safety and efficacy of catheter ablation resulted in the investigation of alternative uses of energy.

Pulsed electric fields (PEF) has gained attention since 2005.[42] It refers to application of intermittent, high-intensity electric fields for micro or nanoseconds, resulting in increased cellular permeability, with penetration of water into the lipid bilayer/water interface. This results in electroporation, creating pores around 10 nm in size form (Figure 14), and generation of selective lesions without tissue heating and preservation of critical surrounding structures.

Differently from radiofrequency and cryothermal energy, PEF are not dependent on contact, have no risk of thrombus formation, and have high tissue specificity. To date, there has been no evidence of phrenic nerve or esophageal injury, or pulmonary venous stenosis. Data from the AF Symposium 2020 reported 113 paroxysmal atrial fibrillation patients treated in three centers and by five operators, with no complications. In 52 remap procedures, durable pulmonary vein isolation was present in all patients.

PEF-based pulmonary vein and left atrial ablation are feasible and safe procedures, with excellent acute efficacy. Although several aspects of the techniques, such as the durability, level of pulmonary vein isolation, and effect on clinical recurrence of atrial fibrillation remain to be confirmed, PEF ablation is a paradigm-shifting energy source that has the potential to transform the field of AF ablation.

Conclusion

The translational research of cardiac arrhythmias has ensured the development of techniques of percutaneous ablation with superior results, including resolution of some supraventricular tachyarrhythmias, such as VTs without structural heart disease and some cases of paroxysmal AF. Some frontiers of knowledge, such VT with structural cardiopathy and long-standing persistent AF, are important medical challenges that require extensive clinical and experimental research.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Author Contributions

Conception and design of the research: De Paola AAV. Acquisition of data: De Paola AAV. Analysis and interpretation of the data: De Paola AAV. Writing of the manuscript: De Paola AAV. Critical revision of the manuscript for intellectual content: De Paola AAV.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

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VIEWPOINT

Controversies in the Indications of Percutaneous Angioplasty Or Coronary Artery Bypass Grafting In The Treatment Of Left Main Disease

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Introduction

Left main coronary artery (LMCA) disease is a high-risk clinical situation, since this artery is responsible for the irrigation of more than two-thirds of the myocardial tissue,[1] LMCA disease is associated with increased risk of adverse cardiac events.[2] Traditionally, the gold standard of treatment for significant LMCA disase, understood as a stenosis> 50%, is coronary artery bypass grafting (CABG) surgery.[3-7]

The technological evolution of percutaneous treatment and its safe application for LMCA disease in the PRECOMBAT study made it a viable alternative, initially restricted to patients at high surgical risk and with LMCA disease confined to the proximal portion of the trunk.[8] Subsequent studies have suggested the equivalence of percutaneous coronary intervention (PCI) and CABG in low and moderate complexity LMCA disease,[9] which was reflected in the most recent guidelines (Table 1). Clinical registries, with real-patient outcomes,[10-15] and long-term results from the EXCEL study,[16] contest this notion of equivalence between therapies in terms of mortality. The study was controversial, especially regarding the definition of clinical outcomes.

Motivated by recent studies showing divergent results on the comparison between surgical and percutaneous approach for LMCA disease, in this article we briefly review the results of the two forms of treatment, focusing on the recent evidences and controversies, but mainly on the lessons learned from these studies and their applicability in clinic care.

Coronary artery disease and myocardial revascularization

There is a tendency towards more conservative approaches in stable coronary artery disease (CAD), considering the absence of benefit from revascularization as demonstrated in the COURAGE trial[17] and, more recently, in the ISCHEMIA trial.[18] Even patients with areas of significant ischemia have not benefited from an invasive approach, so the tendency is to use revascularization to treat symptoms, without necessarily aiming to improve prognosis. In patients with CAD and severe ventricular dysfunction, the STICHES study demonstrated a reduction in long-term mortality from CABG compared with clinical treatment.[19] The ASCERT study, which was based on clinical records of CABG (n = 86244) and PCI (n = 103549), showed a relative risk reduction of mortality of 21% with CABG in the four years follow-up, when compared to PCI.[20] The results were observed in all subgroups of this large sample.

In the clinical trials mentioned above, patients with LMCA disease were not included. LMCA disease is present in 4 to 6% of all patients undergoing angiography and is associated with multivessel disease in approximately 70% of the cases.[21] The disease affects the distal portion of the LMCA in 60 to 94% of patients. When LMCA disease is

Keywords

Left Main Coronary Artery; Coronary Artery Disease; Coronary Artery Bypass; Percutaneous Coronary Intervention; Coronary Restenosis; Coronary Angiography; Myocardial Revascularization.

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Table 1 - Recommendations of the European Society of Cardiology (2018) and the American Heart Association (2017) guidelines for choosing the method of revascularization in patients with stable LMCA disease considering a scenario of favorable anatomy for both types of treatment (coronary bypass artery grafting and percutaneous coronary intervention) and a low surgical risk

Extension of coronary artery disease	Class and level of recommendation			
	CABG		PCI	
	ESC	AHA	ESC	AHA
LMCA disease with low SYNTAX score (0-22)	I (A)	I	I (A)	IIA
LMCA disease with intermediate SYNTAX score (22-33)	I (A)	I	II a (A)	IIB
LMCA disease with high SYNTAX score (≥33)	I (A)	I	III (B)	III

AHA: American Heart Association; ESC: European Society of Cardiology; LMCA: left main coronary artery disease; CABG: coronary bypass artery grafting; PCI: percutaneous coronary intervention

restricted to proximal or medial portions of the vessel, PCI is technically simpler than in distal lesions and is associated with low rates of restenosis.[1] The current recommendation is that all patients with stenosis ≥ 50% in the LMCA should undergo revascularization, regardless of the presence of symptoms or ischemia in functional tests.[4]

Anatomical particularities and severity of CAD are important factors when choosing the most adequate revascularization strategy.[22] Other variables should also be considered: ventricular function, form of presentation (acute or stable disease), chance of achieving complete revascularization, surgical risk and the patient's preference after being clarified about treatment options.

The indication for surgery in LMCA disease, in addition to the theoretical concept of the extensive myocardial area at risk, is based on subgroup analysis of two studies of surgical revascularization against clinical treatment, published in the 1980s.[3,5] Together, these studies included 185 patients with LMCA disease and demonstrated a mortality benefit at 5 and 10-year follow-up. These studies were conducted during a period when modern pharmacological treatment was not available, and only 66% of patients received some type of beta-blocker and 19% received acetylsalicylic acid (ASA).[1]

LMCA disease patients represent a high-risk group, but it is not homogeneous. These older studies identified subgroups that carry a worse prognosis, such as left main stenosis ≥ 70%, left ventricular dysfunction and previous infarction.[6,7] However, even the low-risk groups showed a very high mortality of around 20-30% in four years when treated conservatively.

Clinical trials and guidelines recommendations

Surgical revascularization is a class I indication for treatment of LMCA disease, according to the guidelines of the American Heart Association (AHA)[23] and the European Society of Cardiology (ESC),[22] regardless of the complexity of the coronary lesions. More recent studies and registries have shown adequate results for the percutaneous treatment of ostial or medial LMCA disease when the anatomy is less complex. The two guidelines differ in degrees of recommendation. According to the ESC guidelines, PCI is a class I indication when anatomical complexity is low, defined as a SYNTAX score below 22 and a class IIA indication when SYNTAX score denotes a moderate complexity (score between 22 and 33). In the AHA guideline, these conditions receive class IIA and IIB indications, respectively. The procedure is not recommended (class III) when SYNTAX is equal to or greater than 33, being compatible with a complex anatomy, both in the ESC and the AHA guidelines. The guidelines also coincide in the recommendation to carry out an individualized assessment of each case, considering, in addition to the coronary anatomy, the surgical risk (calculated using the score of the Society of Thoracic Surgeons) and patient's preference. In this scenario, the role of the Heart Team, which receives class I indication in both guidelines, is fundamental.

The guidelines were based on pre-specified subgroups of patients with LMCA disease in the SYNTAX study[24,25] and in two less powerful studies: the LE MANS[26] and the PRECOMBAT[27] studies. These studies included a reduced sample (total of 1,410 in the sum of the three studies) and

were performed when second-generation stents weren´t available. Two larger studies that specifically evaluated revascularization strategies for LMCA disease were the EXCEL[16] and the NOBLE trials[28] (Table 2). Even the most recent revascularization guidelines, published by the ESC in 2018,[22], were made without the availability of the long-term results of these studies,[29,30] but it gave a class recommendation for PCI in patients with low complexity LMCA disease, and maintained class IIA indication for moderate complexity anatomies.

The EXCEL study was the largest clinical trial to date regarding the treatment of LMCA disease; 1,905 patients from 126 centers spread across 17 different countries were randomized.[16] The primary outcome, a compound of death, stroke and myocardial infarction (MI), occurred in 22.0% of the patients in the PCI group and 19.2% in the CABG group (difference, 2.8 percentage points; 95% confidence interval [CI], -0.9 to 6.5; P = 0.13). In the five-year follow-up, but not in the prior publication with 3-year follow-up, PCI was associated with higher mortality, 13.0% vs. 9.9% (difference, 3.1 percentage points; 95% CI, 0.2 to 6.1), and the highest rate of repeat revascularization (16.9% vs. 10.0%; 95% CI, 3.7 to 10.0). CABG was associated with a higher rate of periprocedural MI, but with a lower risk of MI after surgery. The study was criticized for using its own definition of MI, as discussed later in this article. PCI was associated with a better quality of life and faster recovery in 30 days. In three years, however, the two modalities had similar results of quality of life.

In the NOBLE study, 1,201 patients were included in 36 European centers. The primary outcome was a composite of all-cause mortality, MI unrelated to the procedure, stroke

Table 2 – Main studies comparing percutaneous and surgical treatment in patients with left main coronary artery disease

Trial	Year	N	SYNTAX score	DM	Multivessel disease	Primary outcome (PCI vs CABG)	Main secondary outcomes (PCI vs CABG)
LE MANS	2008	105	N.D.	18%	91%	Change of LVEF (1 year): 3.3% vs 0.5% (p= 0.047)	No difference in mortality, MI, RR in 10 years
SYNTAX LM	2010	705	30	25%	68%	Death, stroke, RR (1 year): 15.8% vs 13.6% (P= 0.44)	5 years: Stroke: 1.5 vs 4.3 % (P = 0.03) RR: 26.7% vs 15.3% (P<0.001)
Boudriot	2011	201	23	36%	41%	Death, stroke, RR (1 year): 19.0% vs 13.0% (P= 0.19)	Similar rates of death, MI, stoke in 1 year (P for non inf. < 0.001) RR: 14 vs 5.9% (P for non inf. = 0.35)
PRECOMBAT	2011	600	25	32%	73%	Death, stroke, MI, RR (1 year): 8.7% vs 6.7% (P for non. = 0.01)	No difference in mortality, MI, stroke in 5 years RR: 13% vs 7.3% (P=0.02)
EXCEL	2017	1905	21	29%	51%	Death, stroke, MI in 3 years: 15.4% vs. 14.7% (P = 0.98)	Mortality in 5 years: 13.0% vs. 9.9% (difference, 3.1 percentage points; 95% CI, 0.2 a 6.1)
NOBLE	2017	1201	22	15%	N.D.	Death, stroke, MI, RR in 5 years: 29 % vs 19% (P=0.0066)	Similar rates of death and stroke in 5 years MI: 7 % vs 2% (P=0.004) NRE: 16 % vs 10% (P=0.032)

LVEF: left ventricular ejection fraction; N: number of included patients; DM: diabetes mellitus; MI: myocardial infarction; RR: repeat revascularization

and repeat revascularization.[28] The event rate estimated by Kaplan-Meier over five years was 28% for PCI and 19% for CABG (Hazard ratio [HR] 1.58 [95% CI 1.24–2.01]). CABG was superior to PCI for the primary outcome (P = 0.0002), due to the lower rate of MI unrelated to the procedure and less need for new revascularization.

