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ORIGINAL ARTICLE

Improvement in Semiconductivity on the Measurement of Blood Pressure After an Educational Intervention in Health Professionals

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Abstract

Background: Measuring blood pressure is a simple method, but it is subject to errors.

Objective: to evaluate the theoretical and practical knowledge of the steps of blood pressure measurement in health professionals, before and after the educational intervention.

Methods: The theoretical knowledge questionnaire on indirect blood pressure measurement was used to assess theoretical knowledge; to assess practical knowledge, the simulation strategy was applied in a standardized clinical setting and environment. The assessments were reapplied after one month. For data analysis, descriptive statistics were used.

Results: 30 health professionals from different categories; 19 of whom were males aged 41 ± 9.4 years and 11 were females aged 35 ± 9.5 years. Improvement was observed in most stages of theoretical and practical knowledge when compared to pre-and post-intervention, with an emphasis on the theoretical stages: "Position of the lower limbs" 2 (6.6%) x 16 (53.3%) and "Forceps with adequate position" 1 (3.3%) x 6 (20%). In the assessment of practical knowledge, it should be highlighted: "Do not speak during the measurement" 6 (20%) x 28 (93.3%) and in the "ideal size clamp" stage 0 (0%) x 5 (16.6 %).

Conclusion: The theoretical and practical knowledge on the stages of BP measurement by health professionals in this sample was insufficient. However, after the educational intervention, there was an improvement in the technique in most stages. (Int J Cardiovasc Sci. 2021; 34(1):1-7)

Keywords: Blood Pressure; Measument Equipment; Sphygmomanometers; Stethoscppes; Hypertension; Knowledge; Questionnaires; Health Personal; Inservice Training.

Introduction

Systemic Arterial Hypertension (SAH) is characterized by high and sustained levels of blood pressure (BP), being a multifactorial clinical condition, as well as one of the most important risk factors for the development of renal, cardiovascular and cerebrovascular diseases.[1] There are about 17 million hypertensive Brazilians, 35% of the population aged 40 years or older. The number is growing and the disease manifests itself early. It is estimated that about 4% of children and adolescents are also carriers. The burden of disease represented by morbidity and mortality is very high and, for all this, it is a serious public health problem in Brazil and worldwide.[2] Approximately 49% of the Brazilian population is made up of adults and deserves an effective approach to cardiovascular risk assessment and primary preventive measures. Thus, it is essential to implement continuing education for health professionals regarding the appropriate BP measurement and care for patients with SAH.

Although the indirect method for measuring BP is simple, it is subject to errors that may be related to those who perform the measurement, the equipment

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used, the sphygmomanometer and the stethoscope, the patient, the place (the doctor's office or outside it) and the technique itself.[3]

To assess theoretical knowledge on BP measurement, Machado et al.,[4] developed and validated a Theoretical Knowledge Questionnaire on Indirect Blood Pressure Measurement (Q-CTMIPA) for the population of nursing professionals in a Coronary Unit, contributing to the construction of evidence of this knowledge among different health professionals. This study evidenced the importance of training and promoting intervention on direct measurement of BP by health professionals, so that they can identify, evaluate and define assertive behaviors.

Given the above, the objective of this study was to evaluate the effects arising before and after an educational intervention on indirect BP measurement, with a single group of health professionals, in relation to their theoretical and practical knowledge.

Methods

This is a quasi-experimental study, developed at the Mobile Emergency Service (SAMU) located in a city in the interior of the state of São Paulo, in 2017.

The eligible population was SAMU health professionals and the sample was for convenience, regardless of gender or ethnicity. Professionals who expressed interest in participating in the pre-and post-educational intervention assessment were included.

The instrument used to assess theoretical knowledge on the steps of indirect BP measurement was the Q-CTMIPA,[4] composed by 7 questions related to the profile of the research participants (age, sex, time elapsed from the last training on BP measurement) and 20 questions related to the steps of indirect BP measurement, based on the 7th Brazilian Hypertension Guideline[2], with 15 open and 5 closed questions concerning patient preparation before BP measurement, conditions of the device for BP measurement and care with its accessories; care with patient positioning (arm height and position of legs); rigorous recording of values obtained and recommendations on calibration of the BP measuring device.

To evaluate the participants' practical knowledge on the indirect BP measurement procedure, the simulation strategy was applied, in a standardized clinical setting and environment. Realistic simulation, in an educational context, is an educational plot based previously on a created situation that allows people to experience the representation of a real event in order to practice, learn, test and understand systems or human actions.[5] To apply the instruments, three medical students participated in this study: an actor, an observer of the activities, and an analyst responsible for transferring the consultation data to the information system.

The actor waited for the participant in a room always sitting with his arms on his lap and with his legs crossed. The consultation started and the actor referred to a standardized history in which he/she denied symptoms of full bladder, food intake and consumption of alcohol, smoking or coffee. In addition, the patient denied long walks before the consultation and the use of continuous medication. The observer recorded performance aspects based on a checklist that followed the recommendations of the 7th Brazilian Hypertension Guideline,[2] divided into 4 stages: patient preparation and environment (9 items), patient position (8 items), measurement steps (4 items) and registration of values (8 items), totaling 31 items. The analyst (medical student) was able to identify, using the checklist, if the participant did not execute (0), performed incompletely (1), performed incorrectly (2) or performed (3) and, for each option, a value was considered using the Likert scale.

The practical evaluation was carried out in an isolated room, which became a realistic simulation of a doctor's office. The participant, the actor, the observer, the analyst, who fed the information system, in which he detailed the entire procedure using a checklist spreadsheet and could compare the results before and after the intervention, were in the room. After the first theoretical and practical evaluation, an educational intervention was carried out. During this intervention, the students of the medical course intervened actively in the mistakes evidenced by each participant regarding the steps of BP measurement, in addition to allowing the participant to clear their doubts on semiology. In addition, immediately after the intervention, each participant was given an educational booklet with information on the semi-technique of indirect BP measurement. The educational intervention continued with safe practical experience, based on scientific evidence and critical and reflective knowledge, aware of the reasons that underlie each of these stages. During the educational activity, the following topics were addressed:

Preparation of the patient and the environment: for the measurement, the environment must be calm and quiet,

with the patient relaxed for 5 minutes before checking the BP, not talking during the procedure; check on bladder emptying, not having performed physical exercises, eating food, coffee or alcoholic beverages, and smoking.

Patient positioning: sitting position, legs uncrossed, feet flat on the floor, relaxed. The arm is always at heart level, free of clothes and supported, with the palm of the hand facing up and the elbow slightly flexed.

BP measurement steps: obtaining the brachial circumference and selecting the corresponding cuff; cuff over the brachial artery; Osler's maneuver to estimate systolic pressure by palpation of the radial artery; stethoscope positioning; insufflation of the cuff to obtain systolic BP 20 to 30 mmHg above the estimated; determination of systolic BP in the first Korotkoff sound; determination of diastolic BP to the disappearance of sounds.

Record of values: Record of values in millimeters of mercury (mmHg) without rounding and record of the arm used.

One month after the educational intervention was carried out, the same Q-CTMIPA instrument and the same methodology for assessing practical knowledge were reapplied in all participants, so it was possible to compare whether there was a change in relation to knowledge before and after the intervention.

This study was approved by the Human Research Ethics Committee, CAAE: 41876615.5.0000.5495, and all participants signed an informed consent form, in accordance with Resolution 466/12.

Statistical analysis

All information obtained during data collection was entered twice in a database using Microsoft Excel Software. Next, they were transferred to the statistical program STATA 9.0 for calculations of absolute and relative frequency. Descriptive statistics were used to synthesize the information and characterize the sample, with measures of central tendency (mean) and variability (standard deviation).

Results

Thirty health professionals from the Mobile Emergency Care Service (SAMU) participated in the study, 19 (63.3%) men and 11 (36.6%) women, with a mean age of 41 ± 9.4 and 35 ± 9.5 years, respectively. Among these health professionals were: Doctors, Nurses, Nursing Technicians, First Aid and Medical Regulation Assistant Technicians (TARM).

Regarding the level of education of the participants, only 1 (3.3%) had incomplete high school and 11 (36.6%) completed high school; 1 (3.3%) incomplete higher education and 14 (46.6%) had complete higher education; only 3 participants reported having a degree at the post-graduate level, of whom 2 participants (6.6%) had completed a lato sensu postgraduate course and 1 participant (3.3%) had a postgraduate master's degree.

Table 1 shows the frequency distribution of the responses referred to in relation to the last formal training on indirect BP measurement.

The assessment of theoretical knowledge before and after the educational intervention, in health professionals, using the Q-CTMIPA instrument, are shown in Table 2, with the percentage of correct answers according to each step of the procedure.

According to the answers pointed out in each step of the procedure, some of them expressed a lack of theoretical knowledge of the participants, with emphasis on "Recommended position for the upper limb", "Calibration conditions of the device" and "Ideal clamp size in relation to the patient's upper limb". The other items in question presented a remarkable improvement in knowledge after the educational intervention.

In order to characterize the practical knowledge on the sequential stages of the indirect measurement of BP before and after the educational intervention, health professionals were evaluated through a simulation exam, using a checklist for verification. Table 3 presents the results pointed out according to each step performed.

The results of the practical evaluation indicated gaps in the "Steps of measurement", since "obtaining the circumference of the patient's arm" and "selection of the clamp of adequate size" presented lower scores compared to all other items, resulting in a small improvement after educational intervention. However, the "Patient position" stage was characterized by better performance in the pre- and post-intervention phases.

Discussion

The study found an improvement in all evaluated items, both in the theoretical and practical questionnaires. However, a limitation of the intervention was observed in the following parameters: "Recommended position

Table 1 – Distribution of the frequency of responses indicated regarding the last formal training on indirect BP measurement, by health professionals (n = 30), in 2017.

Questions	Yes		No	
	n	%	n	%
The training was satisfactory	28	93.3	2	6.6
Received training only during the course	24	80	6	20
Last training time less than 6 months	0	0	30	100

Source: the authors.

Table 2 – Distribution of the frequency of the number of correct answers among the health professionals on the steps of indirect BP measurement, based on the adapted Q-CTMIPA, (n = 30), in the theoretical assessment, performed in 2017.

Steps of the BP measure	Pre-intervention		Post-intervention	
	n	%	n	%
Preparation of patient				
Mentioned asking questions to the patient before measuring their BP	4	13.3	14	46.6
Mentioned resting of at least 5 minutes	4	13.3	14	46.6
Mentioned recommended position for upper limb	0	0	2	6.6
Mentioned recommended position for lower limbs	2	6.6	16	53.3
Preparation of the environment				
Reported the ideal environment to carry out the BP measurement	1	3.3	7	23.3
Care with the device				
Referred to the calibration conditions of the automatic device	0	0	0	0
Agreed that clamp of inappropriate size can influence values	29	96.6	30	100
Considered removing from use armband structure and extensions with any problems/damage	2	6.6	7	23.3
Referred to the calibration period of the automatic device	7	23.3	13	43.3
Values obtaining and recording				
Referred to the ideal size of the cuff according to the patient's upper limb	0	0	1	3.3
Agreed that it is possible to obtain different BP values between the patient's right and left upper limb	28	93.3	29	96.6
Considered different BP values between the right and left upper limbs	9	30	10	33.3
Considered the position of the cuff on the patient's upper limb	1	3.3	6	20
Agreed that it is important to record the limb used to measure BP	28	93.3	28	93.3
Allowed 1 minute interval between two measurements	6	20	16	53,3
Considered the recording of BP values in millimeters of mercury	29	96.6	30	100
Considered the recording of BP values without rounding	13	43.3	20	66.6

n = number of correct answers.
Source: authors.

Table 3 – Distribution of the number of correct answers on the steps of BP indirect measurements, based on the role-play, among health professionals (n = 30), in the practical evaluation, performed in 2017.

Steps of the BP measure	Pre-intervention		Post-intervention	
	n	%	n	%
Patient preparation and environment				
Explained the procedure to the patient	25	83.3	30	100
Allowed the patient to rest for at least 5 minutes in a calm environment	8	26.6	16	53.3
Provided a calm and quiet environment	29	96,6	30	100
Oriented the patient not to talk during the measurement	6	20	28	93.3
Made sure that the patient was not with full bladder	4	13.3	13	43,3
Certified that the patient did NOT exercise in the previous 60 minutes	13	43.3	27	90
Certified that the patient did NOT drink alcohol in the previous 30 minutes	8	26.6	26	86.6
Certified that the patient did NOT drink coffee in the previous 30 minutes	4	13.3	16	53.3
Certified that the patient did NOT smoke in the previous 30 minutes	9	30	21	70
Patient position				
Kept sitting in a relaxed position	30	100	30	100
Kept his/her back on the chair	18	60	30	100
Kept legs uncrossed	16	53.3	29	96.6
Kept feet flat on the floor	15	50	28	93.3
Removed clothes from the arm to put the cuff on	20	66.6	29	96.6
Positioned arm at heart level	26	86.6	30	100
Kept his/her arm supported	26	86.6	30	100
Kept his/her palm upside down	26	86.6	30	100
Kept his/her elbow slightly bent	26	86.6	30	100
Measuring steps				
Obtained the circumference of the patient's arm	0	0	1	3.3
Selected the right size arm cuff	0	0	5	16.6
Placed the cuff without leaving clearances 2 to 3 cm above the cubital fossa	28	93.3	30	100
Centered the middle of the compressive part of the armband over the brachial artery	29	96.6	30	100
Registration of securities				
Recorded systolic / diastolic values	24	80	30	100
Waited 1 to 2 minutes for new measurements	9	30	27	90
Reported the BP values obtained for the patient	29	96.6	30	100
Noted the BP values obtained without rounding	4	13.3	16	53.3
Recorded member on which BP was checked	6	20	20	66.6
Checked whether the time between the recordings was less than 5 min	30	100	30	100
Recorded values in mmHg	18	60	24	80
Kept silent during the procedure.	7	23.3	29	96.6

n = number of correct runs.
Source: authors.

for the upper limb", "Instrument calibration conditions", "Ideal clamp size in relation to the patient's upper limb", being the greatest deficiencies observed in the "obtaining of the circumference of the arm of the patient" and the "selection of the clamp of suitable size" results.

The position of the upper limb during BP measurement is of great value for the veracity and accuracy of the measurement obtained. When the arm is hyperinduced along the axis of the body, the pressure is lower than the intra-arterial pressure measured directly, and that decreases with abduction of the arm. In addition, the same study states that, depending on the type of chair, armchair or patient's own posture, muscle tension can cause changes in BP measurements. F, the patient should be relaxed with his/her back supported on the back of the chair.[6] It is evident, therefore, that the patient's position and the arm supported at the height of the heart with the palm facing upwards are indispensable for a good evaluation of BP by indirect measurement. Thus, it is clear that the approach used for this issue needs to be modified so that more reliable indirect BP measurements can be obtained in the future.

The reference to adequate calibration time of the BP measurement device was correctly made by only 23.3% of the professionals in the pre-intervention stage and, in the post-intervention stage, by 43.3%. These evidences are based on a study on the evaluation of the conditions of the use of sphygmomanometers in health services, which revealed that most respondents (76.6%) did not know how often the aneroid apparatus should be calibrated.[7] It is also worth noting that 0% of the participants knew how to evaluate the calibration of the automatic devices because they were not available in the institution. Therefore, since there is a current tendency to replace aneroid devices by automatic devices, it would be extremely important that trainings are carried out in order to prepare professionals to deal with this novelty.

Inadequately sized sleeves result in incorrect BP measurements. Tiny cuffs used to measure BP in people with a larger than expected waist circumference overestimate the diagnosis of hypertension, whereas larger cuffs underestimate BP readings.[8] One study showed that approximately 97% of practitioners do not check the appropriate measures given by the formula "Correct width cuff = 0.40 x Arm Circumference / Sleeve Width".[9] This same situation was observed in 83.8% of the participants, who did not measure the brachial circumference, and were completely unaware of the purpose of the measurement.[3] Thus, it can be inferred that providing adequate cuffs is essential to achieve BP measurements closer to the theoretical ideal.

Despite the gaps identified during the theoretical and practical evaluation of the BP measurement steps, the number of correct answers was lower during the pre-intervention stage, with a significant improvement in the post-intervention period. A survey conducted at the University of Mississippi compared the measurements acquired by current medical professionals with professionals trained by the American Heart Association and found a difference in SBP of 5.66 mmHg and a decrease in DBP of -2.96 mmHg.[10] The study reinforces our data and suggests that periodic training favors the adequate measurement of BP even though all of these professionals have already been trained.

In Minas Gerais, researchers[11] applied a simulation training strategy for health professionals on the management of patients with acute coronary syndrome and observed an impact on the acquisition of knowledge and confidence of the learners using the training model. This study reinforces evidences of a positive impact of realistic simulations on performance.

In fact, with the educational intervention, we noticed an improvement in the BP measurement technique. Providing specific training after the training of professionals is required for their updating and for the proper functioning of the institution.

The study carried out presented limitations regarding the small sample size, which allows for considering the results found only for the population in question.

Conclusion

Based on the results of this study, it is possible to note that both theoretical and practical knowledge of health professionals on the stages of BP measurement was insufficient. In general, the professionals presented gaps regarding the accomplishment of the "Measurement steps", especially when "obtaining the circumference of the patient's arm" and "selecting the appropriate size cuff" in the pre-intervention assessment. However, the educational intervention had a positive influence and brought improvements in relation to the knowledge gaps presented. Educational strategy plans should be carried out, with institutional actions aimed at the permanent training of all professionals, with an emphasis on detailing the correct and effective performance of each procedure performed in the process of patient care.

Author contributions

Conception and design of the research: Bachur CK. Acquisition of data: Silveira GB, Sousa SGO, Hercos Neto J. Analysis and interpretation of the data: Candido SS. Critical revision of the manuscript for intellectual content: Veiga EV.

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 the *Universidade de Franca* under the protocol number 41876615.5.0000.5495. 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

Impact of Continuing Education on the Quality of Blood Pressure Measurement

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Editorial referring to the article: Improvement in Semiconductivity on the Measurement of Blood Pressure after an Educational Intervention in Health Professionals

Cardiovascular diseases are the leading cause of death worldwide, and a key risk factor for these diseases—hypertension—is unquestionably the most prevalent disease in the population.[1] Cardiovascular semiology is extremely important in the setting of hypertension (HTN), since the determination of blood pressure values through established indirect measurement techniques plays an essential role in initiating further diagnostic investigation, prompting treatment, and allowing monitoring of patients with HTN. The environment in which measurement is performed; the patient's dietary habits, use of tobacco and alcohol, and engagement in physical activity before measurement; the adequacy of cuff size in relation to the limb; and proper cuff positioning are among the several important aspects which may interfere with measurement reliability. In this context, assessing the technical knowledge of healthcare providers is critical to preventing diagnostic errors.[2]

Differences in magnitude between office BP and mean daytime BP can be attributed both to the environment and to the technical quality of blood pressure measurement by the examiner. Beckett et al. obtained an average of three manual BP readings from 481 hypertensive patients in family practices. The average clinic BP (151/83 mmHg) was significantly (P<0.001) higher than the daytime mean BP measured by ambulatory blood pressure monitoring (ABPM) (142/80 mmHg).[3]

Keywords

Hypertension/complications; Cardiovascular Diseases/mortality; Blood Pressure; Physical Activity; Diet; Quality of Life.

Dawes et al.,[4] in a study with almost 6,000 patients, encouraged family physicians to perform 24-hour ABPM in the largest possible number of patients versus manual blood pressure measurement by the study physician. The average of three readings recorded manually in the office before ABPM was 164/96 mmHg, compared to a mean daytime ABPM of 149/90 mm Hg. In another series of 309 patients referred for 24-hour ABPM, the last office BP (recorded manually) was 152/87 mmHg, significantly (P<0.001) higher than the mean daytime BP recorded by ABPM (134/77 mmHg). Data from these studies show a consistent difference of up to 5 mmHg between daytime ABPM and routine office BP. This is a relevant finding, because this difference can be attributed at least partly to measurement errors secondary to poor semiologic technique.[5]

Marchi-Alves et al.,[6] conducted a study of manual blood pressure measurement (with a handheld sphygmomanometer) by nursing providers across five health facilities in the city of Londrina, Paraná. This was a quantitative, observational, cross-sectional study of 80 providers observed from August 2013 to January 2014. The results showed high rates (93.8 to 100%) of of failure to perform the preparatory stages of blood pressure measurement (i.e., preparing the patient before the actual measurement is taken). Sphygmomanometer calibration was not checked, and there were no different cuff sizes available. The authors concluded that there are significant gaps in the procedures adopted by nursing providers to measure blood pressure, indicating a need for corrective educational measures.

The article published by Bachur CK et al.,[7] in this issue aims to evaluate the theoretical and practical knowledge of blood pressure measurement technique among health professionals before and after an educational

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intervention. Among the providers evaluated, significant rates of improvement in the blood pressure measurement technique were observed after the educational intervention. These findings reflect that educational interventions and training in proper semiologic technique for blood pressure measurement semiotics are important actions in the Brazilian context, considering their impact on the diagnosis and treatment of HTN in this population.

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ORIGINAL ARTICLE

Lipoprotein(a) Levels in Children and Adolescents: Ouro Preto Study

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Abstract

Background: Lipoprotein (a) is a cardiovascular risk factor in adult. Studies have shown the presence of this emergent risk factor in school children, which may contribute to the development of atherosclerosis in adulthood.

Objective: To evaluate the association between lipoprotein (a) and cardiovascular risk factors in school children.

Methods: Lipoprotein (a) levels were measured in 320 school children (6-14 years) selected from a population survey carried out in Ouro Preto (southeast of Brazil). Demographic (sex and age), biochemical (total cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, triglycerides, and glucose), anthropometric (body mass index, waist circumference, body fat percentage), clinical (arterial blood pressure, pubertal stage and birth weight) and economic (family income) parameters, as well as family history (obese and/or hypertensive parents) were analyzed. Non-parametric analysis was used to evaluate lipoprotein (a) levels in each subgroup. Variables with $p \leq 0.20$ in the univariate analysis were included in binary regression logistic model. Differences with $p < 0.05$ were considered significant.

Results: Lipoprotein (a) levels were associated with total cholesterol (p=0.04), body fat (p=0.009), and mother´s systolic (p=0.02) and diastolic blood pressure (p=0.04). In a logistic regression analysis, children with high lipoprotein (a) levels and body fat, and children born from hypertensive mothers were, respectively, at 3.2(p=0.01) and 1.4 (p=0.03) times higher risk than other children. In clustering these factors, elevated lipoprotein (a) was 2.6 times more likely to be seen in school children with high body fat and born hypertensive mothers.