Panoulas et al.,[31] published a retrospective analysis of 6,383 consecutive patients undergoing CABG or PCI with contemporary technology.[3]

[1] All patients were from the same center in the United Kingdom between 2007 and 2015. The average follow-up was 3.3 years. Left main disease represented 30.6% of the sample in the CABG group and 13.4% in the total sample, which underwent both Cox regression analysis and propensity score matching to reduce the effects of selection bias and other confounding factors. Surgery showed a mortality benefit (HR 3.24, 1.37 to 7.71), more pronounced than in the group of patients with three-vessel disease (HR 2.49, 1.22 to 5.1). Mortality in the study by Panoulas et al.,[31] was higher than that reported in the meta-analysis by Head et al.,[9] as would be expected when real-patients results are compared with randomized clinical trials. This article also showed the excellent results of CABG in the contemporary era: 2.1% of in-hospital mortality and 95.7% of one-year survival.

Head et al.[9] carried out a meta-analysis with individual data of the 11 clinical trials published up to July 2017 which compared PCI and CABG for treatment of LMCA disease.[9] A total of 11,518 patients were included, 4,478 (38.8%) with LMCA disease. They found similar five-year mortality in the groups (10.7% PCI vs 10.5% CABG , HR 1. 07, 95%CI 0.87–1.33; P = 0.52), regardless of the SYNTAX score and the presence of diabetes.

Incomplete revascularization is associated with increased mortality,[32] which may explain the benefit of surgical revascularization in patients with a more complex anatomy, reflected as a high SYNTAX score. The Heart Team, in other words, a thoughtful discussion of the best procedure for each individual patient by a clinical cardiologist, an interventional cardiologist and a cardiovascular surgeon, is crucial in complex scenarios, as occurs in patients at high surgical risk (mortality estimated ≥ 8%),[1,22] always based on current guidelines. On the other hand, it must be considered that some factors known to influence surgical results, such as frailty and social support, are not present in the scores traditionally used.[33]

Few studies have compared different angioplasty techniques that could potentially affect the outcomes. There is a consensus that drug-eluting stents should be used,[22] as they reduce complications when compared to bare-metal stent, especially when the implant is performed using IVUS.[34] The DK-CRUSH V study[35] demonstrated better results in one year with the double kissing crush technique when compared with provisional stenting, in terms of treatment failure (5% versus 10.7%, P = 0.02) and risk of stent thrombosis (0.4% versus 3.3%, P = 0.02). These technical details are important and may have an influence on clinical outcomes and should be specifically addressed in upcoming trials.

Controversies and perspectives

The publication of the 5-year results of the EXCEL study brought controversies.[29] In this article, the risk of death, MI and stroke was similar between surgical and catheter revascularizations (19.2% with CABG and 22% with PCI; P = 0.13). The list of authors, however, did not include David Taggart, the Principal Investigator of the surgical group. He requested the removal of his name from the publication for two reasons: the primary endpoints of the study had been altered to favor PCI, and reduction in mortality, observed in favor of surgery (13.0% versus 9.9%, OR 1.38; 95% CI 1.03 –1.85; p = 0.002), had not been the central focus of the publication. Another point of controversy was the definition used for MI in the study, which was not in accordance with the universal definition of infarction.[36] The study developed and applied a new criterion, which had no previous evidence of clinical relevance. Its definition disfavors the surgical result, since small enzymatic changes are expected in the postoperative period, due to manipulation of myocardial tissue, without necessarily representing a clinically significant myocardial injury.[37]

The definition of MI can significantly change the incidence of periprocedural infarction. Cho et al.[38] demonstrated that in PCI, as compared with CABG, the incidence of infarction varies according to the applied criteria: 18.7% against 2.9% using the second universal definition, 3.2% against 1.9% using the third universal definition and 5.6% against 18.3% according to the Society for criteria Cardiovascular Angiography and Interventions criteria. Accordingly, the incidence of perioperative MI in the EXCEL study (6.2%)[16] was much higher than that observed in the FREEDOM (1.7%) and SYNTAX (2.9%) studies. The biochemical definition of infarction and the inclusion of this variable as a part of the primary outcome statistically favors PCI. In addition, previous studies comparing CABG and PCI have not clearly shown that periprocedural infarction influences long-term outcomes.[39] However, after the 30-day period, the risk of death, stroke

or heart attack was 44% higher in the PCI group than in the CABG group (11.5% vs 7.9%; p = 0.02).

The study's lead author, Gregg Stone, agreed that mortality was higher in the ACTP group, but diminished the importance of the finding by claiming that the study had no statistical power to assess mortality, despite the large relative difference of 38%. Although the EXCEL study had 1,905 patients, the initial plan was to include 2,634 patients, but it was reduced due to a lower than expected recruitment rate.

Following the emergence of controversies related to the EXCEL study, the European Society of Cardiothoracic Surgery withdrew its support for the myocardial revascularization guidelines,[5] claiming that it is not safe to recommend decision making on LCMA disease treatment based on the local Heart Team. In response, the study sponsors called for an independent audit to analyze the results.

Due to these statements, other societies have also issued statement on LMCA disease treatment. American surgeons, through the Society of Thoracic Surgeons, reported that the final interpretation of the outcomes of the EXCEL study should await independent analysis. The Brazilian Society of Cardiovascular Surgery accompanied the European society and suggested that the recommendations in the LMCA disease chapter of the European guideline should be disregarded.

On the other hand, the ESC maintained its position, claiming that the guidelines are also based on other studies, but that it could be changed accordingly to new evidence. Meanwhile, interventional cardiology societies, both Brazilian (SBHCI) and American (SCAI) have supported the current the guidelines. They believe that there isn´t enough evidence to justify a new recommendation.

Conclusions

It is widely recognized that the left main is easily accessible by catheter, making it possible to perform PCI safely and with good immediate results when the lesion is in the proximal or medial part of the artery. The question is whether medium and long-term results are equivalent to the surgical results, which have been supported by clinical studies and registries through decades of follow-up.

Previous clinical registries, *i.e.*, data obtained outside clinical trials, showed higher rates of MI, higher rates of cardiovascular events and higher medium and long-term mortality when PCI was compared with CABG. Meanwhile, recent clinical trials have shown the viability of percutaneous treatment, with immediate outcomes similar to surgical ones, especially in cases of low anatomy complexity, as in proximal lesions away from the bifurcation and in the absence of significant disease of other major vessels.

However, survival curves between the two forms of treatment dissociate in favor of greater survival in the surgical series during longer follow-up, as is generally observed when the PCI and CABG are compared. Difference becomes clearer as the complexity of the lesions increases and are highlighted when the anterior descending artery is also affected, in patients with diabetes and in the presence of ventricular dysfunction.

Such evidence must be considered in choosing the best option for each patient. PCI should be chosen for patients with less complex anatomy, elderly with reduced life expectancy, patients at high surgical risk, patients with important comorbidities, and for situations when the immediate clinical benefit is more important than the long-term results. We summarize this approach in a flowchart (Figure 1).

Individualization of treatment, including a complete review by the Heart Team composed of enlightened professionals with no conflict of interests and who prioritize patient´s benefit is fundamental for good practice in the treatment of left main disease.

Author contributions

Conception and design of the research: Kalil RAK, Sant´Anna RT, Salles FD. Writing of the manuscript: Kalil RAK, Sant´Anna RT, Salles FD. Critical revision of the manuscript for intellectual content: Kalil RAK, Sant´Anna RT, Salles FD.

Potential Conflict of Interest

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

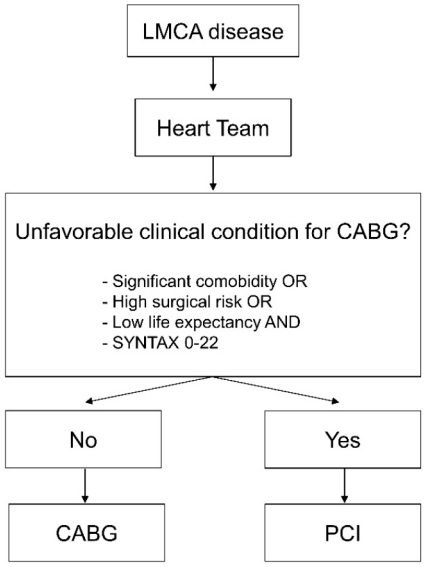

Figure 1 – Flowchart of the approach proposed for left main disease. LMCA: left main coronary artery; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention (PCI)

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VIEWPOINT

Severe Cardiovascular Complications of COVID-19: a Challenge for the Physician

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Introduction

Since December 31, 2019, when China reported the appearance of cases of acute respiratory failure caused by a new species of coronavirus, SARS-CoV-2, which causes the disease called COVID-19, almost 20 million cases were confirmed, causing 726 thousand deaths worldwide.[1] In Brazil, on August 8th, 2020, there was approximately 3 million cases and 100 thousand death by the disease.[1]

Its rapid spread, its high potential for hospitalization, and its high lethality, especially in the most fragile groups such as geriatric patients and those with comorbidities, particularly cardiovascular ones, make this pandemic a challenge never faced by modern medicine. To date, we have no specific medication that has effective and safe results for the treatment of COVID-19. The scientific community has sought to research drugs with therapeutic plausibility, and controlled and randomized studies are underway. Many therapeutic proposals are based on in vitro experiments. The medications used are described in case records, with no solid scientific evidence for their use, and with a high probability of causing damage due to their adverse effects alone or in combination.[2]

In this context, multiple clinical and experimental studies with cell cultures mainly from China, suggested that chloroquine, a drug that has been used for more than 70 years in the treatment of malaria, and as an anti-inflammatory in autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis, could play a role in the treatment of COVID-19.[3] Currently, more than 80 studies using chloroquine and hydroxychloroquine alone or in combination with other drugs were registered worldwide, seeking to transpose the benefits described in cell cultures to human studies.[2]

Both chloroquine and its more recent analogue, hydroxychloroquine, have a direct effect on the replication of SARS-Cov-2 in experimental studies, reducing the efficiency of virus binding to ACE2 (angiotensin-2 converting enzyme) and increasing the lysosomal pH, preventing the virus-cell fusion proces.[4] One of the main problems to be faced in these studies is the complex pharmacokinetics of 4-aminoquinolines, which makes it difficult to extrapolate concentrations of culture media to doses in humans.[5]

Studies from China, with a questionable methodology, for not presenting a description of the results, study protocols, doses, side effects, and statistically significant benefits between the groups, made their use in the treatment of COVID-19 quite debatable. One of these

Keywords

COVID-19/complications; Pandemics; Betacoronavirus; Cardiovascular Diseases/complications; Arrhythmias, Cardiac; Stroke Volume; Death, Sudden; Chloroquine; Hydroxychloroquine; Azythromycin.

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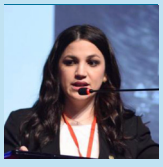

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studies with a small number of patients showed that chloroquine was associated with a higher percentage of clinical and virologic cure and started to be adopted in that country in the treatment of COVID-19.[6]

Its use was approved by the United States Food and Drug Administration (FDA) with the blessings of President Donald Trump,[7] although numerous side effects have been described such as fulminant liver failure, left ventricular failure, and arrhythmias (especially when prescribed in association to azithromycin).[8]

Azithromycin is a macrolide antibiotic widely used in clinical practice for upper and lower respiratory tract infections. It has also been studied for its in vitro effect against the Zika and Ebola viruses, and is often used to prevent serious respiratory tract infections when administered to patients suffering from viral infection.[9-11] As a complementary therapy in the treatment of SARS-Cov-2, a small French study with 36 patients, with non-randomized controls from another cohort, reported that hydroxychloroquine with or without azithromycin reduced the detection of viral RNA in respiratory swabs, the most significant effect being associated with azithromycin.[12]

Currently, the FDA recommends the use of these medications "out of compassion", alone or in combination, until we have scientific evidence of their effectiveness.[7] The Brazilian Ministry of Health, as of March 25, 2020, started to adopt chloroquine as an adjuvant therapy in the treatment of severe forms exclusively, without other support measures being neglected in its favor.[13] Worldwide, this association has been used off-label in severe cases, outside of research protocols, but there is still no scientific evidence.

Although the safety profiles of chloroquine / hydroxychloroquine and azithromycin are suitable for isolated use in chronic diseases, both medications have the potential to prolong the QT interval, which greatly increases the risk of ventricular tachycardia (mainly Torsades de Pointes), bradycardia, and sudden death, especially in scenarios of systemic inflammation caused by epidemic respiratory viruses.[14-16]

It is observed that the highest incidence of events occurs in people with other predisposing factors, such as long QT syndrome, structural cardiovascular diseases, or the use of other drugs that prolong QT.[17] In addition, it was demonstrated that approximately 20% of patients with COVID-19 have myocardial injury, 10% have myocarditis, and 10 to 30% evolve with shock,[18] which would multiply the probability of adverse effects in a pro-inflammatory and pro-thrombotic environment. These patients possibly have greater substrates for arrhythmia and electrolyte disturbances, and still in the critical phase of the disease, most patients admitted to intensive care units are treated with multiple combined therapies, such as vasoactive amines, diuretics, and serotonin 5-ht3 receptor antagonists, among others.

Both chloroquine / hydroxychloroquine and azithromycin have a known effect in prolonging the QT interval by blocking IKr (hERG) channels.[19-20] Concomitant use was uncommon until the current pandemic. There are reports of prophylactic use in malaria and some sexually transmitted diseases and little data on increasing the QT interval with their combined use.[21] Furthermore, although drug-induced QT is a reliable indicator of high-risk Torsades de Pointes (TdP), this correlation is not linear. Some drugs increase the QT interval without increasing the risk of sudden death, while others increase the risk of TdP without necessarily extending the QT interval.[22]

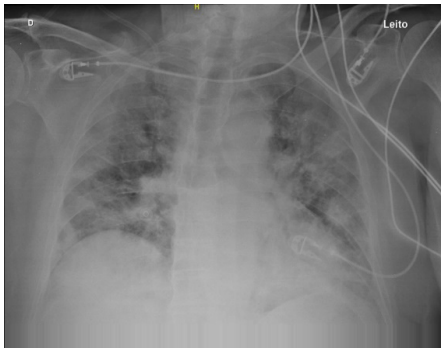
Next, we describe 2 cases of patients admitted to the Intensive Care Unit with COVID-19, who used the association of hydroxychloroquine sulfate or chloroquine diphosphate with azithromycin, and presented with severe cardiovascular complications. The aim was to illustrate the observations described above, with emphasis of the lack of safety of combination therapies not tested in clinical trials capable of generating robust scientific evidence.

Case 1

A 70-year-old male patient sought the emergency room with a complaint of runny nose associated with dry cough for 5 days. One day ago he developed fever, mental confusion, lack of appetite and prostration. As a personal history, he reported arterial hypertension and epilepsy on carbamazepine. On physical examination, she was feverish, with an axillary temperature of 37.8ºC, heart rate of 110bpm, blood pressure of 140x80mm Hg, respiratory rate of 25 irpm and 83% saturation in room air. Lung auscultation revealed crackles on the left base.

Laboratory tests showed lymphopenia, increased C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, and D-dimer. Other examinations and laboratory progress are shown in Table 1. The admission chest radiography showed a discrete bilateral infiltrate (Figure 1). The diagnostic hypothesis of sepsis of pulmonary focus with influenza syndrome was made, and the possibility of infection by SARS-CoV-2 was

A – Admission to the ICU



B – 1st day of hospitalization

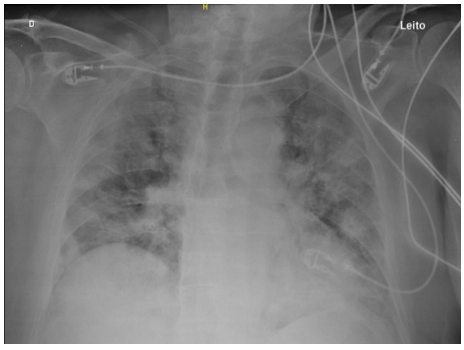


Figure 1 – Radiographic evolution of the patient Case 1. A – Admission to the ICU, B – 1st day of hospitalization. ICU: Intensive Care Unit.

raised. Antibiotic therapy with Piperacillin-Tazobactam, azithromycin, and oseltamivir was started, viral panel and PCR collected for COVID-19 (which proved to be positive in 24 h) and the patient was referred to the ICU.

On the second day of admission to the ICU, the patient developed respiratory failure and decreased level of consciousness, being submitted to orotracheal intubation and initiation of invasive mechanical ventilation. The transthoracic echocardiogram showed no relevant changes, with preserved ejection fraction. Due to the clinical worsening, it was decided to start enteral hydroxychloroquine and to suspend other medications commonly associated with an increase in the QT interval, such as ondansetron, bromopride and haloperidol. The QTc interval was monitored from the first day of ICU admission with a daily electrocardiogram (ECG) as shown in Figure 2, which remained within the normal range until the sixth day of ICU. On the seventh day, the patient presented sinus bradycardia, enlargement of the QTc interval, and Q wave in D1 and in AVL, accompanied by hemodynamic worsening, with severe hypotension, hyperlactatemia, and metabolic acidosis. A new transthoracic echocardiogram was performed, which showed diffuse hypokinesia with a drop in ejection fraction to 30% and an increase in the levels of ultra-sensitive troponin I (1038ng / dL), with a reference value of up to 25ng / dL. Dobutamine was started in a progressively higher dose up to 15 mcg / Kg / min, with stabilization of the condition. There were no hydroelectrolytic disturbances. Hydroxychloroquine and azithromycin were suspended. On the ECG the following day, the QT interval had normalized, with no further QT prolongation after medication was discontinued. Repeated echocardiogram with partial recovery of the left ventricular ejection fraction to 45%.

The patient evolved with multiple complications during hospitalization with acute renal failure requiring hemodialysis, epileptic seizures, and urinary tract infection, progressing to death on the 22nd day of hospitalization.

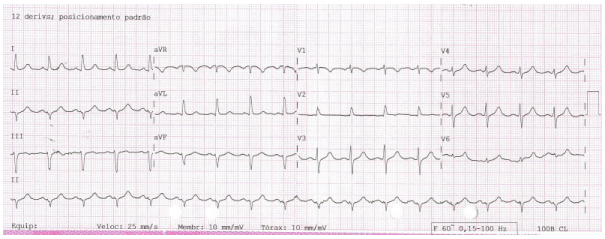
Case 2

Female patient, 92 years old, brought by her daughter to the emergency room with a history of dyspnea for 1 day, associated with generalized indisposition and weakness. She denied fever or flu-like symptoms. Daughter reported previous history of arterial hypertension, previous stroke with motor sequelae, lung cancer with radio surgery 6 years ago, and renal neoplasia with left nephrectomy 10 years ago, both without evidence of current disease.

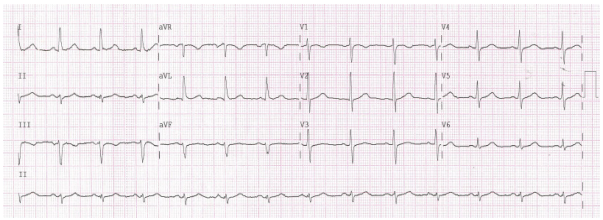
Physical examination revealed dyspnea, with blood pressure 208x102 mm Hg, heart rate 134 bpm, respiratory rate 25 irpm, saturating 75% in room air, with cyanosis of the extremities. Lung auscultation demonstrated diffuse bilateral crackles. Oxygen support was started with a reservoir mask at 10 L / min with good clinical response, as well as infused nitroglycerin and administered furosemide.

On admission examinations, patient with leukocytosis and relative lymphopenia, high CRP, in addition to increased D-dimer, troponin, and BNP. Other

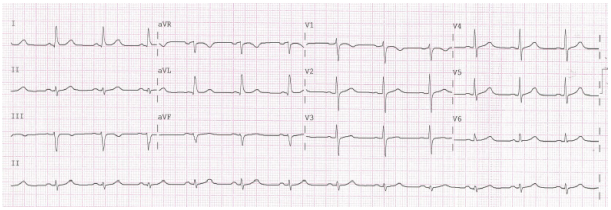
A – ECG at admission. HR 100bpm, QT 360ms QTc 423ms



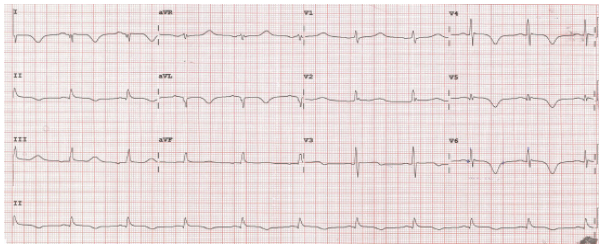
D – 6th day in the ICU. HR107bpm, QT 360ms, QTc 432ms



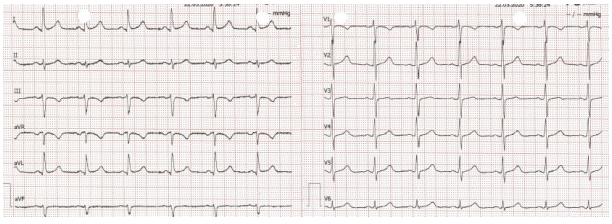
B – 2nd day in the ICU. HR 75BPM QT 360ms QTc 391ms



E – 7th day in the ICU. HR 60bpm, QT 580ms, QTc 603ms



C – 4th day in the ICU. HR 83bpm, QT 360ms, QTc 340 ms



F – 8th day in the ICU. HR 100bpm, QT560ms, QTc 465ms

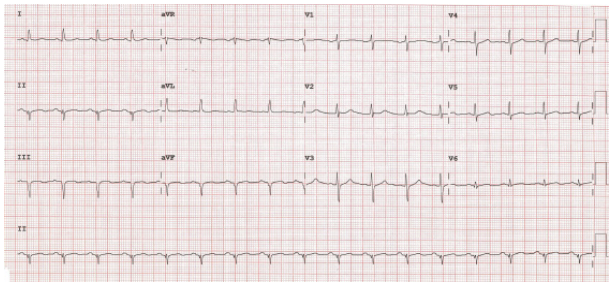


Figure 2 – Electrocardiographic evolution of the patient Case 1. A – Admission to the ICU, B – 2nd day in the ICU – day of prescription of chloroquine C – 4th day in the ICU, control of the onset of chloroquine; D – 6th day in the ICU; E – 7th day in the ICU – enlargement of the QTc interval (≈600ms) and appearance of lateral inactive area, F – 8th day in the ICU – normalization of the interval. ECG: electrocardiogram; HR: heart rate; ICU: intensive care unit.