Conclusions: Lipoprotein (a) was correlated with cardiovascular risk factors in children and adolescents. Persistence of these risk factors in childhood suggests a contribution of elevated lipoprotein (a) to future cardiovascular disease. (Int J Cardiovasc Sci. 2021; 34(1):10-18)

Keywords: Children; Adolescents; Lipoproteins; Cholesterol; Hypertension; Body Mass Index; Adiposity; Bod Fat; Epidemiology.

Introduction

The high prevalence of cardiovascular diseases and associated risk factors has led to increased morbidity and mortality in various countries, including Brazil.[1] In many cities of Brazil, including Ouro Preto (Southern Brazil), cardiovascular diseases are the main cause of mortality and the second highest cause of hospitalization among adults aged 20 years or older.[1] Classical risk factors, such as high blood pressure, diabetes mellitus, dyslipidemia and obesity have been detected among children, adolescents,[2] and young adults, and may lead to cardiovascular diseases in adult life. In addition, these risk factors are associated with emerging risk factors, such as increased lipoprotein (a) levels, contributing to the process of atherosclerosis in childhood and adolescence.[3-5] Although the mechanisms by which lipoprotein (a) promotes atherosclerosis are not clearly understood, proposed mechanisms include increased lipoprotein (a)-associated cholesterol in the arterial

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intima, inflammatory cell recruitment, presence of proinflammatory oxidized phospholipids, impairment of fibrinolysis by inhibition of plasminogen activation, and enhancement of coagulation by inhibition of the tissue factor pathway inhibitor.[5] Studies have demonstrated an association of lipoprotein (a) with cardiovascular risk factors in children and adolescents, especially among those with a family history of cardiovascular diseases.[6,7] In a previous study in Ouro Preto city, it was observed that in the adult population, lipoprotein (a) levels were associated with ischemic heart disease and a high Framingham risk score.[8] The purpose of the present study is to evaluate whether serum lipoprotein (a) levels are associated with cardiovascular risk factors in a Brazilian paediatric population living in Ouro Preto.

Materials and Methods

A cross-sectional survey was conducted in Ouro Preto city (Brazil) among school children, chosen by simple random selection and stratified by age and gender, in all public (n=14) and private (n=2) schools of the city. Lipoprotein (a) was analyzed in 320 subsamples of the cross-sectional study. As a criterion for non-inclusion, children with special needs were not evaluated in this study. Participation in the study was entirely voluntary. Child's consent and signed informed consent from the parents or legal guardians of each participant were obtained before the study.

Data were collected by a team of trained research assistants from March to December 2006. The following variables were included: demographic (sex and age); biochemical (levels of total cholesterol, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol, triglycerides, and glucose); anthropometric (body mass index [BMI], waist circumference, and body fat percentage); clinical (arterial blood pressure, pubertal stage, and birth weight); physical activity (active and inactive); socioeconomic status (family income); and family history (obese and/or hypertensive parents).

Blood samples were collected via venipuncture after overnight fasting (12h). The samples were analysed by enzymatic-colorimetric assays using commercial kits (In Vitro Diagnóstica, Itabira, MG, Brazil) and an Airone 200 analyser (Crony Instruments, Rome, Italy). Lipid and fasting glucose levels were classified in accordance with the Brazilian Society of Cardiology[9] and the Brazilian Society of Diabetes[10] criteria, respectively. Apolipoprotein (a) values (units/L) were determined using the ELISA method (Mercodia In, Upsala, Sweden). Lipoprotein (a) levels were obtained by the conversion method suggested by the manufacturer: 1 unit of apo(a) is approximately equal to 0.7 mg lipoprotein (a) protein. This assay is very sensitive and highly specific and produces no measurable cross-reactivity with plasminogen and apolipoprotein B; in addition, it minimizes the possible interference of heterogeneity in apo(a) isoforms in the results; the detection limit is 0.0035 mg/dL; the overall coefficient of variation for lipoprotein (a) measurements in this study was 5.3%. Serum aliquots were stored at -80°C until analysis.

Weight was determined using a Tanita BF542® scale (Tanita Corporation of America, Arlington Heights, IL, USA), while height was determined using a WCS® stadiometer (Cardiomed, Curitiba, Brazil). Waist circumference was measured midway between the lowest rib and the iliac crest. In the absence of national reference values, the 90th percentile of the distribution was used to identify individuals at risk, considering their gender and age. The BMI for children and teenagers, which is gender and age specific, was defined according to the World Health Organization criteria.[11] Body fat was estimated with the bipolar foot-to-foot bioelectrical impedance technique using the Tanita BF542® scale and the tetrapolar bioelectrical impedance technique by Quantum II® BIA-T(RJL Systems Inc., Michigan, USA). Reference values for body fat percentage were defined as 25% for boys and 30% for girls, in accordance with Williams et al.[12] To assess subcutaneous fat, the skinfold thickness at the following sites was measured: suprailiac, subscapular, triceps, and biceps, using Cescorf® skinfold callipers (Cescorf Inc., Porto Alegre, Brazil). All measurements were obtained in triplicate on the right side of the body by a team of trained technicians. The average of the three measures taken from each site was calculated, and equations were used to predict the fat percentage, as proposed by Deurenberg et al.[13] Body fat percentage was defined in accordance with Lohman et al.[14]

Arterial blood pressure was measured three times at 10-min intervals using an Onrom 705CP® blood pressure monitor (Onrom Healthcare, Kyoto, Japan) while the children were sitting down with their left arm at the level of the heart. When mean values of blood pressure exceeded the 90th percentile, measurements were repeated with auscultation. The blood pressure range was classified by age, sex, and height percentiles. A systolic and/or diastolic blood pressure ≥90th percentile was classified as hypertension risk.[15]

Pubertal stage was determined based on Tanner's criteria and assessed using a self-report questionnaire: prepubertal (1–2 Tanner stage), pubertal (3–4 Tanner stage) and postpubertal (5 Tanner stage).

Information concerning birth weight, physical activity, and socioeconomic status was obtained from the participants and their parents or legal guardians by face-to-face interviews. Birth weight was initially self-referred and further checked by telephone for those parents or guardians who could not remember; cross verification was performed using the child's birth control card. School children were considered physically inactive sedentary if they performed less than 300 min/week of physical activity.[16] Sedentary activities included watching television, playing video games, and sitting in front of the computer for more than 2 h a day.[17] Family income was based on the Brazilian minimum wage at the time of the study (US$230/month).

The BMI and blood pressure values of the progenitors (father and mother) were analysed in accordance with the guidelines established by the World Health Organization[18]and the Brazilian Society of Cardiology,[15] respectively.

Statistical analysis

Non-parametric analysis (Wilcoxon and Kruskal-Wallis test) was used to evaluate statistically significant differences in lipoprotein (a) levels (non-normal distribution) between each category of the demographic (gender, age, pubertal stage, skin color), economic (familiar income), anthropometric (body mass index, waist circumference, body fat by skinfold thickness, bipolar body fat, tetrapolar body fat, mother's/father´s BMI), biochemical (LDL-c, total cholesterol, HDL-c, triglycerides, fasting glucose), life style (physical activity, sedentary habits) and clinical parameters (systolic and diastolic blood pressure, mother's/father´s systolic and diastolic blood pressure, weight at birth) using median and interquartile range levels to guide interpretation. For binary logistic regression analysis, associations between lipoprotein (a) (above and below median) and each category of independent variables were assessed. Variables with p≤0.20 in the univariate analysis were included in binary regression logistic model. The analysis was carried out using the SPSS software (version 20.0; SPSS Inc, Chicago, IL, USA). Differences between values were considered statistically significant for p-values < 0.05.

This study was approved by the Institutional Review Board of the Federal University of Ouro Preto (Protocol Number 2004/46).

Results

The total sample was composed of 320 individuals, 49.1% (n=157) girls, with a mean age of 10.4±2.4 years. Lipoprotein (a) exhibited an asymmetrical distribution in this population, with a mean ± standard deviation of 33.7±27.6mg/dL, and median of 25.5mg/dL. Lipoprotein (a) levels above 30mg/dL and null values occurred in approximately 43.8% and 2.5% of the individuals, respectively. Table 1 presents median/range the lipoprotein (a) levels by demographic and economic variables. No significant difference was found in lipoprotein (a) serum levels between these subgroups.

Table 1 - Lipoprotein(a) levels by demographic and economic variables

Variables	n	Median / range	p*
Gender			0.24
Female	157	26.1 / 107.2	
Male	163	24.7 / 106.6	
Age (years)			0.25
6-9	126	24.2 / 107.2	
10-14	194	26.0 / 106.6	
Pubertal Stage			0.37
Pubertal	145	23.3 / 105.1	
Prepubertal	100	27.4 / 107.2	
Postpubertal	75	25.9 / 106.6	
Skin color			0.55
White	50	21.7 / 98.5	
Mixed race	248	25.7 / 107.2	
Black	12	35.3 / 85.2	
Family Income†			0.25
>4	29	22.1 / 95.4	
1-4	228	24.9 / 107.2	
<1	26	42.7 / 101.8	

** Kruskal Wallis test; † Based on the minimum wage (MW)*

Table 2 presents median (range) of lipoprotein (a) levels by biochemical and clinical variables. Non-significant associations were found for lipoprotein (a) levels and low-density lipoprotein-cholesterol, high density lipoprotein-cholesterol, triglycerides, or fasting glucose. However, in children with a high range of total cholesterol, lipoprotein (a) levels [38.7mg/dL (106.6)] were significantly higher than those in individuals with normal and moderate total cholesterol levels [24.3mg/dL (102.3) and 20.3mg/dL (107.2), respectively]. Lipoprotein (a) levels did not vary significantly with changes in clinical variables, or changes in systolic (p=0.17) and diastolic blood pressures (p=0.68). Additionally, no associations were observed between lipoprotein (a) levels and weight at birth (p=0.46).

In Table 3, no associations of lipoprotein (a) levels with BMI, waist circumference, or body fat measured by skinfold thickness were found. However, lipoprotein (a) levels were significantly higher in school children with excess weight [31.2mg/dL (107.2)] than in those with normal body fat [24.5mg/dL (106.6)]. Furthermore, median lipoprotein (a) levels were higher in individuals with excess weight, as measured by tetrapolar methods, than in individuals with normal weight [22.9mg/dL (107.2) and 38.6mg/dL (105.1), respectively]. No associations were observed between lipoprotein (a) levels and sedentary habits (p = 0.77). However, a consistent upward trend in lipoprotein (a) levels was observed in sedentary school children [26.0 mg/dL (107.2)] in comparison with active individuals [21.8 mg/dL (106.6)].

Table 4 presents lipoprotein (a) levels by family variables. There was no association between lipoprotein (a) levels of school children and blood pressure of their fathers, although this result may be unreliable because many fathers did not allow measurement of their blood pressures. Similarly, there was no association between lipoprotein (a) levels and familial BMI. However, lipoprotein (a) levels were significantly higher in children born from mothers with high systolic (p=0.02) and diastolic (p=0.04) blood pressure than in those with normotensive mothers.