Table 1 – Case 1 clinical and laboratory data

	Admission	D1	D2	D3	D4	D5	D6	D7	D8	D 10
Hemoglobin (g/dL)	14.8	13.1	13.4	12.7	13.2	13.5	14	14.1	13.8	8.9
Hematocrit (%)	45.4	38.6	41.4	38.5	40.2	41.3	42.2	42.9	41.1	28.2
Leukogram (cells/mm^3)	8050	9170	12610	8900	9730	14950	14010	17780	14080	37580
Band cells (%)	4%	5%	3%	2%	1%	1%	0	7%	3%	2%
Neutrophils (%)	76%	83%	80%	78%	80%	80%	87%	79%	80%	80%
Lymphocytes (cells/mm^3 - %)	805-10%	642-7%	1261-10%	1602-18%	681-7%	1047-7%	981-7%	1067-6%	1408-10%	12%
Platelet (cells/mm^3)	233.000	204.000	243.000	244.000	290.000	327.000	340.000	280.000	341.000	261.000
Urea (mg/dL)	53	38		37	53	67	107	63	61	131
Creatinine (mg/dL)	1.50	1.20	1.72	2.05	2.23	3.27	4.73	2.57	2.64	0.67
Sodium (mEq/L)	135	136	141	139	139	141	140	139	130	135
Potassium (mEq/L)	3.7	3.3	3.6	3.4	2.9	3.2	3.4	4.8	4.5	5.5
Ionic calcium (mmol/L)	1.08	1.01	1.15	0.97	0.96	0.95	0.97	0.96	1.09	0.97
Phosphorus (mg/dL)		3.3	1.02		4.5	4.2	3.6	4.5	2.5	
Chlorine (mmol/L)		107			92	93	92	97	103	101
Magnesium (mg/dL)		2.0	1.8		1.6	1.7	2.0	1.9	1.4	1.6
BNP (pg/mL)		18		23	25	110	1120	1540	1000	154
Troponin (mg/dL)		>5	>5	>5	>5	>5	1038	115	192	109
Ferritin (ng/mL)		631				1137	1248	1755	1471	5095
D-dimer (ng/ml)	928	1200	1470	2035	2561		6064	5163	4813	8322
CRP (mg/dL)	24.9	28.13	30.57	32.11	35.72	36.35	36.16	26.03	12.55	11.30
Lactate (mg/dL)	18	18	14	23	22	32	41	35	24	20
LDH (UI/l)		448	576	499	526	533	539	439	237	543
SWAB-COVID-19	Positive									
				Clinical Data						
Use of vasopressors		X	X	X	X	X	X	X	X	
Use of inotropic								X	X	
Mechanical ventilation		X	X	X	X	X	X	X	X	
LVEF (echocardiogram)	64%						30%		45%	
Hemodialysis							X			X

BNP: brain natriuretic peptide; PCR: C-reactive protein; LDH: lactate dehydrogenase; QTc: corrected QT interval; LVEF: left ventricular ejection fraction.

examinations and laboratory evolution are available in Table 2. Imaging tests showed bilateral infiltrate with irregular and peripheral distribution pattern on chest radiography and echocardiogram with preserved ejection fraction (61%), without segmental changes, with mild diastolic dysfunction (Figure 3).

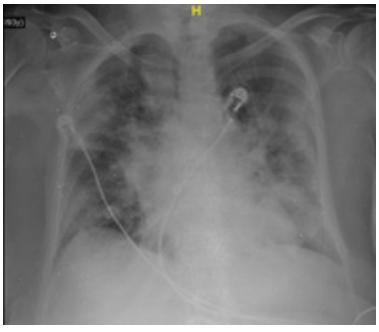
Diagnostic hypotheses were made for acute hypertensive lung edema, associated with probable sepsis of pulmonary focus. Even without a typical clinical condition, due to the radiological pattern and the current pandemic context by COVID-19, it was decided to collect viral panel and CRP for SARS-Cov-2, in addition to starting empirical antibiotic therapy with ceftriaxone, azithromycin and oseltamivir. After reassessment, the ICU team decided to start chloroquine diphosphate on suspicion of COVID-19 (later confirmed).

Since then, other medications with the potential to prolong the QT interval were avoided and the patient was submitted to ECG daily - the QTc interval did not change in any routine ECG, as shown in Figure 4. On the second day of evolution, the patient presented increased troponin, without repercussions on ECG and ventricular function. On the fourth day of evolution, in the absence of clinical improvement, the antibiotic was switched to Piperacillin-Tazobactam. The next day, the patient developed acute respiratory failure, being submitted to orotracheal intubation and initiation of mechanical ventilation. After a few hours, she presented ventricular tachyarrhythmia with progression to cardiorespiratory arrest (CRA); electrocardiographic monitoring at the time of CRA demonstrated Torsades de Pointes (Figure 4F). After cardiopulmonary resuscitation awith defibrillation, the perfusion rate returned. The ECG after the event showed only right bundle branch block, which disappeared on a routine ECG the following day. The transthoracic echocardiogram after CRA maintained preserved EF (60%), without segmental deficit. After the event, the patient evolved with progressive clinical worsening due to multiple organ dysfunction, progressing to death on the 7th day of ICU stay.

In both cases presented, in addition to the combined use of chloroquine or hydroxychloroquine with azithromycin, patients were aging adults and were in the ICU in critical condition, which increases the chance of cardiovascular complications, both of ventricular dysfunction and ventricular arrhythmia. The first patient possibly had myocarditis (drop in ejection fraction, elevation of troponin and appearance of Q wave in DI and AVL), evolving with bradycardia and cardiogenic shock. The prolongation of the QT interval results from the combination of chloroquine and azithromycin, facilitated by bradycardia and myocardial injury. Myocardial inflammation alters the membrane's action potential and the inflammatory mediators, including cytokines, and potentiate the blocking of hERG channels, predisposing to Torsades de Pointes.

In the second case, the patient had a sudden evolution to Torsades de Pointes, without documentation of the prolongation of the QT interval, which may have punctually preceded the arrhythmic event. The presence of atrial bigeminy eventually contributed to the dispersion of repolarization due to the irregularity of the

A – Admission to the ICU



B – First day of admission

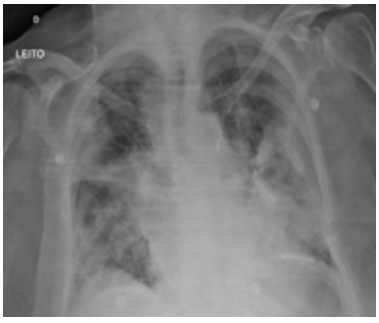
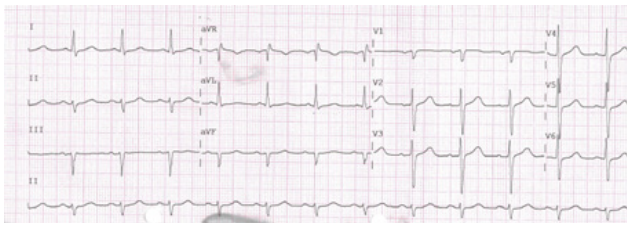
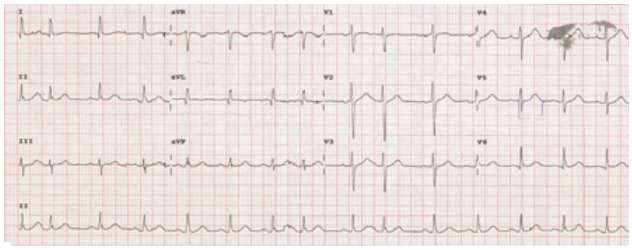


Figure 3 – Radiographic evolution of Case 2. A – Admission to the ICU, B – 1st day of hospital admission. ICU, intensive care unit.

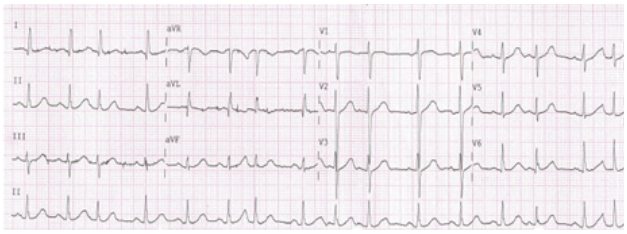
A – ECG at admission. HR 88bpm, QT320ms, QTc 369ms



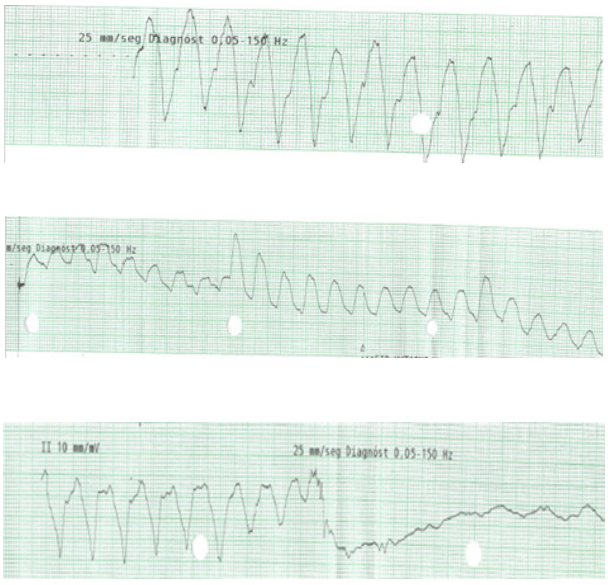
B – 1st day in ICU. HR 93bpm, QT 360ms, QTc 415ms



C – 5th day in ICU – Daily routine ECG CRA. HR 103bpm, QT 360ms, QTc 424ms



D – Monitor cardiometry – moment of CRA



E – ECG after CRA in sinus rhythm. HR 125bpm, QT 360ms, QTc 440ms

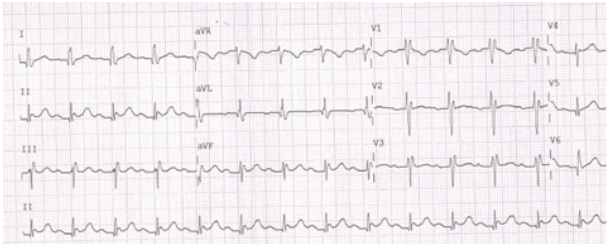


Figure 4 – Electrocardiographic evolution of Case 2. A – Admission, B – 1st day in the ICU, C – 5th day in the ICU – routine ECG on the day of CRA. Periods of atrial bigeminy, D – Monitor cardiometry - time of CRA, E – ECG after CRA in sinus rhythm, with new final conduction delay and first-degree AVB. ECG: electrocardiogram; HR: heart rate; CRA: cardiorespiratory arrest; ICU: intensive care unit.

RR interval. There were also a PR prolongation, a new final conduction delay, observed after CRA, in addition to early inferior repolarization, demonstrating the transmural dispersion in the plateau phase of the action potential, which may have potentiated arrhythmogenesis or be just an electrical phenomenon after CRA.

This will probably be the reality for most of the patients in whom these drugs will be administered for the treatment of severe COVID-19 infection - they will often be older adults, hemodynamically unstable using one or more vasopressors and on mechanical ventilation, with delicate handling of volume, often resulting in electrolyte disturbances.

If the option is to use these medications, it is necessary to use tools to identify the subgroup of individuals who, either by genetic predisposition (such as Long QT syndrome, with an incidence of 1:2000) or by the presence of multiple modifiable and non-modifiable factors for long acquired QT, have a greater risk for exposure to drugs that prolong QT. A risk score validated by Tisdale and colleagues to predict QT prolongation in hospitalized patients can be used for this purpose.[23] The Tisdale score ≤ 6 indicates low risk, 7-10 moderate risk, and ≥ 11 high risk of prolonged QT related to drug use (Chart 1).

Therefore, the position at the moment is to employ the association of chloroquine / hydroxychloroquine with

Table 2 – Clinical-laboratorial data Case 2.

	Admission	D1	D2	D3	D4	D5	D6
Hemoglobin (g/dL)	11.5	11.2	10.1	10.5	13.3	10.3	10.4
Hematocrit (%)	34.1	331	30.1	32.6	39.4	29.2	30.9
Leukogram (cells/mm^3)	15990	9850	11800	10830	5290	9300	16980
Band cells (%)	0	0	0	0	3%	3%	0
Neutrophils (%)	54%	80%	87%	70%	74%	77%	84%
Lymphocytes (cells/ mm^3 - %)	1339-8.5%	985-10%	1298-11%	1083-10%	952-18%	1023-11%	2038-12%
Platelets (cells/mm^3)	249.000	204.000	198.000	240.000	166.000	272.000	298.000
Urea (mg/dL)	43	47	53	59	52	49	37
Creatinine (mg/dL)	1.13	1.04	1.48	1.37	1.27	1.09	0.80
Sodium (mEq/L)	129	131	134	139	137	139	135
Potassium (mEq/L)	4.2	3.0	3.0	3.2	2.9	3.5	3.6
Ionic calcium (mmol/L)		1.05	1.18	1.18	1.14	1.13	1.41
Phosphorus (mg/dL)			4.1	3.8		3.8	
Chlorine (mmol/L)						92	
Magnesium (mg/dL)		1.5	2.4	1.7	1.5	1.6	2.1
BNP (pg/mL)	1220		916		483	309	347
Troponin (mg/dL)	55	224	109	40	35	25	490
Ferritin (ng/mL)		807	554	640	772	761	2653
D-dimer (ng/ml)	2054		1418				
CRP (mg/dL)		8.16	15.27	17.76	16.27	13.92	1.27
Lactate (mg/dL)	23	14	8	8	14	10	119
LDH (UI/l)		416	397	440	447	545	143
SWAB-COVID-19	Positive						
			Clinical Data				
Use of vasopressors						X	X
Use of inotropic						X	X
Mechanical ventilation						X	X
Ejection Fraction (echocardiogram)		61%					60%

BNP: brain natriuretic peptide; CRP: C-reactive protein; LDH: lactate dehydrogenase; QTc: corrected QT interval; LVEF: left ventricular ejection fraction.

azithromycin with caution in patients with heart disease, and minimize the use of expendable drugs that prolong the QT interval directly (potassium channel blockers) or indirectly (by drug interaction). Electrocardiographic monitoring should be strengthened in patients who develop myocardial injury or cardiac arrhythmias.

Author Contributions

Conception and design of the research: Crivelari NC, Hajjar LA. Acquisition of data: Souza AC, Hajjar LA. Writing of the manuscript: Crivelari NC, Oliveira GQ, Park CHL, Riemma GC, Costa IBSS. Critical revision of the manuscript for intellectual content : Lacerda MVG, Oliveira GMM, Darrieux F, Sacilotto L, Hajjar LA.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the *Hospital Pró-Cardíaco* under the protocol number CAAE: 3348.4020.8.0000.5533. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Tisdale risk score	
Risk factors	**Points**
Age ≥ 68 years	1
Female sex	1
Loop diuretic	1
Serum K + ≤ 3.5 mEq / L	2
ECG admission with QTc ≥450ms	2
Acute Myocardial Infarction)	2
≥ 2 drugs that prolong QTc	3
Sepsis	3
Cardiac insufficiency	3
A drug that prolongs QTc	3
Maximum risk score	**21**

Chart 1- *Tisdale risk score for the prediction of QT prolongation in hospitalized patients.*

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VIEWPOINT

Difficult Times: The Coronavirus Pandemic and Cardiology Residency – The Experience of the Rio Grande do Sul Cardiology Institute

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Medical residency programs were first established in 1889 in Baltimore, Maryland, at John Hopkins University. At the time, Dr. William Healstead realized that seriously ill patients treated by recently certified clinicians had higher mortality rates. In response to this, and in the hopes of increasing the quality and success rates of patient care, Healstead created a new type of training program, in which emerging clinicians would receive their final training in the hospital environment itself. This model, replicated globally, is currently known as medical residency.[1]

In Brazil, the Orthopedic Department at Hospital of Clínicas, associated with the University of São Paulo (USP), pioneered the first Brazilian medical residency program in 1945. However, this training model was not officially adopted in the country until September 5, 1977, through decree No. 80281, which instituted residency training as a formal component of medical graduate training. [2-4] Since then, physicians worldwide have been able to train in specialized medical residency programs that not only deepen their theoretical understanding, but also provide a supervised environment for development of the practical skills required by their desired area of expertise.

After being identified on December 1, 2019 in Wuhan, China, with the first cases reported on December 31, a novel infectious disease – coronavirus disease 2019, or COVID-19 – a quickly emerged as a global concern.[5]

Keywords

Betacoronavirus; Pandemics; Information Security; Confidentiality; Containment of Biohazards; Internship and Residency.

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The World Health Organization (WHO) subsequently declared the COVID-19 outbreak a pandemic, and the highly transmissible virus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[5]

The WHO pandemic declaration raised serious concerns in the medical community, as well as in the residency programs themselves. It became necessary to restructure medical services to minimize the risk of contagion and further spread of the disease, while maintaining patient care and providing guidance to the general population. Patients undergoing cardiological treatments are among those facing the highest risk for COVID-19, and at the same time cannot be deprived of ongoing medical care due to elevated risks of decompensation or dangerous cardiovascular events.

Apart from this, new paradigms have emerged considering the best approaches to manage cardiology patients, including the crucially important early and accurate diagnosis of COVID-19. These aspects should be considered in order to implement the best available treatments according to the most updated protocols and valid medical literature.[6] Throughout the COVID-19 pandemic, corollary cardiological conditions linked to this disease have become evident (including myocarditis and myocardial damage with increased biomarkers), demanding greater attention to patient complexities and the implementation of differential diagnosis. [6,7]

According to the available data, the mortality rate for COVID-19 in the general population is around 2%, vs. 15% in geriatric patients and those over the age of 80. In addition, considering the high transmissibility of COVID-19, the predicted infection rate for the overall population is 70%.[8] COVID-19 is transmitted in both

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aerosol and droplet forms, through the air or by means of contact or close proximity with the infected person. The symptoms resemble those of the common cold, including cough, fever, and/or dyspnea, in some cases developing into respiratory failure. The majority of those infected are asymptomatic, and in cases where symptoms are present they generally appear between 2 and 14 days after infection; the average incubation time is 5 days.[8]

Approximately 90% of infected individuals seeking hospitals are able to recover without intensive medical care. Those over the age of 60 or with pre-existing respiratory or cardiovascular conditions, as well as diabetes, present much higher chances of developing a more serious form of COVID-19.[8]

The predicted spread of this disease has positioned it as one of the greatest pandemics of all time, with impact not only on the medical sector, but also the on political and economic arenas. General medicine, specialization, and accreditation programs have been greatly affected by the pandemic, which created unprecedented challenges and led physicians to confront innumerable and unexpected situations on a daily basis. Hence, these programs and every other educational system across the board needed to undergo fundamental changes in order to adapt to the new reality.[9]

The Cardiology Institute-University Foundation of Cardiology (IC-FUC) was founded in Porto Alegre, Brazil in 1966 by Dr. Ruben Rodrigues with the aims of fostering medical education and research, improving medical care, and promoting regional development in cardiology. In the following years, these objectives were attained and the institute sealed a partnership with the state government and the Federal University of Health Sciences of Porto Alegre (UFCSPA). In 1969, a new center inaugurated at Princesa Isabel avenue became a new hub for cardiological advancement in the region. Remaining loyal to its three pillars: education, research, and patient care, and to the principles that underpinned its creation, the University Foundation of Cardiology is today recognized nationally and internationally for its excellence, leadership, and advancements in cardiology. It harbors the largest cardiology residency program in southern Brazil, with 341 inpatient hospital beds and an average of 996 hospitalizations per month in this sector; 54 hospital beds for intensive adult therapy (divided between coronary and postoperative intensive care units [ICUs]), 13 pediatric inpatient beds, and 10 pediatric ICU beds. The Institute is also responsible for approximately 10000 urgent and cardiac emergency attendances monthly and 9582 electrophysiological tests, apart from having performed 2515 cardiopulmonary bypass surgeries in 2019 alone.

The medical residency program in cardiology has trained nearly 1000 cardiologists since 1966, which represents 50% of the total number of practicing cardiologists in the state of Rio Grande do Sul. Today, the program accepts 20 residents in the general cardiology program every year, and all residents complete their mandated training hours with hands-on experience in every sector of the hospital. This includes the emergency room, therapy patient care, the hemodynamics lab, cardiac surgery, and training with electrophysiology and a plethora of cardiological exams.

With the onset of COVID-19, it was clear that major structural modifications were needed in the Institute's residency program to minimize the effects on the training of both cardiologists and those pursuing more specialized training (on echocardiograms, electrophysiology, and hemodynamics). A thorough contingency plan was elaborated by means of strategic planning and practical implementation and included the following measures: the creation of a COVID wing (Figure 1), intensive training on the clinical management of all suspected cases (including the use of personal protective equipment [PPE] and orotracheal intubation), the establishment of an intubation room in the emergency ward, fast sequence intubation training with video laryngoscopy, cricothyroidotomy training, the reinforcement of biosecurity measures, alterations in the conduction of class presentations and case discussions (online and video conferencing), the prevention of agglomerations in all hospital areas, selective restriction of outpatient care, and extended use of telephonic communications for all patients under hospital care.

The Cardiology Institute also took measures to reduce the risk of infection throughout the entire hospital grounds and between hospital staff and third-party vendors through continuous training, restrictions of visits to patients, and screening and triage using key symptoms (such as temperature checks) and vital signs on all entrances to the medical center.

It is important to mention that other illnesses do not cease to exist during the pandemic and, sadly, still present high registers. In addition, patients with existing cardiovascular conditions not only have higher chances of developing a more serious form of COVID-19 but are

Figure 1 – Negative pressure room in the emergency sector (COVID wing)

also burdened with a much greater chance of mortality linked to the cardiovascular disease itself. It is now well established that SARS-CoV-2 has the potential to attack the cardiovascular system in various ways and could cause arrhythmic activity (16%), myocardial ischemia (10%), myocarditis (7.2%), and shock (1-2%). Based on this dire scenario, it is extremely important to adopt and codify all of the recommended preventive measures.[10]

Since the first cases in 2019 , the spread of SARS-CoV-19 has posed an immense challenge to the global population. Nevertheless, the experience of an infectious disease pandemic on a global scale is not without precedent, considering for example the Spanish flu of 1918. Thankfully, medicine has experienced a true revolution since then, and the performance and dissemination of scientific research now happens in real time, promoting the sharing of recent developments and best practices in this unique time.[11] Alongside these major changes, unique opportunities emerge in the development and education of the resident doctors who are currently in training. Online-based educational tools also offer unique possibilities.[12] The challenges are inevitable, but sufficient preparation in the renovation and support of residency programs can ensure professional growth, development, and well-being for residents, while also protecint the highest possible quality of patient care. These measures are currently essential to face the pandemic and reduce the exposure and transmission among medical staff and patients, without failing to provide the best theoretical and practical training for medical residents as they pursue and engage with their specialties in cardiology.

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This article does not contain any studies with human participants or animals performed by any of the authors

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VIEWPOINT

Potential Role of Hematological Parameters in Patients with Acute Myocardial Infarction: viewpoint

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Acute myocardial infarction (AMI) is one of the most important cardiovascular diseases, leading to disability and death worldwide. Atherosclerosis is the main etiology of AMI, which is characterized by a series of highly specific cellular and molecular responses that can best be described, in aggregate, as an inflammatory disease.[1] Risk factors such as arterial hypertension, diabetes mellitus, smoking, dyslipidemia, obesity, emotional stress and family history are not, in themselves, sufficient for in-hospital risk assessment of patients with AMI. Recently, several studies have found an association between oxidative stress, due to inflammation, and hypoxemia processes, with hematological changes and coronary arterial diseases, suggesting their usefulness in identifying the risk of death. These studies have shown the association of hematological parameters with prognostic biomarkers in patients with coronary artery disease.[2-6] This issue of the International Journal of Cardiovascular Sciences includes the paper "Performance of a Hematological Scoring System in Predicting All-Cause Mortality in Patients with Acute Myocardial Infarction", with a proposed scoring system for in-hospital surveillance.