In a logistic regression analysis adjusted by sex and pubertal stage, it was observed that lipoprotein (a) levels vary significantly in school children with high body fat measured by tetrapolar technique (p=0.01) and those whose mothers had elevated systolic blood pressure (p = 0.03). High lipoprotein (a) levels amongst

Table 2 - Lipoprotein(a) levels by biochemistry and clinical variables

Variables	n	Median / range	p*
LDL-c (mg/dL)			0.19
<100	233	23.3 / 107.2	
100-129	69	38.6 / 106.6	
≥ 130	18	22.8 / 91.9	
Total Cholesterol (mg/dL)			0.04
<150	139	24.3 / 102.3	
150-169	79	20.3 / 107.2	
≥ 170	102	38.7 / 106.6	
HDL-c (mg/dL)			0.73
≥ 45	278	25.5 / 107.2	
< 45	42	25.6 / 102.3	
Triglycerides (mg/dL)			0.71
<100	286	25.2 / 107.2	
100-129	34	29.0 / 102.3	
Fasting glucose (mg/dL)			0.70
<110	316	25.5 / 107.2	
≥110	4	32.3 / 95.1	
Systolic blood pressure (percentile)			0.17
< 90	294	26.1 / 106.6	
≥ 90	16	21.2 / 44.2	
Diastolic blood pressure (percentile)			0.68
< 90	298	26.0 / 106.6	
≥ 90	12	22.8 / 41.8	
Weight at birth (g)			0.46
≥ 2,500	208	21.7 / 101.1	
< 2,500	48	35.5 / 104.0	

** Kruskal Wallis test*

Table 3 - Lipoprotein(a) levels by anthropometric and lifestyle variables

Variables	n	Median / range	p*
Body mass index (percentile)			0.30
85	266	24.8 / 107.2	
≥ 85 < 95	39	28.9 / 102.4	
≥ 95	15	27.4 / 86.6	
Waist circumference (percentile)			0.83
≤ 50	214	25.2 / 107.2	
> 50 < 75	53	24.3 / 81.0	
≥ 75< 90	27	31.8 / 95.4	
≥ 90	24	25.4 / 97.9	
Body fat by skinfold thickness (%)			0.26
≤20† , ≤25‡	250	25.1 / 107.2	
20.1-25 † , 25.1-30‡	47	28.9 / 105.1	
>25.1† , >30.1‡	23	26.1 / 67.8	
Body fat (%)			0.05
≤25† , ≤30‡	231	24.5 / 106.6	
>25† , >30‡	87	31.2 / 107.2	
Tetrapolar body fat (%)			0.009
≤25† , ≤30‡	248	22.9 / 107.2	
>25† , >30‡	69	38.6 / 105.1	
Physical activity (min/week)			0.07
≥ 300	58	21.8 / 106.6	
< 300	226	26.0 / 107.2	
Sedentary habits (h/week)			0.77
< 2	36	26.8 / 95.4	
> 2	280	25.3 / 107.2	

** Kruskal Wallis test, † boys, ‡ girls*

Table 4: Lipoprotein(a) levels by family variables

Variables	n	Median / range	p*
Mother's systolic blood pressure (mmHg)			0.02
<130	156	20.7 / 105.1	
≥130-139	34	20.4 / 97.9	
≥140	83	28.9 / 107.1	
Mother's diastolic blood pressure (mmHg)			0.04
<85	132	20.1 / 101.1	
≥85-89	34	36.2 / 105.1	
≥90	107	26.1 / 107.2	
Father's systolic blood pressure (mmHg)			0.42
<130	44	19.2 / 105.1	
≥130-139	30	32.1 / 97.5	
≥140	74	30.1 / 102.3	
Father's diastolic blood pressure (mmHg)			0.22
<85	47	19.2 / 105.1	
≥85-89	29	24.3 / 98.5	
≥90	60	35.4 / 99.9	
Body mass index (Kg/m²)			0.76
<24.9	123	23.0 / 100.2	
≥25.0-29.9	96	24.8 / 100.2	
≥30.0	71	28.9 / 107.2	

** Kruskal Wallis test*

children with high body fat and born from currently hypertensive mothers were, respectively, 3.2 and 1.4 times higher than those of subjects not included in these categories (data not shown). In clustering higher tetrapolar body fat and mother´s systolic blood pressure, we observed that school children with high

body fat, born from hypertensive mothers and those with the two characteristics were 2.7 times, 2.3 times and 2.6 times more likely to have elevated lipoprotein (a) levels compared with normal children (Table 5).

Discussion

In our study, lipoprotein (a) distribution was skewed, with a high frequency of null (2.5%) or low values among children living in Ouro Preto, similar to that observed in the adult population[8] and that reported in another study.[7] This study showed an association of lipoprotein (a) with anthropometric, biochemical and behavioral data, as well as with the progenitors. Serum levels of lipoprotein (a) were not independent predictors of cardiovascular risk factors, but were associated with body fat and the mother's systolic blood pressure.

In contrast to some studies,[19,20] in our study, lipoprotein (a) levels were not associated with any demographic variables. Pubertal stage seems to influence lipoprotein (a) levels. Chen et al.[20]analysed 314 same-sex Chinese twin pairs aged 5–18 years and observed that lipoprotein (a) increased after the onset of puberty and was significantly higher in girls than in boys.

Although we did not find significant associations regarding skin color, this study contributes to the existing literature, in terms of the peculiarities of lipoprotein (a) distribution in a mixed paediatric population. Several studies have shown that lipoprotein (a) levels are higher in blacks than in whites.[21] Unlike the studies conducted in well-defined racially segregated populations, our study was conducted in Ouro Preto city, which has a mixed Brazilian population, including individuals with black ancestry. The reason for this racial difference between lipoprotein (a) levels has not been found. More studies are needed to clarify the influence of mixed race on lipoprotein (a) levels in children and adolescents.

As with other studies, we observed only a significant association between lipoprotein (a) and total cholesterol levels. Dirisamer et al.[13]analysed lipoprotein (a)levels and apo(a) isoforms in children and adolescents with familial hypercholesterolemia and observed that 46% of these individuals had higher lipoprotein (a) levels and lower apo(a) isoform levels than the control group. They concluded that elevated small-isoform lipoprotein (a) levels might be a strong and independent cardiovascular risk factor in hypercholesterolemic children and adolescents. An increase in lipoprotein (a)-associated cholesterol in the arterial intima can trigger mechanisms that lead to atherothrombosis.[5] In childhood, the role of lipoprotein (a) in the onset of atherosclerosis is uncertain. Weigmanet al.[22] have shown that elevated lipoprotein (a) in children with familial hypercholesterolemia is predicative of a parent with premature cardiovascular disease risk. However, Sirachainanet al.[23]demonstrated that lipoprotein (a) levels did not differ between children with thromboembolism and controls. In our study, we expected to find an association between low density lipoprotein-cholesterol and lipoprotein (a), since the dyslipidemic adults of Ouro Preto city, and likely children and adolescents with dyslipidemia,

Table 5 - Distribution of lipoprotein(a) levels by the combined variables: tetrapolar body fat and mother´s systolic blood pressure

Variables		Lipoprotein (a) (mg/dL)		Odds ratio (IC 95%)	p*
Tetrapolar body fat (%)	Mother's systolic blood pressure (mmHg)	< 25.5 *n*	>25.5 *n*		
≤ 25† , ≤30‡	< 130	92	54	1	
> 25† , >30‡	< 130	13	21	2.7 (1.20 – 6.38)	0.01
≤ 25† , ≤30‡	≥ 130	27	37	2.3 (1.23 – 4.45)	0.008
> 25† , >30‡	≥ 130	10	15	2.6 (0.99 – 6.64)	0.05

** Pearson's X^2 test, † boys, ‡ girls.*

have higher frequency of ApoE4 and lower frequency of ApoE2.[24] However, research has shown isolated hyperlipoproteinemia(a) in the presence of normal low-density lipoprotein-cholesterol.[25] More research is needed to answer these questions in children and adolescents.

Our study verified that lipoprotein (a) levels were higher in school children with higher body fat than in school children with normal body fat. After adjusting for age, pubertal stage, cigarette smoking, and alcohol drinking, Chu et al.[26] showed that low-density lipoprotein-cholesterol, Apo B and Apo A were significantly associated with lipoprotein (a) levels, while BMI and waist circumference had no significant correlation. This demonstrated that the association of lipoprotein (a) with other blood lipids was more important than with anthropometric parameters. Of particular importance in this analysis is the evidence that BMI is not a specific anthropometric measurement for determination of body fat,[27] and thus is not the ideal index to evaluate the association between lipoprotein (a), obesity, and cardiovascular diseases. The role of obesity in lipoprotein (a) levels should not be underestimated. Moreover, the location of body fat deposits seems to be especially important in predicting changes in lipid metabolism[28] and consequently, in lipoprotein (a) levels.

Clinical variables such as birth weight, and sedentary habits are not correlated with lipoprotein (a) levels, in contrast to the findings of Cunningham et al.[4] In agreement with Taimela et al.,[29] we observed that school children who performed less than 300 min of physical activity per week had consistent upward trend in lipoprotein (a) levels than those who were physically active. Physical activity must influence lipid parameters[30] and may consequently modify lipoprotein (a) levels.

A family history of cardiovascular diseases is a risk factor associated with lipoprotein (a) levels in children and adolescents.[6,31] In our study, we observed that high arterial blood pressure in the mother is predictive of elevated lipoprotein (a) levels. In a logistic regression analysis, lipoprotein (a) levels vary significantly in school children with high body fat and those whose mothers had elevated systolic blood pressure. We suggest that the presence of familial risk factors for cardiovascular diseases, as well as high body fat or both, may be predictive of elevated lipoprotein (a) levels in children and adolescents.

Our study had some limitations. First, despite the non-parametric analysis, the limited number of subjects in some of the subgroups may have influenced the results. Further studies are needed to identify these possible associations. Second, we did not assess apo(a) isoforms. Apo(a) isoform size is inversely correlated with lipoprotein (a) concentration,[5] and low-molecular-weight apo(a) patterns have been reported as independent risk factors for atherosclerosis.[6,19] Therefore, the evaluation of the apo(a) genotype would have allowed a better understanding of the biological relationship between lipoprotein (a) and risk factors. Lipoprotein (a) was defined by median levels. The values obtained were similar to the age-dependent reference values established by Langer et al.[32]

This study is in agreement with reports by Ferrettiet al.,[5] and Cunningham et al.,[4] who suggested that lipoprotein (a) should be measured once in all subjects at risk for cardiovascular diseases and that this screening should begin in childhood.

Conclusion

Measurement of serum lipoprotein (a) levels in children and adolescents with familial hypertension and obesity might be a useful tool for identifying patients at increased cardiovascular risk. This practice will enable more effective preventative actions against cardiovascular diseases.

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 Ouro Preto* under the protocol number 2004/46. 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: Cândido APC, Machado-Coelho GLL. Acquisition of data: Cândido APC, Mendonça-Mendes A, Cândido DRC, Roney LC Nicolato RLC. Analysis and interpretation of the data: Cândido APC, Mendonça-Mendes A, Cândido DRC, Nicolato RLC, Machado-Coelho GLL. Statistical analysis: Cândido APC, Machado-Coelho GLL. Obtaining financing: Machado-Coelho GLL. Writing of the manuscript: Cândido APC, Cândido DRC, Nicolato RLC, Machado-Coelho GLL. Critical revision of the manuscript for intellectual content: Cândido APC, Mendonça-Mendes A, Machado-Coelho GLL.

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EDITORIAL

Elevated Lipoprotein(A) in Children and Adolescents: Early Identification is Key for Successful Intervention

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Editorial referring to the article: Lipoprotein(a) levels in children and adolescents: Ouro Preto Study

Over the last decades, numerous studies have demonstrated that elevated lipoprotein (Lp)(a) is a powerful and independent risk factor for coronary heart disease,[1,2] ischemic stroke,[3] and calcific aortic stenosis.[4] Even in patients treated with statins who achieve LDL-cholesterol goals below 70 mg/dL, elevated Lp(a) levels remain independently related to an increased risk of atherosclerotic events.[5]

The LDL particle has a unique molecular structure, as exemplified by its covalent bond with an apolipoprotein(a) that bears resemblance to plasminogen and may well represent an evolutionary deviation of this well-known plasmin precursor.[6] Lp(a) is synthesized by the liver and the amount of circulating particles in the bloodstream is almost exclusively determined by inheritance, leaving very little space for environmental influence. The distribution of Lp(a) levels in the population is highly skewed with approximately 80% of people exhibiting plasma concentrations below 50 mg/dL, and the remaining 20% with a wide range of values above that limit.

Despite its unequivocal importance as a cardiovascular risk factor, until recently there had been little interest in aggregating its measurement to the lipid profile determination, and this underappreciation has been reflected even in recent lipid guidelines[7–9]: Lp(a) measurement is recommended, as stated by the aforementioned guidelines, for patients who have experienced an atherosclerotic event unexplained by traditional risk factors, for those with familial hypercholesterolemia and for people who either suffered a premature heart attack, or have a family history of premature atherosclerotic cardiovascular disease. Possible explanations for the gap between epidemiological and genetic evidence and the incorporation of Lp(a) measurement in clinical practice may involve (1) the lack of standardization of its unit (nMol/L or mg/dL); (2) the use of immunoassays based on non-specific antibodies targeted at more than one copy of the kringle-IV2 subtype on the same Apo(a) particle; (3) disagreement about cut-off points to define increased risk and; (4) a perception among the medical community that no therapeutic solution is yet available.

With the publication of a dose-escalating study that assessed the efficacy and safety of an antisense oligonucleotide capable of silencing the messenger RNA responsible for Apo(a) translation,[10] there has been an ever growing interest in the identification of patients who might be candidates for this new therapy, which is currently being studied in a multicenter double-blind randomized outcome study.[11] In 2019, possibly as an acknowledgement of the potential advantage of emerging pharmacological approaches, the European Society of Cardiology prompted to recommend the measurement of Lp(a) at least once in a lifetime, irrespective of the presence of other risk factors.[12]

The Apo(a) gene is fully expressed by the fifth year of life, when plasma levels similar to those observed in adulthood can be reached.[13,14] In children and adolescents, elevated Lp(a) has been reported to be associated with a positive family history of premature cardiovascular disease and early predictors of atherosclerosis such as endothelial dysfunction.[15]

Keywords

Lipoprotein(a); Atherosclerosis; Child; Adolescents; Coronary Artery Diseases; Statins/therapeutic, use; Aortic Stenosis.

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In a previous cross-sectional study carried out in a sample of adults living in Ouro Preto, Minas Gerais, Cândido et al. found an independent relationship of elevated Lp(a) levels with the Framingham risk score and ischemic heart disease.[16] In the present issue of the IJCS, the authors extend their observations on the association of elevated Lp(a) with risk factors to a cohort of 320 school children between 6 and 14 years old from the same town.[17] It is noteworthy that the assay, as stated by the authors, was highly specific for lipoprotein(a) and minimized the interference introduced by heterogeneity in apo(a) isoforms. With a careful definition and assessment of laboratory and anthropometric variables and, as much as possible, with the incorporation of parental variables, the authors explored the possible association of the risk factors with Lp(a) levels. Among schoolchildren, no independent association of Lp(a) with traditional risk factors was found after adjustments by multivariate analysis, but body adiposity and maternal systolic blood pressure seemed to have an influence on the concentration of that lipoprotein. In contrast to studies carried out in racially segregated populations, the authors did not find any influence of skin color on Lp(a) levels, an information that matches with the highly miscigenated character of our population.

As acknowledged by the authors, the statistical significance of some associations might be hampered by the small number of cases in some of the subgroups. This is evident in Table 5, where body adiposity above reference values, clustered with increased maternal systolic blood pressure, yielded a marginal but not statistically significant association with higher Lp(a) concentrations. Conversely, raised maternal blood pressure clustered with body adiposity within reference values had a strong significant association with high Lp(a) values. In the first case, there were only 10 subjects with Lp(a) below 25.5 mg/dL and 15 above this value, raising the possibility of play of chance.

Another source of uncertainty may be the method chosen to assess body adiposity. Although dual-energy X-ray absorptiometry (DXA) is the gold standard method, it is hardly feasible in routine clinical practice, as opposed to bioelectrical impedance analysis. However, some authors cast doubts on the agreement of results between both methods,[18,19] especially at individual level,[19] which could leave room for some degree of inaccuracy in body composition measurement.

A question not addressed by the authors, as it was not the scope of the research, pertains to the ideal age to measure Lp(a) levels. Obesity epidemic has hit hard emerging countries and there is an alarming rate of increase in overweight and obesity amongst children and adolescents.[20] If timely assessed, an elevated Lp(a) should be a strong reason to emphasize the promotion of a healthy lifestyle. Therefore, screening for Lp(a) might target not only children with a positive family history of premature atherosclerotic disease or raised Lp(a), but also, as suggested by the present article, obese and overweight children born from parents with multiple risk factors, especially in the presence of maternal hypertension.

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ORIGINAL ARTICLE

Carotid Intima and Media Thickness Correlation with Central Blood Pressure Measurements by Tonometric and Oscillometric Methods: A Proof of Concept

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Abstract

Background: The early detection of vascular damage in subclinical stages of hypertensive disease may be the key point in the prevention of cardiovascular outcomes.

Objectives: to correlate parameters of structural vascular damage (measurement of the carotid intima-media thickness) with parameters of functional vascular damage (central hemodynamic measurements) in pre-hypertensive and hypertensive patients taking up to two classes of anti-hypertensive drugs.

Methods: This was a cross-sectional descriptive study conducted with a convenience sample of patients attending the *Liga de Hipertensão Arterial*, a multidisciplinary program for the diagnosis and treatment of systemic hypertension, of the Federal university of Goias. Patients with arrythmia, diabetes, previous cardiovascular or cerebrovascular diseases, and end-stage diseases were excluded. Carotid Doppler test, measurements of peripheral and central blood pressure by applanation tonometry (Sphygmocor®) and oscillometry (Mobil-O-Graph®) were performed. The t-test was used for comparisons and the Pearson correlation test for correlations, considering a $p<0.05$ statistically significant.

Results: twenty patients (12 women) were evaluated, mean age 53.8 ± 14.3 years. Higher values of central pulse pressure (42.9±13.9 vs. 34.7±9.6, p=0.01) and pulse wave velocity (PWV) (9.0±1.9 vs. 7.9±1.5, p=0.01) were obtained by applanation tonometry compared with oscillometry. No difference between the methods was observed for the other measures. A significant correlation was found between carotid artery intima-media thickness (CA-IMT) and PWV (r=0.659; p=0.002) by the oscillometric test, but not with applanation tonometry. No correlation was found between central hemodynamic variables and the presence of carotid artery plaques.

Conclusion: PWV, estimated by oscillometry, was the only central hemodynamic parameter that correlated significantly with CA-IMT in pre-hypertensive and hypertensive patients at low cardiovascular risk. (Int J Cardiovasc Sci. 2021; 34(1):22-29)

Keywords: Cardiovascular Diseases/prevention and control; Carotid Intima - Media Thickness; Blood Pressure; Vascular Stiffness; Hypertension; Manometry/ methods; Oscillometry/methods.

Introduction

The early detection of vascular injury in subclinical hypertensive disease may be the key point to delay or even prevent major cardiovascular outcomes.[1]

The measurement of the carotid artery intima-media thickness (CA-IMT) using ultrasound is a low cost, available, reproducible method, with no risks associated, and with good histopathological correlation.[2] It is useful as a non-invasive assessment method of vascular hypertrophy and atherosclerotic disease;[3] it is considered a robust predictor of cardiovascular events and surrogate marker of atherosclerosis. Its clinical use is a component of the risk score for coronary events.[4]

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However, functional vascular damage can also be assessed by central hemodynamic and arterial stiffness parameters.[5] The knowledge of the concepts of pulse wave velocity (PWV), central blood pressure (cBP), central pulse pressure (cPP) and augmentation index (AIx) promotes a broader and clearer view of lesions in the target organ, and its prevention and treatment.[6]

Many non-invasive devices aiming to estimate these parameters have been developed, tested and validated. The analysis is made from pulse waves obtained from arterial beds far from the aorta.[7] In these transfer models, principles and methods of calibration or substitution of different signals (applanation tonometry, oscillometry, ultrasound and magnetic resonance imaging) are used, each with advantages and limitations. The oscillometric method tends to underestimate PWV compared with tonometry and intra-arterial measurements.[8]

SphygmoCor® is an instrument that provides measurement of PWV in the femoral and carotid arteries by applanation tonometry. The system, validated and used for decades, is currently considered the gold standard non-invasive method for acquisition of central hemodynamic measures.[8]

The oscillometric method, here represented by the Mobil-O-Graph® monitor, measures peripheral artery (usually brachial or radial artery) PWV and reconstructs the central pulse wave by applying a transfer function.[9] This is a technically simple method, with a good cost-benefit relationship compared with tonometry.[10]

We performed a proof-of-concept study, aiming to demonstrate that, despite underestimating PWV, the oscillometric method provides the best correlation with structural damage of the artery compared with tonometry in pre-hypertensive patients and low-risk hypertensive patients. To achieve this, we correlated structural vascular abnormalities (CA-IMT) with functional (central hemodynamic) parameters obtained by tonometry (Sphygmocor®) and oscillometry (Mobil-O-graph®).

Methods

This was a descriptive cross-sectional study conducted with patients enrolled in the *Liga de Hipertensão Arterial* (LHA), a multidisciplinary program for the diagnosis and treatment of systemic hypertension, of the Federal University of Goias, Brazil. The study was approved by the ethics committee of the university General Hospital (approval number 000985/2016).

The sample was selected between March and July 2016 from 1,500 patients enrolled in the LHA, by review of active medical records and completion of a specific form, previously developed for the study. Two hundred and forty patients were considered eligible. Inclusion criteria were patients older than 18 years, pre-hypertensive or stage 1 hypertensive patients taking up to two different antihypertensive classes. Exclusion criteria were patients enrolled in other research protocols within less than one year and patients with comorbidities potentially predisposing to endothelial dysfunction, such as diabetes,[11] end-stage chronic diseases, including chronic renal failure and congestive heart failure,[12] and previous cardiovascular and cerebrovascular diseases, such as coronary artery disease and ischemic stroke.

In the second phase of the study, telephone contact was attempted for the eligible patients; after three unsuccessful attempts in different days and times the patients were excluded. When successfully contacted, the patient was invited to attend the LHA in two days – the first for blood pressure measurements and the second (scheduled day and time) for carotid Doppler study.

Thirty-six patients were included. After the interview and imaging tests, two patients were excluded due to history of ischemic stroke, two for arrhythmia, which would affect cBP measurements, and 12 quit participating. Therefore, the convenience sample was composed of 20 participants.

On the first day of the study, each patient was seen in a private room and instructed about the study, and those willing to participate signed an informed consent form. Subsequently, the patients completed a questionnaire on anthropometric data, lifestyle, previous diseases, and underwent central and peripheral blood pressure measurements and carotid Doppler ultrasound.