Several studies have shown that hypoxemia and infection are the main stimulus to differentiation processes in distinct hematological cell lines in the bone marrow, when hematological diseases, cancer, congestive heart failure, acute and chronic anemias are excluded.[4,7] These cells originate from a single progenitor cell called the stem cell, when for example, blood exposure to low oxygen concentrations over a long period results in differentiation and increased production of red blood cells. This stimulus to the bone marrow is produced by erythropoietin, a glycoprotein, 90% of which is produced in the kidneys, the rest being mostly formed in the liver, in response to hypoxemia. Infectious diseases cause the differentiation and final formation of specific types of leukocytes for each pathogen. Platelets have an important role in hemostasis, inflammation and innate immunity. In the last five decades, with the advent of automated counting, the hemogram was transformed into a useful clinical tool to demonstrate the daily variability in the hematopoietic response according to the patient's injury.[7,8] In recent years, a large number of studies have provided a better knowledge of these hematological parameters, with independent information on pathophysiology and risk stratification. For example, nucleated red blood cells (NRBCs) are immature erythrocyte cells present in the bone marrow in the process of hematopoiesis. In a healthy adult, there are no NRBCs in the peripheral blood. Therefore, the presence of NRBCs in the peripheral circulation is associated with a poorer prognosis.[9-12] The neutrophil to lymphocyte ratio (NLR), a combination of two independent markers of inflammation, is considered a simple and nonspecific marker of inflammation. White blood cells, particularly lymphocytes, cause a major important modulation in the inflammatory response. Clinical and experimental

Keywords

Myocardial Infarction; Nucleated Red Blood Cells; Mean Platelet Volume; Neutrophil to Lymphocyte Ratio; Atherosclerosis; Inflamatory Diseases; Mortality.

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studies have associated lymphopenia with progressive atherosclerosis.[13,14] Basem et al.,[15] demonstrated that NLR is a strong predictor of short- and long-term mortality in stable and unstable coronary insufficiency. Patients with non-ST-segment elevation myocardial infarction with NLR >4.7 have a mortality rate of 29.8%, whereas those with NLR <3 have a mortality rate of 8.4 (p <0.001).[15] In another study, using a 2.54 cut-off point, NLR was a predictor of severe atherosclerosis, with a sensitivity of 74% and specificity of 53% (ROC curve 0.627; 95% CI: 0.545-0.704, p = 0.004).[6] There are also studies demonstrating the association between NLR and the extent and severity of coronary artery disease.[16,17] Large platelets are metabolically and enzymatically more active than small platelets and are characterized by an elevation in mean platelet volume (MPV). In the study by Uysal et al.,[6] an MPV value greater than 10.4 is considered a predictor of severe atherosclerosis, with a sensitivity of 39% and specificity of 90% (ROC curve: 0.631, 95% CI: 0.549-0.708, p = 0.003), and can be used as a predictor and cardiac risk identifier in patients with coronary artery disease.[6] MPV has thus been identified as an independent risk factor for acute myocardial infarction in patients with coronary artery disease.[18,19]

Numerous other hematological parameters with prognostic markers for coronary artery disease are being studied. However, a scoring system associating NRBC, NLR and MPV represents a full blood count and its changes are related to all causes of hypoxemia and inflammation during the hospitalization of patients with AMI, as shown in Table 1. This hematological scoring system divided the patients into two groups (low and high risk), and had a scale ranging from 0 to 49, where higher values were associated with higher risk of in-hospital death.[20]

The potential role of an in-hospital surveillance laboratory model is feasible. However, this hematological scoring system needs to be validated with more clinical research. It is a simple and objective model, easy to interpret by all members of the multidisciplinary team and, based on evidence from existing studies, can be used for the safety of inpatients with AMI.

Author contributions

Acquisition of data: Monteiro Júnior JGM and Sobral Filho DC. Analysis and interpretation of the data: Monteiro Júnior JGM and Sobral Filho DC. Writing of the manuscript: Monteiro Júnior JGM and Sobral Filho DC. Critical revision of the manuscript for intellectual content: Monteiro Júnior JGM and Sobral Filho DC.

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Table 1 – Sensitivity, specificity, positive predictive value and negative predictive value of the point scale in predicting mortality from the point scale proposed in the study.

	In-hospital Mortality	
Proposed Scale of Points	**Yes**	**No**
≥ 26 points	49	134
<26 points	6	274
Validation measures	Percentage value	CI (95%)
Sensitivity	89.1%	0.809 – 0.973
Specificity	67.2%	0.626 – 0.717
Positive predictive value	26.8%	0.204 – 0.332
Negative predictive value	97.9%	0.962 – 0.996
C Statistic	86.8%	0.818 – 0.918

CI: Confidence Interval

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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International Journal of Cardiovascular Sciences. 2020; 33(5):589-590

LETTER TO THE EDITOR

Declaring Physical Activity as 'Essential' during the COVID-19 Pandemic May not be a Good Measure

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Dear Editor,

We congratulate the authors on the viewpoint entitled "Should Physical Activity Be Considered Essential During the COVID-19 Pandemic?",[1] and we are thankful for the opportunity to provide some contributions on this current and relevant topic.

We agree with the evidence that the practice of physical activity improves the immune response and promotes benefits for the mental health and cardiovascular and metabolic systems, and that this practice might not be interrupted during the pandemic. We highlight that exercise should be performed at home or in the neighborhood areas whenever possible, and always following the recommendations of local governments, according to recommended by the American College of Sports Medicine. We also agree that people should avoid remaining seated, lying down or using electronic gadgets for long periods – in other words, a sedentary behavior should be avoided. However, we do not agree that there is enough scientific evidence to justify a government declaration stating that the practice of physical activity is an essential activity, and herein we present our arguments.

The Brazilian legislation, according to the Decree number 10282 (March 20, 2020), defines essential activities as indispensable services that, if not provided, would endanger the survival, health, and safety of the population. Nevertheless, the subjectivity of the term "essential" cannot be disregarded and may cause diverse interpretations.

There is strong consensus among epidemiologists that, in face of the high transmissibility of the new coronavirus (SARS-CoV-2), even among asymptomatic individuals, and absence of a vaccine or specific treatment for COVID-19, social distancing is the most efficient measure to flatten the epidemic curve.[2]

Keywords

COVID-19; Pandemics; Betacoronavirus; Motor Activity; Exercise; Sports; Social Distancing; Mental Health.

In the opposite direction, the Brazilian government published the Decree number 10344 on May 11, 2020, defining, among others, activities performed in "sports centers (all modalities), following the determinations of the Ministry of Health, as "essential". In our opinion, this could lead to a boom in the number of cases in the country. In a study held in Cheonan, South Korea, 112 people were infected by SARS-CoV-2 after 24 days of dance fitness classes in 12 sports centers.[3] We believe that the best way for the government to establish different levels of social distancing is by considering risk classification, taking into account the reality of each state and city, as it has been happening in countries that managed to overcome the most critical phase of COVID-19 pandemic.

It is true that Brazil, beyond the economic and sanitary crisis caused by COVID-19, also goes through a political crisis, with resignation of two health ministers during the pandemic, and lead of the Ministry of Health under an interim minister for more than 15 days already. Furthermore, there are frequent statements by the Brazilian President minimizing the severity of the pandemic situation and the increasing number of deaths, which has even caused foreign reactions.[4] Public opinion polls, published by the Datafolha Institute, held on May 25- 26, 2020, with 2,069 adult Brazilian from all states of the country, (all had a mobile phone), with a margin of error of 2%, showed that the percentage of people supporting social distancing decreased from 76% in the beginning of April to 65%.

The authors of the viewpoint commented that when both France and the United Kingdom declared more severe restrictive measures admitted the possibility of the practice of physical activity in open spaces. However, the French capital, after evaluating the non-deceleration of the disease, banned the practice of activities in open areas between 10 a.m. and 7 p.m. In addition, the epidemiological situation in Brazil today is much worse than when these countries enacted such measures, with a total of 498,440 cases, 33,274 new

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daily cases and more than 1,000 deaths per day, registered on more than three consecutive days.[5] Then, it is needed to consider cultural and epidemiologic differences of these countries in comparison with Brazil, a country of continental dimensions with huge social inequalities, and where part of the population lives in extreme poverty.

It is worth pointing out that, out of the three articles mentioned by the authors, highlighting the importance of being physically active during the COVID-19 pandemic, two articles are points of view and one is a comment, and one of them were published by the same authors of the referred text. The two opinions indicate the importance of the practice of physical activities at home or in open areas, but they also reinforce the need to observe and respect the recommendations of the local sanitary authorities about the use of public spaces.

There is no scientific evidence supporting that the deaths caused by the interruption or lowering of a regular practice of physical activities, even for a short time, could be more harmful than the risk of a massive contamination by SARS-CoV-2. Other issues must be investigated, such as: does the practice of physical activities on a daily basis do promote immunological benefit against COVID-19? How much time of physical exercise would be necessary? How long would it take to a person lose this supposed benefit?

It is a challenge for governments to determine when the benefits of reduction in cardiovascular risk and improvement in mental health and immune system, promoted by physical activity, overcome the need for strict measures to contain the pandemic.

In our opinion, it is the role of the governments to hold educational campaigns that stimulate and guide the practice of physical activities at home, through a variety of medias, while the restrictive measures are in force. But, to officially decree that physical activities are "essential" activities, seems to be a risky and reckless alternative considering the epidemiological and political contexts in Brazil today. The incentive to the circulation of people in the present sanitary conjuncture can cost lives and lead to the need of a more prolonged time of restrictive measures, or even a lockdown.

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Erratum

On pages 589-590:

Where it read:

"We congratulate the authors on the viewpoint entitled "Should Physical Activity Be Considered Essential During the COVID-19 Pandemic?", and we are thankful for the opportunity to provide some contributions on this current and relevant topic."

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1. Aquino EML, Silveira IH, Pescarini JM, Aquino R, Souza-Filho JA, Grupo de síntese da Rede CoVida. Social distancing measures to control the COVID-19 pandemic: potential impacts and challenges in Brazil. Cien Saude Colet. 2020;25(Suppl.1):2423-46.

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Read:

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CASE REPORT

Case Report: Myocardial Bypass in Left Descending Artery — A Rare Congenital Anomaly

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Abstract

Myocardial bypass (MB) is known to have scientific relevance and is present in several studies with great statistical significance regarding its clinical manifestations and complications. There are still questions about MB in its relationship with heart disease and repercussion in life-threatening conditions. We present a case report of a MB in the left anterior descending coronary artery, whose objective is to identify this rare congenital anomaly and to highlight the patient's clinical outcome in order to elicit greater contributions about the presence of this variant in the emergency room, its diagnosis by angiography and therapeutic management.

Introduction

Myocardial bypass is defined as a portion of the myocardial tissue that bypasses a segment of the coronary artery, with a greater number of cases in the left anterior descending coronary artery.[1] The true prevalence of the myocardial bypass is not fully recognized. What is known is that myocardial bypasses are usually found over the left anterior descending coronary artery and are rarely found over the right coronary artery or the left circumflex coronary artery.[2]

Keywords

Myocardial Bridging; Heart Defects, Congenital; Myocardial Ischemia; Cardiac Electrophysiology; Angiography / methods.

Although myocardial bypass is generally considered a benign condition, several studies have shown an association between the myocardial bypass and acute coronary syndromes, chest pain, arrhythmia, left ventricular dysfunction, Takotsubo cardiomyopathy and sudden death.[3,4] Schwarz et al.,[5] proposed the following classification of myocardial bypass in the absence of coronary artery disease: type A, clinical symptoms and no objective signs of ischemia; type B, clinical symptoms and objective signs of ischemia by noninvasive stress testing; and type C, clinical symptoms and objective abnormal intracoronary hemodynamics (by quantitative coronary assessment / coronary flow reserve / intracoronary Doppler).

In addition, it is understood that beta-blockers or calcium channel antagonists are generally the first line of treatment in type A and B patients, whereas patients with refractory type C myocardial bypass are treated with surgical interventions such as myotomy (unroofing) or coronary artery bypass surgery or coronary stenting as a second-line option.[5,6]

We present a rare case of myocardial bypass in the left anterior descending coronary artery in a 55-year-old female patient, where we will discuss drug treatment and coronary intervention therapy in association with clinical outcomes.