Peripheral blood pressure was measured at the office according to standard procedures recommended by the Brazilian guidelines on blood pressure.[12] A semiautomated device (OMRON®, model HEM-705CP) was used, which was validated by international centers and has been recommended for epidemiological studies.[13]

Measurement of cBP was made using two different methods – applanation tonometry, performed using a SphygmoCor® device, which was calibrated, and clinically validated by the European Society of Hypertension (ESH) and the European Society Cardiology (ESC).[14] The instrument consists of a

tonometer (portable pressure transducer or sensor) coupled to a computer with dedicated software for collection and analysis of the data. Patients' personal and anthropometric data, medications used, and peripheral blood pressure (pBP) assessed during the first visit were inserted to the system. When used on the radial artery, SphygmoCor® also obtains measures related to central systolic (cSBP) and diastolic blood pressure (cDBP), pulse pressure amplification (PPA), cPP and AIx by transfer function. When used on carotid and femoral arteries, the system also calculates the carotid-femoral PWV.[14]

The oscillometric method was performed using the Mobil-O-Graph®, a validated device that estimates cBP from pulse wave acquired from the brachial artery using a pressure cuff.[8] Data are analyzed by a dedicated software.[8] Similar to the SphygmoCor®, the Mobil O'Graph also allows the determination of cBP, PWV, AIx, cPP and PPA, and parameters related to arterial resistance and compliance. Central BP measurements were made with patients in siting position, as previously established.

On a second day, carotid Doppler test was performed to assess early structural vascular changes based on the IMT. The test was performed at the Division of Echocardiography of Federal University of Goias General Hospital the using the Toshiba Xario ultrasound system, with a wideband, linear array transducer, central frequency of 7.5 MHz (5.0 – 11.0 MHz) in a longitudinal section – two-dimensional B-mode imaging.[4] The test was performed with patient in supine position, head at 45º in the opposite direction to the side examined.

CA-IMT measures were obtained from distal right and left common carotid arteries, 1 cm from the carotid artery bifurcation, considering the distance between the two echogenic lines represented by the lumen-intima and the media–adventitia interfaces of the arterial wall, following the American Society of Echocardiography (2008)[15] and the European Society of Echocardiography[14] consensus.

Statistical analysis

First, a descriptive statistical analysis was carried out, using absolute and relative frequencies for qualitative variables and mean, standard deviation (SD) and 95% confidence interval for quantitative variables.

The t-test was used for comparisons of central pressure measures between the methods (SphygmoCor® and Mobil-O-Graph®) and of arterial stiffness indices between patients with and without plaques in the carotid arteries.

The Pearson correlation test was used for correlations of CA-IMT measures with pBP, cBP and central hemodynamics. For analysis of CA-IMT, the highest value obtained from the carotid arteries as well as the mean of the measures were used for analysis.

A data analysis and statistical software, Stata, version 14.0, was used for the statistical analyses. A $p<0.05$ was set as statistically significant.

Results

Twenty individuals (12 women, 60%), mean age of 53.8 ± 14.3 years participated in the study. Mean body mass index was 28.4 ± 5.2 Kg/m^2. Five (25%) patients did not take any medication, eight (40%) took only one class of anti-hypertensive drugs; angiotensin receptor blockers were the most used. Most patients had a sedentary lifestyle, did not consume alcohol, and did not smoke (Table 1).

Central hemodynamic measures obtained by the SphygmoCor® and the Mobil-O-Graph® were not different, except for cPP and PWV, which were lower

Table 1 – Characteristics of the study sample regarding use of anti-hypertensive drugs and lifestyle (n = 15)

Variable	n	%
Class of drugs		
Angiotensin receptor blocker	11	73.3
Angiotensin converter enzyme inhibitor	02	13.3
Diuretics	06	40.0
Beta-blockers	02	13.3
Calcium channel blockers	01	6.6
Physically active		
Yes	06	30.0
No	14	70.0
Alcohol consumption		
No	10	50.0
Yes	08	40.0
Ex-consumer	02	10.0
Smoker		
No	15	75.0
Yes	03	15.0

using the Mobil-O-Graph® than the SphygmoCor® (Table 2).

No correlation was found between CA-IMT and pBP or cBP. CA-IMT correlated with PWV values obtained by the oscillometric method (Mobil-O-Graph®) (Table 3). Mean CA-IMT also correlated with PWV (Table 4).

Arterial stiffness parameters (AIx and PWV) were not different between patients with and without carotid artery plaque (Table 5).

Table 2 – Central blood pressure measures estimated by SphygmoCor® and Mobil-O-Graph® (n = 20)

Variable	Sphygmocor		Mobil-O-Graph		p
	Mean±SD	95%CI	Mean±SD	IC95%	
cSBP	123.6±23.1	112.8-134.4	116.8±25.1	105.1-128.6	0.05
cDBP	80.0±15.6	73.5-88.1	81.4±14.6	74.6-88.2	0.79
cPP	42.9±13.9	36.4-49.4	34.7±9.6	30.1-39.1	0.01
PPA	12.2±8.8	8.1-16.3	11.3±4.1	9.4-13.2	0.63
AIx	22.4±11.0	17.3-27.6	22.4±11.0	17.3-27.5	0.98
PWV	9.0±1.9	8.1-9.9	7.9±1.5	7.1-8.6	0.01

T-test; cSBP: central systolic blood pressure; cDBP: central diastolic blood pressure; cPP: central pulse pressure; PPA: pulse pressure amplification; AIx: augmentation index; PWV: pulse wave velocity

Table 3 – Correlation between carotid intima-media thickness (the greatest measure) and peripheral and central blood pressure obtained by Sphygmocor® and Mobil-O-graph®

Variables	Device	r	p
Peripheral measures			
Peripheral systolic pressure	OMRON®	0.298	0.201
Peripheral diastolic pressure	OMRON®	0.190	0.420
Central measures			
Central systolic pressure	Sphygmocor®	0.317	0.172
	Mobil-O-graph®	0.215	0.361
Central diastolic pressure	Sphygmocor®	0.280	0.231
	Mobil-O-graph®	0.100	0.679
Central pulse pressure	Sphygmocor®	0.288	0.217
	Mobil-O-graph®	0.440	0.052
Pulse pressure amplification	Sphygmocor®	0.006	0.809
	Mobil-O-graph®	-0.007	0.751
Augmentation index	Sphygmocor®	0.111	0.640
	Mobil-O-graph®	0.185	0.434
Pulse wave velocity	Sphygmocor®	0.266	0.255
	Mobil-O-graph®	0.659	0.002

Pearson correlation test

Table 4 – Correlation between mean carotid intima-media thickness and peripheral and central blood pressure measures obtained by Sphygmocor® and Mobil-O-graph®

Variables	Device	r	p
Peripheral measures			
Peripheral systolic pressure	OMRON®	0.29	0.217
Peripheral diastolic pressure	OMRON®	0.216	0.361
Central measures			
Central systolic pressure	Sphygmocor®	0.334	0.151
	Mobil-O-graph®	0.291	0.213
Central diastolic pressure	Sphygmocor®	0.242	0.305
	Mobil-O-graph®	0.120	0.614
Central pulse pressure	Sphygmocor®	0.287	0.219
	Mobil-O-graph®	0.437	0.054
Pulse pressure amplification	Sphygmocor®	0.020	0.932
	Mobil-O-graph®	-0.05	0.805
Augmentation index	Sphygmocor®	0.148	0.533
	Mobil-O-graph®	0.236	0.317
Pulse wave velocity	Sphygmocor®	0.271	0.247
	Mobil-O-graph®	0.579	0.008

Table 5 – Correlation between presence of carotid artery plaques and arterial stiffness indices obtained by Sphygmocor® and Mobil-O-graph®

Variable	Absence of plaque (n=14)	Presence of plaque (n=06)	p
AIx (Sphygmocor)	21.8±11.4	23.8±10.9	0.724
AIx (Mobil-O-Graph)	23.1±10.7	20.8±5.0	0.687
PWV (Sphygmocor)	8.8±2.0	9.6±1.8	0.422
PWV (Mobil-O-Graph)	7.4±1.5	8.8±1.3	0.078

AIx: Augmentation index; PWV: pulse wave velocity

Discussion

The detection of vascular damage at subclinical stages has potential additional value in cardiovascular risk stratification. In the last years, new vascular parameters evaluating both structural and functional properties of the arteries have been introduced as surrogates for outcomes in clinical trials.[15]

Elevated CA-IMT is a morphological indicator of vascular damage. Functional changes usually precede structural changes and can be detected by arterial stiffness detected by hemodynamic indices like PWV.[16]

Both CA-IMT and PWV have a linear and progressive odds ratio for major cardiovascular outcomes, even in case of slight increases.[17] The increase in CA-IMT was associated with progression of coronary lesions evaluated by coronary angiography and carotid ultrasound in 558 individuals. When mean IMT was over 1.15 mm, patients had a 94% probability of having coronary artery disease.[18]

In addition, there is evidence indicating that CA-IMT and PWV are associated with the severity of coronary lesions in angiographic analysis of 100 patients.[1] A longitudinal study with 274 elderly patients followed by eight years showed the importance of these two parameters as indicators of future cardiovascular events, especially when concomitantly used.[19]

In this context, both CA-IMT and PVW are considered important markers of cardiovascular risk by the most important guidelines on arterial hypertension, especially in the initial stages of hypertension and in hypertensive patients at low- or intermediate risk.[14]

In the present study, the correlation between CA-IMT and arterial stiffness was determined ($r = 0.659$, $p = 0.002$) with PWV estimated by oscillometry (Mobil- O-graph®), but not with PWV estimated by SphygmoCor®.

Most of the few studies available correlating IMT with PWV have used applanation tonometry as it is considered the gold-standard method, and a few studies using plethysmography.[20-23]

A clinical trial with 271 type 2 diabetic patients and 285 healthy controls showed a statistically significant correlation ($p<0.001$) between CA-IMT and aortic PWV, obtained by tonometry, in both groups.[20]

A study with hypertensive adolescents reported a significant correlation ($p<0.05$) between IMT and brachial-ankle PWV.[21] Similarly, a study with 135 individuals showed an independent correlation between IMT and brachial-ankle PWV ($p<0.0001$) in adults younger than 70 years.[22] However, one limitation of both studies is the method, since although plethysmography is an easy-to-use, automated method, the PWV values estimated by the method are still questionable as compared with tonometry.[23]

In our study, no difference was found between tonometry and oscillometry for most of the variables studied (Table 3). The lower standard deviation of the values obtained by oscillometry suggests a higher reproducibility of the method compared with tonometry. Lower (or underestimated) values of arterial stiffness measures (cPP and PWV) were found for oscillometry compared with tonometry.

Therefore, one hypothesis for the correlation found between CA-IMT and PWV by the Mobil-O-graph® is the increased specificity resultant from the underestimation of PWV by the oscillometric method.

A study with 254 untreated hypertensive patients compared three non-invasive methods for assessment of cBP – the oscillometric, the piezoelectronic and the tonometric techniques – and showed low reproducibility between the values obtained by the different methods.[24] Another study, however, conducted with 89 patients, showed high similarity (with high reproducibility and reliability) in PWV obtained by the oscillometric (Tel-O-graph) and the tonometric (SphygmoCor®) method, which has not been reported by studies using the Mobil-O-graph®.[25]

Another study with 564 subjects established an association of IMT and carotid plaques with PVW obtained by tonometry, with an independent association for the presence of carotid plaques.[26] In contrast, in our study, the presence of carotid plaques did not show correlation with PVW, regardless of the method.

The pathophysiology of atherosclerotic plaque development is different from the IMT progression. In carotid plaque, intimal thickening occurs predominantly with foam cells, smooth muscle cells, macrophages, lipid core, and fibrous cap depending on the stage of plaque development.[27]

A study with 561 individuals without established coronary artery disease evaluated the correlation of arterial stiffness with carotid plaque echogenicity. Mean PWV was not different between patients without carotid plaques and patients with carotid plaques showing low echogenicity. Increased echogenicity was considered a determinant of the association between the presence of carotid plaque and aortic PWV.[28]

Some echocardiographic parameters related to the plaque help in the determination of cardiovascular risk. The degree of stenosis, surface irregularity, echogenicity and texture, which are components of the total plaque risk score, were predictors of ischemic events in the San Daniele study, a general population-based study of 1,348 subjects followed for 12 years. The addition of the plaque characteristics significantly increased the area under the ROC curve compared with the Framingham score alone, indicating that the total plaque risk score is a potential tool for predicting ischemic events.[29]

Therefore, the low association between arterial stiffness indices and the presence of carotid plaques in our study may be explained by morphology and/or severity of the lesions. Most of the plaques detected were small (≤30%), with low degree of calcification, corresponding to intermediate echogenicity. Plaque of approximately 45% was identified in only one patient, with significantly increased PWV values, obtained by both Sphygmocor® and the Mobil-O-graph®.

One limitation of the study was the small sample size. However, the correlation established between structural and functional parameters of vascular damage is important and may serve as a basis for further studies focusing an earlier detection of vascular lesions with potential cardiovascular risk.

Conclusion

The correlation between IMT and central hemodynamic measures was established in pre-hypertensive and low-risk hypertensive patients. This was true only when PWV calculated by oscillometry (Mobil O'graph®) was considered, and this method is still little explored in this regard.

We did not find any correlation between the presence of carotid plaque and PWV, regardless of the assessment method.

Most of cBP parameters were not different between the two methods, except for cPP and PWV, which were underestimated by oscillometry.

Author contributions

Conception and design of the research: Melo MA, Vitorino P, Arantes AC, Sousa ALL, Jardim PC, Jardim T, Souza WKSS. Acquisition of data: Melo MA, Gonçalves C, Berigó JA, Arantes AC. Analysis and interpretation of the data: Melo MA, Vitorino P, Jardim PC, Jardim T, Souza WKSS. Statistical analysis: Melo MA, Vitorino P, Souza WKSS. Writing of the manuscript: Melo MA, Vitorino P, Arantes AC, Rezende J, Jardim T, Souza WKSS. Critical revision of the manuscript for intellectual content: Melo MA, Vitorino P, Jardim PC, Jardim T, Souza WKSS.

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 HC-UFG under the protocol number 000985/2016. 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

Study of Arterial Stiffness - Based on Scientific Evidence, What are the Current Tools for the Study of Arterial Stiffness?

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Editorial referring to the article: Carotid Intima and Media Thickness Correlation with Central Blood Pressure Measurements by Tonometric and Oscillometric Methods: A Proof of Concept.

One of the biggest challenges in modern medicine is the early identification of patients with higher cardiovascular risks. The early identification of vascular damage in hypertensive patients is a challenge for cardiologists around the world in their attempt to reduce the risk of cardiovascular complications in patients.[1]

We know how important it is today to measure the thickness of the carotid intima-media complex through ultrasound examination in order to identify a greater or lesser cardiovascular risk.[2] Arterial stiffness has proven to be a marker of arterial disease, which is why it has become an important parameter for the assessment of cardiovascular risk.[3] It is also well-known that ventricular ejection generates a pressure wave that travels through the heart at a certain speed, which is known as the pulse wave velocity (PWV). The study of PWV in the carotid and femoral arteries is considered the gold standard in the assessment of arterial stiffness.[4]

The pulse wave generated by ventricular ejection travels through the arterial system and is regulated by peripheral vascular resistance. The study of the reflected speed in a bifurcation site and the moment of the cardiac cycle when this reflected speed occurs is of great importance. In young patients, the arteries have greater elasticity and, therefore, the reflected wave is slow in reaching the heart during diastole, generating an increase in diastolic pressure levels, thus favoring the perfusion of coronary arteries.[5] Other methods, such as central systolic blood pressure measurements and augmentation indexes, are applicable methodologies, but these are influenced by drugs, heart rate, and age, making them less reliable. Aging is always associated with arterial stiffening, but it is well-known that hypertensive disease anticipates and accelerates the process of arterial stiffening .[6]

Several cardiovascular risk factors can be associated with increased arterial stiffness, the main ones being: sedentary lifestyle, smoking, dyslipidemia, glucose intolerance, metabolic syndrome, and diabetes.[7] In Hypertensive heart disease and Diabetes, the arterial wall undergoes changes, changes that can lead to increased arterial stiffness. Elevated levels of adiponectin have also been associated with aortic stiffness in diabetic patients.[8,9] The identification through complementary methods of increasing arterial stiffness may suggest damage to the target organ, which is why the study of non-invasive arterial stiffness is so important nowadays.[10]

Other study methodologies can be used, such as applanation tonometry, a method that studies the pressure waves obtained in the carotid and femoral arteries, which is an accurate non-invasive tool in obtaining central hemodynamic measurements. The oscillometric method can also be used. This method studies the pressure waveforms in the brachial or radial arteries, is highly accurate, and can be performed in a simpler manner and with a better cost-benefit ratio, when compared to applanation tonometry.

Keywords

Vascular Stiffness; Pulse Wave Analysis; Elasticity: Circulatory System; Blood Pressure; Carotid Intima Media Thickness.

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The article "Carotid Intima and Media Thickness Correlation with Central Blood Pressure Measurements by Tonometric and Oscillometric Methods: A Proof of Concept", notes that early detection of vascular damage in subclinical stages of hypertensive disease may be the key to further optimizing prevention of cardiovascular outcomes. The increase in carotid artery intima-media thickness (CA-IMT) is a morphological index capable of detecting early damage, and today it is a variable used in stratifying cardiovascular risk. The assessment of arterial stiffness obtained through pulse wave velocity (PWV) and CA-IMT are considered, by the main guidelines of arterial hypertension, important markers of cardiovascular risk, especially in the early stages of hypertension and in groups of low and intermediate risk.[11]

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ORIGINAL ARTICLE

The Role of Cardiovascular Risk Factors and Risk Scoring Systems in Predicting Coronary Atherosclerosis

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Abstract

Background: Comparative data on the performance of cardiovascular risk scoring systems (CRSSs) in patients with severe coronary artery disease (CAD) are lacking.

Objectives: To compare different CRSSs regarding their ability to discriminate patients with severe CAD.

Method: A total of 414 patients (297 men; 61.3±12.3 years of age) undergoing coronary angiography were enrolled and evaluated for major risk factors. Cardiovascular risk and risk category were defined for each patient using the Framingham, Systemic Coronary Risk Evaluation (SCORE), and Pooled Cohort Risk Assessment Equation (PCRAE) tools. Severe CAD was defined as ≥ 50% stenosis in at least one major coronary artery and/or previous coronary stenting or coronary artery bypass grafting. A $p < 0.05$ was considered statistically significant.

Results: Severe CAD was identified in 271 (65.4%) patients. The ROC curves of the 3 CRSSs for predicting severe CAD were compared and showed no significant difference: the area under the ROC curve was 0.727, 0.694, and 0.717 for the Framingham, SCORE, and PCRAE tools, respectively ($p > 0.05$). However, when individual patients were classified as having low, intermediate, or high cardiovascular risk, the rate of patients in the high-risk group was significantly different between the PCRAE, Framingham, and SCORE tools (73.4%, 27.5%, and 37.9%, respectively; $p < 0.001$).

Discussion: PCRAE had higher positive and negative predictive values for detecting severe CAD in high-risk patients than the Framingham and SCORE tools.

Conclusion: We can speculate that currently used CRSSs are not sufficient, and new scoring systems are needed. In addition, other risk factors, such as serum creatinine, should be considered in future CRSSs. (Int J Cardiovasc Sci. 2021; 34(1):32-38)

Keywords: Cardiovascular Diseases; Coronary Artery Diseases; Risk Factors; Atherosclerosis; Epidemiology; Coronary Angiography; Diabetes Mellitus; Hypertension; Renal Insufficiency; Heredity.

Introduction

Coronary artery disease (CAD) is the leading cause of mortality and morbidity in developed countries.[1] According to the chronic disease report, there are about 2 million patients with CAD in Turkey[1]. About 17 million people all over the world and 200 000 living in Turkey are losing their lives because of cardiovascular diseases.[2]

Along with developing technology, a general rise in the consumption of high-fat and high-calorie foods and a decrease in physical activity have led to an increase in atherosclerosis and hypertension. Stroke and peripheral artery diseases, such as CAD, which are influenced by the same risk factors, also increase health care costs to a great extent and cause significant loss of labor force. Prevention and early detection of CAD have a substantial impact on

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the decrease of cardiovascular mortality, morbidity, and health expenditures.[3]

While the Framingham Heart Study has provided invaluable data on atherosclerosis and the natural history and epidemiology of CAD, modern medicine has introduced the concept of "risk factors" in cardiovascular disease. Risk factors can be described as parameters that predict future cardiovascular events. Potential coronary risk factors associated with biochemical-, genetic-, and lifestyle-related pathways have been well established with the understanding of the pathophysiology of atherosclerosis over the past 50 years, which has led to significant reductions in age-related cardiovascular mortality.[4]

The results of the Framingham Heart Study have served as a basis for other studies and have led to the development of new risk scales. In addition to the Framingham risk score (FRS), other risk probability models used to calculate total cardiovascular risk include the World Health Organization (WHO), Systemic Coronary Risk Evaluation (SCORE), Prospective Cardiovascular Münster (PROCAM), Joint British Societies 2 (JBS-2), QRISK, Scottish Intercollegiate Guidelines Network (SIGN), and Pooled Cohort Risk Assessment Equation (PCRAE) models. Many of these algorithms are based on age, sex, blood pressure, smoking, diabetes, and lipid levels. There are also relatively new scoring systems that focus on the number of additional risk factors, such as antihypertensive treatment, family history of coronary heart disease, social deprivation, high-sensitivity C-reactive protein (hs-CRP), and hemoglobin A1c (HbA1c) levels at a younger age.[5]

In all the different scoring systems that use the proposed quantitative risk assessment model to reduce the prevalence of cardiovascular disease in asymptomatic individuals, the most important aspect is that the low-risk population representing the largest group affected by the disease will not benefit from a high-risk strategy alone. In addition, risk models have disadvantages such as inability to quantitatively predict short-term absolute risk, inability to follow changes in the risk factor level or intensity (because the model focuses only on categorical risk factors), and the fact that the effect of advancing age is smaller than the progressive effect on absolute risk. Other problems that current risk scoring models need to overcome include the fact that they have not yet been adequately tested in clinical practice, they obscure the history of the risk factor (and therefore the changes in the risk factor level from one visit to the next), they focus on short-term rather than long-term risk assessment, and perhaps most importantly, whether they are adaptable to all populations remains uncertain.[6]

It is known that geographic region plays an important role in the distribution of risk factors. It is expected that risk factor distribution and density will be different according to geographic region. While PCRAE and FRS originated in North America, SCORE, PROCAM, the Reynolds risk score, and QRISK were developed mainly based on European societies. This reveals the need to test and compare the validity of risk models in different countries.