Case report

Previously healthy 55-year-old female patient was initially admitted to another hospital. She reported three days of constant severe oppressive chest pain radiating to the left upper limb, associated with cold, intermittent

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sweating, presyncope and dyspnea on moderate exertion. The patient denies fever, nausea, vomiting, genitourinary disorders, history of systemic arterial hypertension, diabetes mellitus and allergies. She reported that, for most of the day, she presented normal levels of vigilance, concentration, and was very anxious, distressed and worried. Subsequently, myocardial necrosis markers were serialized, showing creatine kinase (CK) -MB of 48 U/I (reference value 25 U/I) and negative troponin. Admission electrocardiogram showed slightly abnormal ventricular repolarization in the inferior and septal walls.

The patient was transferred to our Interventional Cardiology service. Physical examination revealed poor general condition, no pain improvement, nasal catheter 2 L/min of O_2, the patient was agitated, lucid and oriented in time and space, pale (++/4+), acyanotic, anicteric, afebrile and hydrated. Blood pressure 154 x 98 mmHg, regular strong pulses with 76 beats per minute, heart rate 76 beats per minute, respiratory rate of 21 breaths per minute, 93% oxygen saturation in ambient air. Inspection of non-visible and non-palpable ictus cordis cardiovascular system in two digital pulps, cardiac auscultation with regular two-stroke heart rhythm and normophonetic heart sounds without murmurs. Examination of the respiratory tract without further abnormalities. A new electrocardiogram revealed (Figure 1) anterior ischemia and positive serialized troponin. Anti-ischemic therapeutic measures (acetylsalicylic acid 100 mg, clopidogrel 75 mg, sodium enoxaparin 40 mg every 12 hours, metoprolol succinate 50 mg, atorvastatin 40 mg) were then initiated.

Coronary angiography was chosen (Figure 2) and 30% lesion was found in the proximal third of the left anterior descending artery and myocardial bridge in the middle third. Absence of atherosclerotic disease implied stress echocardiography to assess previous ischemia possibly caused by the myocardial bypass. Stress echocardiography (Figure 3) was performed under physical stress demonstrating grade I diastolic dysfunction, diffuse hypokinesia with mild systolic dysfunction, more pronounced hypokinesia in the apical region and thickened mitral valve with mild regurgitation, thus contributing to the correlation of this patient's existing myocardial bypass with the ischemia findings.

Bisoprolol (beta-blocker) 2.5 mg in the morning and citalopram (selective serotonin receptor inhibitor) 5 mg daily were prescribed, with discontinuation of platelet antiaggregant and anticoagulant, with no recurrence of in-hospital chest pain. The patient was discharged in good clinical condition.

Discussion

It is understood that the clinical and pathophysiological factors that may unmask or exacerbate myocardial

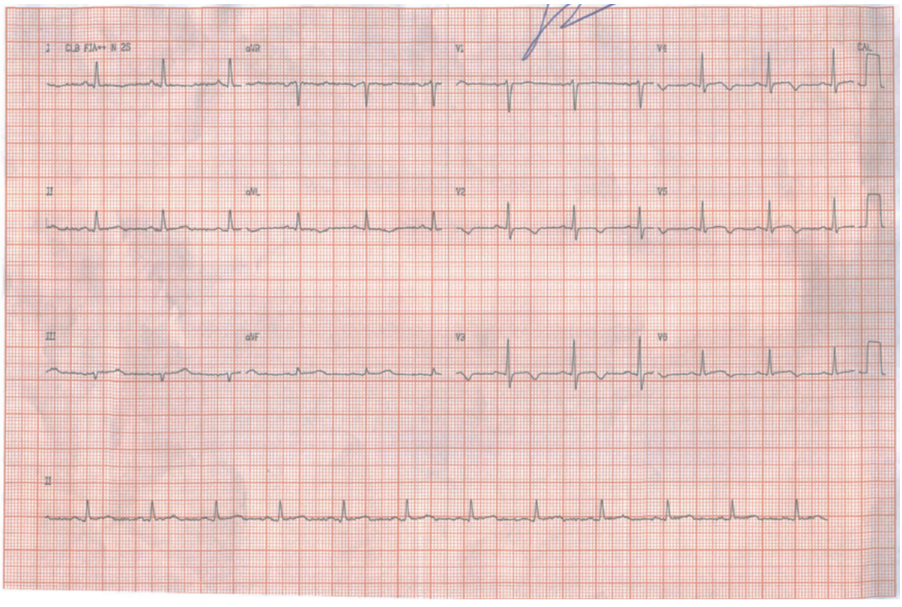

Figure 1 - Admission electrocardiogram at the Interventional Cardiology service, showing previous ischemia.

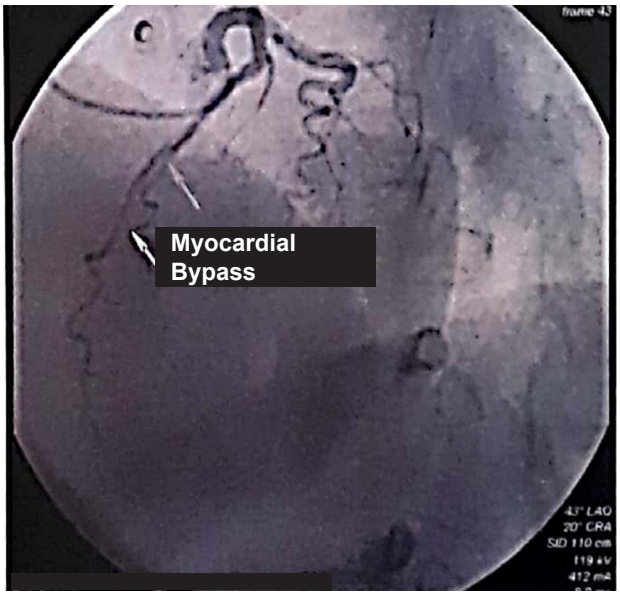

Figure 2 - Coronary angiography revealing myocardial bypass in the middle third in left axial anterior descending coronary artery projection during systole.

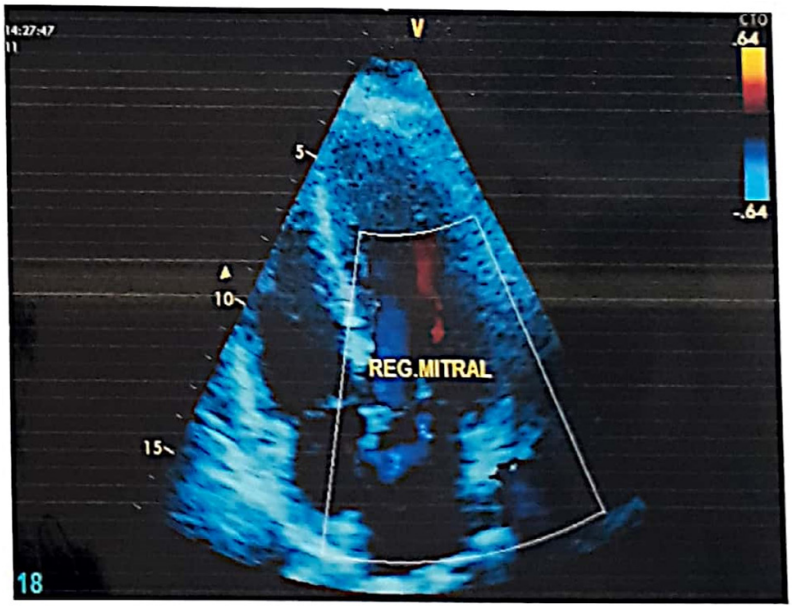

Figure 3 - Stress echocardiography showing thickened mitral valve with mild regurgitation and diffuse hypokinesia with mild systolic dysfunction.

bypass are the patient's age, heart rate, left ventricular hypertrophy and the presence of coronary atherosclerosis.[6] In this regard, the patient in this report has thickened mitral valve corroborating studies that favor the onset of symptoms of chest pain, similar to those of acute coronary syndrome. Increased left ventricular diastolic

dysfunction associated with aging, left ventricular hypertrophy and coronary atherosclerosis may worsen not only the mismatch of oxygen supply imposed by the myocardial bypass but also reduce microvascular reserve by microvasculature compression.[6,7]

In addition, the patient had generalized anxiety and diastolic dysfunction and stress echocardiography revealed that. Similarly, studies clarify that increased sympathetic activity due to vigorous physical exercise or situations of emotional stress and anxiety reduce myocardial flow and perfusion by decreasing diastolic perfusion time in line with increased epicardial coronary vasoconstriction and myocardial bypass contraction over the left anterior descending coronary artery.[8] Another factor is the coronary spasm that persists during diastole because the arterial vascular smooth muscle relaxation time is delayed compared to the diastole duration, especially associated with the aforementioned circumstances, which contributes to worsening of coronary perfusion.[8]

The impairment resulting from diastolic flow has two secondary pathophysiological consequences related to heart rate and severity and duration of epicardial arterial compression. These consequences are subendocardial/transmural ischemia and septal ischemia.[6-9] The latter is caused by depressurization of septal branches within the myocardial bypass, resulting in decreased intravenous perfusion pressure due to a Venturi effect. This is elucidated because the pressure difference starts with the Bernoulli equation, which can be written as follows: $p1 + ½\ \rho.v12 = \text{constant}$.[9]

The terms of this equation are

p = Pressure exerted by the fluid (pa);

ρ = fluid density (kg/m^3);

v = Flow rate (m/s)

As the myocardial bypass creates an environment with two distinct regions in the left anterior descending coronary artery, applying this equation gives us: $p1 + ½\ \rho.v12 = p2 + ½\ \rho.v22$. Because the myocardial bypass area is thinner, it will have a higher flow velocity, so equality in the Bernoulli equation will only be maintained if the pressure in this area is lower, which actually occurs in the septal branches within the myocardial bypass.[9]

Several factors have been postulated to explain the differences between the rates of myocardial bypass observed at necropsy compared with angiographic observations. Reasons include: myocardial bypass thickness and length, reciprocal orientation of the coronary artery and myocardial fibers, presence of atheromatous plaques, presence of aortic tract obstruction (in which the systolic tension that develops in the myocardial bypass exceeds intracoronary artery pressure), presence of a proximal coronary obstruction (which decreases the distal intracoronary pressure), myocardial contractility status, heart rate at the time of angiography, and examiner experience.[10]

The original definition and classification of myocardial bypass was developed with invasive coronary angiography. On the other hand, due to the lack of a real gold standard for the diagnosis of myocardial bypass, several forms of diagnosis were used to assess its anatomical, morphological and functional significance. Besides, myocardial bypass may cause significant diastolic pressure gradients and artificially normal or negative systolic pressure gradients. This phenomenon can produce an artificial increase in the mean pressure used to determine cardiac injury by using fractional reverse flow (FRR), which is the measurement of coronary artery blood flow in the event of some type of obstruction, resulting in underestimation of the myocardial bypass hemodynamic significance.[11] What is observed with stress echocardiography is that as the myocardial bypass generates dynamic stenosis caused by chronotropic and inotropic stimulation, the simple dilation of the artery with adenosine underestimates the hemodynamic significance of most bypasses.[11] Therefore, this suggests an element of coronary spasm or fixed stenosis rather than identifying significant myocardial bypass activity.[11]

When invasive tools to assess the ischemic potential of myocardial bypass are not available, functional noninvasive imaging tests may be helpful. Stress echocardiography, stress magnetic resonance imaging, single-photon emission computed tomography, and positron emission tomography can detect myocardial bypass in the left anterior descending coronary artery. Compared to others, cardiac magnetic resonance imaging has a better spatial resolution to detect segmental and subendocardial perfusion defects.[12]

Regarding drug treatment, considering the classification proposed by Schwarz et al.,[5] described above, data from a 5-year follow-up based on this classification showed that types B and C responded well to beta-blockers or calcium channels antagonists,

while patients with refractory type C myocardial bypasses were better treated with stent placement.[6] Beta-blockers are considered first-line therapy because of their negative chronotropic and inotropic effects and because of decreased sympathetic nervous system activation by exertion or induction of physical and emotional stress.[13]

Vasodilators such as nitroglycerin or sodium nitroprusside are not recommended because they may worsen symptoms due to increased systolic compression of the tunneled artery, induce tachycardia and proximal vessel dilation, which may worsen flow reversal in the proximal coronary segment.[14] On the other hand, ivabradine reduces heart rate by specifically inhibiting If-ion channels (activated during action potential repolarization) and can be considered as therapy alone or associated with a lower dose of beta-blockers and calcium channel antagonists.[14]

A lifestyle change is recommended because of the risk of developing myocardial bypass-induced atherosclerosis. Antiplatelet therapy should be considered when subclinical atherosclerosis is detected.

Conclusion

Based on previous pathophysiological concerns and the case report of a rare congenital anomaly, healthcare and treatment should focus on relieving potential triggers and hemodynamic disorders that worsen myocardial bypass, such as hypertension, ventricular hypertrophy, increased heart rate, reduced diastolic coronary filling duration, inadequate coronary artery contractility and compression.[7-8] Consequently, beta-blockers are considered the first-line therapy because of their negative chronotropic and inotropic effects, and because of decreased sympathetic nervous system activation, either by exertion or induction of physical and emotional stress.[6] Thus, it was chosen to use this class of drugs associated with a selective serotonin reuptake inhibitor due to the generalized anxiety disorder that may cause neurovegetative symptoms and increased heart rate.[7]

Author contributions

Conception and design of the research: Carvalho VP, Rocha IBS. Acquisition of data: Baptista AC, Vilela SB. Analysis and interpretation of the data: Paes JEH, Textor D. Writing of the manuscript: Carvalho VP, Júnior JPM. Critical revision of the manuscript for intellectual content: Carvalho VP, Moraes ERFL, Ribeiro HS, Fontana AP, Júnior JPM.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the CEP – UNIVR under the protocol number 2.557.630. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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CASE REPORT

Pacemaker Implantation in Dextrocardia with Congenitally Corrected Transposition of the Great Arteries: A Case Report

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Introduction

Dextrocardia is a rare congenital cardiac malformation with an incidence of 0.83 per 10,000 births, characterized by displacement of the cardiac apex to the right of the thoracic midline.[1,2] Congenitally corrected transposition of the great arteries (CCTGA) is a congenital malformation characterized by atrioventricular (AV) and ventriculoarterial discordance where patients are at increased risk of conduction system blocks and need for pacemaker (PM) implantation.[3–5] PM implantation is a complex procedure in patients with situs inversus dextrocardia (SID) and CCTGA because of altered anatomy and operator inexperience. Herein we present a case of SID) and CCTGA who underwent a successful transvenous permanent PM implantation via left subclavian vein for permanent complete heart block.

Case report

A 13-year-old girl with SID, CCTGA, ventricular septal defect (VSD), subvalvular pulmonary stenosis (PS), atrial septal defect (ASD), right anterior aorta, and atypical ductus arteriosus had undergone a left Blalock-Taussig (BT) shunt between the left subclavian artery and the pulmonary artery at the age of 7 days, and Rastelli operation with ventricular septal defect closure, pulmonary stenosis relief, and epicardial PM implantation for postoperative permanent complete AV block at the age of 5. At the age of 10, the pulse generator was exhausted. The patient was near predicted adult height and considered tall enough to be eligible for left ventricular endocardial pacing. No residual interventricular shunt was detected at the time of endocardial pacing system implantation, and so the risk of systemic embolism after the intervention could be discarded. Also, since the patient did not have sinus node disease, an atrial synchronous ventricular pacemaker (VDD mode) without atrial pacing lead was planned to be implanted. A PM pocket was opened in the left pectoral region due to the right-handedness of the patient. In anteroposterior (AP) fluoroscopic view, the left subclavian vein was cannulated and an endocardial passive PM lead with an atrial sensing ring was advanced through superior vena cava, morphological right atrium, and mitral valve to reach the apex of the non-systemic, morphological left ventricle (Figure 1A). The final position of the lead was confirmed in a right anterior oblique 40° view. Sensing and pacing parameters were as follows: R wave sensing amplitude of 20.2 mV; P wave sensing amplitude of 1.6 mV; ventricular pacing threshold of 0.3 V at a pulse width of 0.5 ms. A VDD pulse generator was placed beneath the left prepectoral fascia. The pacing parameters were set as follows: basic and upper tracking rates of 60 bpm and 130 ms, respectively; sensed and paced AV delays of 120 ms and 150 ms, respectively; ventricular pacing output of 5.0 V at a pulse width of 0.5 ms; ventricular and atrial sensing thresholds of 2.8 mV and 0.3 mV, respectively. After PM implantation, the patient did well with no postoperative complications, and normal functional capacity. Figure 1B depicts postimplantation ECG showing the right-sided precordial lead placement, PM in ventricular inhibited mode (VVI) due to a low atrial sensing (0.4 mV). The problem was then corrected by increasing the atrial sensing to 0.18 mV and tracking of sinus p waves was ensured.

Keywords

Dextrocardia, congenitally corrected transposition of the great arteries, pacemaker implantation.

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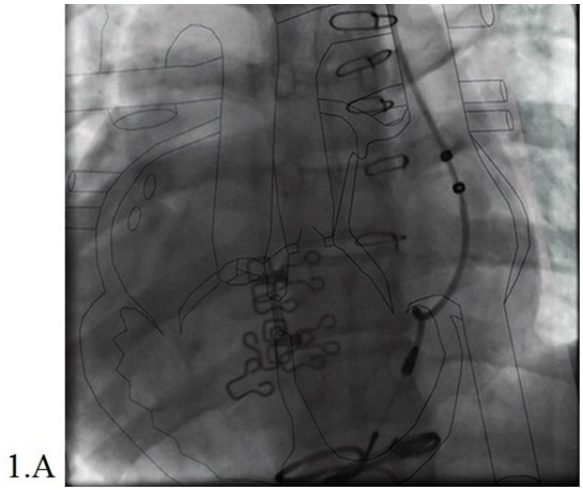
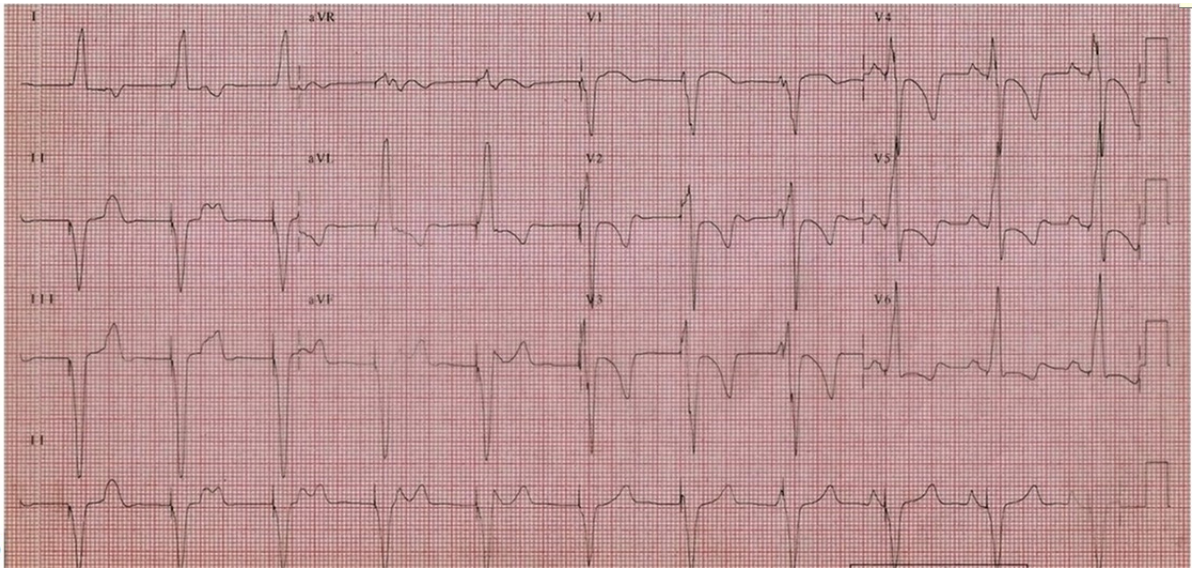


1.A



1.B

Figure 1 - 1A: Fluoroscopic view of the pacemaker leads mounted on a schematic representation of the anatomy of the heart. 1B: post-implantation ECG. 323 x 265 mm (72 x 72 DPI)

Discussion

Dextrocardia with situs inversus, also known as mirror-image dextrocardia, accounts for nearly 40% of all dextrocardia cases and is characterized by heart chambers located exactly opposite to their normal positions.[1,2] CCTGA may co-occur in nearly 8% of dextrocardia with situs inversus.[1] In CCTGA, the abnormal location of the AV node and the elongated His-Purkinje conduction system (His bundle)[3–5] increase the risk of complete heart block, both before and after corrective or palliative interventions,[6,7] with an annual risk of 2%.[7] Daliento et al.[8] followed patients with isolated CCTGA for 5 to 37 years and reported an incidence of 29% (5 out of 17 patients) of complete AV block, which was preceded by first- and second-degree AV block in two patients. Of note, one of these patients died, but it was not clear whether it was due to complete heart block.[8] Surgical AV block after repair operations for CCTGA occurs at a rate of 3% and 16%, with higher risk with arterial switch operation (12%) than the Rastelli procedure.[9] Anatomical factors possibly involved in the development of AV block include each of the AV node, the proximal or His bundle, or the more distal bundle branches.[9] In situs inversus dextrocardia with CCTGA, the sinus node is located in

the left-sided atrium, having a normal, but mirror-image, anatomical relationship with the terminal crest and superior vena caval entry into the left-sided atrium. In situs inversus CCTGA, the atrioventricular node is normally located at the apex of the Koch's triangle, and continues in the AV bundle. The bundle branches then end in the cord-like right bundle branch, and the fan-like left bundle branch, in the right and left side of the septum, respectively.[9-11] PM implantation may be challenging in dextrocardia with CCTGA because of venous anomalies,[12] altered cardiac position, and altered course of great vessels and cardiac veins.[13] In dextrocardia with situs inversus and CCTGA, both right and left subclavian veins can be used for intravenous access; the ventricular lead is usually positioned in the apex of the non-systemic, morphological left ventricle, while the atrial lead, if used, is placed into the right atrial appendix. Since in dextrocardia with situs inversus the cardiac image is the mirror image of normal anatomy, the ventricular lead should be directed towards the spine in the right anterior oblique 40° view and the cardiac apex in the left anterior oblique 30° view during normal-oriented fluoroscopic imaging. It may also be useful to invert the fluoroscopic image from left to right to simulate normal anatomy.[14] We had successful access to the left subclavian artery and no venous anomaly was observed. We then performed PM lead placement in anteroposterior view and confirmed the correct position of the lead using RAO 40º view. We added the fluoroscopic static overlay of the PM lead to schematic drawing of cardiac anatomy to ease the understanding of lead localization.

In conclusion, implantation of permanent endocardial PM may be needed in patients with dextrocardia with situs inversus and CCTGA. Interventional cardiologists and electrophysiologists should be familiar with this condition. A good knowledge of cardiac anatomy may facilitate PM implantation in this population.

Author contributions

Conception and design of the research, Çiftci O. Acquisition of data: Atar İ, Özin MB. Analysis and interpretation of the data: Çiftci O, Doğanözü E, Yılmaz M, Yılmaz KC. Critical revision of the manuscript for intellectual content: Özin MB.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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