The present study aimed to determine and compare the ability of FRS and SCORE, risk assessment systems commonly used in practice, and especially of the relatively new PCRAE risk assessment system to detect high-risk patients in the Turkish population. It also aimed to determine the risk factors that may constitute a cardiovascular risk in these patients and that can be easily detected in routine examination by evaluating them one by one using logistic regression.

Methods

Study Patients

We conducted a prospective cross-sectional study of consecutive patients who underwent coronary angiography for the risk of coronary ischemia in 6 consecutive months in the year 2014 in the Department of Cardiology at the Gulhane Military Medical Academy, Ankara, Turkey. Eligible participants were all patients aged ≥ 18 years whose laboratory results were available from the hospital database. There were no exclusion criteria. In sample size calculation, we hypothesized that PCRAE would correctly predict 60% of the high-risk patients and, to detect a 15% difference with the FRS, we calculated that at least 364 patients needed to be included in the study, with a type I error of 0.05 and power of 80%. At the end of 6 consecutive months, we had enrolled 414 patients, which exceeded in approximately 10% the required sample size. Approval to conduct the study was obtained from the local ethics committee. Patients were informed about the study and individual consents were provided.

Preparation of the Database

For all patients, important medical history information was investigated, including age, sex, cardiac complaints, level of education, exercise frequency, nutritional

habits, smoking and alcohol consumption, coexistence of hypertension, hyperlipidemia, and diabetes mellitus, history of cardiac, neurologic, or other chronic disease, family history, and current medical treatment. Physical examination findings, such as blood pressure, height, and waist-to-thigh ratio, and laboratory findings, including complete blood count and available biochemical parameters, were evaluated in face-to-face preoperative visits for risk score analysis and other subgroup analyses. The FRS, SCORE, and PCRAE risk scoring systems were chosen for their popularity and conformity. Coronary angiograms were examined for disease extent and severity using the Gensini score. Patients who had coronary intervention or ≥ 50% stenosis were defined as having severe CAD.

Statistical Analysis

Continuous variables with normal distribution were expressed as means (SD). Normality of the data was examined by the Shapiro-Wilk test. Categorical variables were expressed as numbers and percentages. The sign test was used for paired comparisons of the mean risk levels calculated by the different risk scoring systems. The Friedman and sign tests were used to compare different risk scores. Stepwise multivariable logistic regression analysis with backward elimination was used to identify independent predictors of cardiovascular disease. C-statistics were used to compare receiver operating characteristic (ROC) curves. All variables with a $p < 0.05$ in the univariate analysis were included in the multivariable model. For each variable, the odds ratio (OR) and the corresponding 95% confidence interval (CI) were calculated. Each risk system had its variables weighted according to the regression coefficient. The discriminatory power of the risk model was assessed by calculating the area under the ROC curve (AUC). Cutoff values were defined as the highest values of the sum of sensitivity and specificity. Statistical analyses were performed using Medcalc and SPSS for Windows (version 20.0; SPSS, Inc, Chicago, IL). Statistical significance was set at $p < 0.05$.

Results

A total of 414 patients were included in the study. Of these, 297 (71.7%) were men and 117 (28.3%) were women, with a mean (SD) age of 61.3 (12.3) years. Demographic, clinical, and laboratory characteristics of the study population are shown in Table 1.

Table 1 - Demographic, clinical, and laboratory characteristics of the study population

PHYSICAL EXAMINATION	N = 414
Sex (female), n (%)	117 (28)
Age (years), mean ± SD	61.3 ± 12.3
Body mass index (kg/m^2), mean ± SD	28.2 ± 4.6
Systolic blood pressure (mm Hg), mean ± SD	130.5 ± 20.9
Diastolic blood pressure (mm Hg), mean ± SD	78.8 ± 12.5
Pulse pressure (mm Hg), mean ± SD	51.6 ± 15.3
COMORBIDITIES	
Hypertension, n (%)	241 (58.2)
Diabetes mellitus, n (%)	116 (28.0)
Smoker, n (%)	111 (26.8)
Chronic kidney disease, n (%)	66 (15.9)
Family history of coronary artery disease, n (%)	164 (39.6)
LABORATORY	
Hemoglobin (g/dL), mean ± SD	13.8 ± 1.9
Leukocyte (102/mm^3), mean ± SD	7.6 ± 2.8
Thrombocyte (102/mm^3), mean ± SD	243.70 ± 73.7
Fasting blood glucose (mg/dL), mean ± SD	124.8 ± 59.1
Urea (mg/dL), mean ± SD	36.3 ± 14.3
Creatinine (mg/dL), mean ± SD	1.0 ± 0.39
eGFR (mL/min) , mean ± SD	85.9 ± 27.6
Total cholesterol (mg/dL), mean ± SD	197.5 ± 44.6
LDL cholesterol (mg/dL), mean ± SD	123.4 ± 39.8
HDL cholesterol (mg/dL), mean ± SD	44.2 ± 10.6
Triglycerides (mg/dL), mean ± SD	166.6 ± 94.8
HbA1C (mg/dL), mean ± SD	7.3 ± 2.1

eGFR: estimated glomerular filtration rate; LDL: low-density lipoprotein; HDL: high-density lipoprotein; HbA1C: hemoglobin A1C.

The rate of patients with severe CAD was significantly high with all 3 risk scores used in the study. As expected, the Gensini score, which indicates prevalence in the group with severe vascular disease, was also high (Supplementary Table 1).

Patients were divided into low-risk, intermediate-risk, and high-risk groups according to the FRS, SCORE, and PCRAE scoring systems. Although the same population

was assessed by the 3 risk scoring systems, the distribution of risk groups was significantly different between them (Friedman test, X2 = 269.686, p < 0.001). When low-, intermediate-, and high-risk patients were scored as 1, 2, and 3 points, respectively, the mean risk category score of PCRAE was significantly higher than that of the other 2 systems (Supplementary Table 2). The rate of patients in the high-risk category was also significantly higher in the PCRAE system than in the other systems. Post hoc analysis showed a statistically significant difference in the binary comparisons between the 3 risk scoring systems (sign test, p < 0.001 for all comparisons).

There was no significant difference between the groups in AUC values (Supplementary Table 3) when comparing the power of ROC curves to determine the presence of severe vascular disease in subgroups considered to be at high risk according to the different risk scores.

After the patients were grouped according to risk category, as assessed by the 3 different risk models, the ROC curves were evaluated in relation to Gensini scores. The AUC values were 0.727, 0.717, and 0.694 for the FRS, PCRAE, and SCORE risk models, respectively (Supplementary Table 4), with a significant association of high Gensini score with severe coronary atherosclerosis.

A logistic regression test was performed to determine the effects of classical risk factors (age, sex, hypertension, diabetes, hyperlipidemia, and smoking) and renal insufficiency (estimated glomerular filtration rate [eGFR] < 60 mL/min) on predicting the likelihood of severe CAD ("likelihood"). The applied logistic regression model was found to be statistically significant (X2: 87.050, p < 0.001). The model described 27% of the severe CAD variance (Nagelkerke R2), with 73.8% of cases correctly classified (sensitivity of 89.0%, specificity of 44.1%, positive predictive value of 75.6%, and negative predictive value of 67.4%). The effects of the 5 variables included in the model (hypertension, hyperlipidemia, diabetes, male sex, and renal insufficiency) were statistically significant (Table 2).

Discussion

The primary goals of the present study were to assess the predictive value of risk factors in high-risk patients and to evaluate different risk scoring systems in terms of prediction of severe CAD. The cardiovascular risk category was higher in our sample compared with the general population as the study included only patients undergoing coronary angiography for suspected ischemia. Because risk factors differ according to geographic region, the effectiveness of risk scoring scales, mainly those developed in Europe and North America, is still uncertain. Therefore, the cardiovascular risk in the Turkish population remains a question to be answered.[7] Furthermore, the identification of the prevalence of potential risk factors may lead to the establishment of a cardiovascular risk score that reflects the overall risk in the Turkish population.

Initially, ROC curve and logistic regression analyses were used to determine the individual effects of risk factors such as age, sex, hypertension, diabetes, hyperlipidemia, chronic kidney disease, and smoking on coronary atherosclerosis. Creatinine and eGFR had the highest AUC values (0.648 and 0.647, respectively)

Table 2 - Logistic regression model for prediction of severe coronary artery disease

	B	SE	DF	P	OR	%95 CI
Hypertension	0.794	0.280	1	0.005	0.452	0.261-0.783
Sex	1.333	0.300	1	0.000	0.264	0.146-0.475
Hyperlipidemia	1.023	0.252	1	0.000	0.260	0.220-0.589
Diabetes mellitus	0.882	0.263	1	0.001	0.414	0.247-0.693
Smoking	0.394	0.281	1	0.164	0.674	0.389-1.168
Age	0.016	0.011	1	0.154	1.016	0.994-1.039
Renal Insufficiency	1.453	0.416	1	0.000	0.234	0.103-0.529
Coefficient	2.723	0.951	1	0.004	15.226	

B: Unstandardized beta; SE: Standard error; DF: Degrees of freedom; OR: Odds ratio; CI: Confidence interval (for OR)

among the parameters evaluated, with similar results obtained in the logistic regression analysis (OR: 0.234; p < 0.001). In the NHANES study, a close relationship was also observed between cardiovascular risk and renal dysfunction (eGFR < 60 mL/min/1.73 m^2): an eGFR reduction of 10 mL/min/1.73 m^2 in patients with eGFR < 60 mL/min/1.73 m^2 resulted in a 1.29 (95% CI, 1.06-1.55) increase in the risk of cardiovascular mortality[8-9] Although creatinine and eGFR are not included in the 3 risk models evaluated here (FRS, SCORE, and PCRAE), they were considered potential risk factors for predicting life-long cardiovascular risk. Subsequently, we evaluated and compared the data between the 3 different risk scoring systems under study. The rate of patients classified in each risk category (low, moderate, or high risk) was significantly different between the 3 systems (Friedman test, X2 = 269.686, p < 0.001).

The number of patients who fell into the high-risk category was significantly higher with the PCRAE tool (271/414 patients) than with the SCORE and FRS tools (121 and 87 of 414 patients, respectively). Also, the highest AUC value for the subgroups considered to be at high risk according to the different risk scores was obtained with the PCRAE risk model (0.673 vs 0.659 for FRS and 0.666 for SCORE). These findings seem to contradict the results of previous studies evaluating the PCRAE risk model. Maryam et al.[10], in a Rotterdam study of 4854 patients comparing the FRS, SCORE, and PCRAE tools, reported that SCORE provided the most appropriate risk model to categorize patient risk level, but all risk models predicted a higher risk than the current level. Additionally, the PCRAE risk model adopted in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines aimed at identifying individuals with higher actual risks to justify targeting them for statin treatment.[10] However, our sample consisted predominantly of high-risk patients, thus precluding a proper comparison of the results.

The association between risk score and CAD severity defined by the Gensini score was significant for all risk scoring systems evaluated. In addition, all scoring systems were able to significantly predict the presence of CAD, with only a slight difference between AUC values (FRS: 0.727, PCRAE: 0.717, and SCORE: 0.694). It should be noted that our study population is different from the original populations from which the models were derived. For example, age ranged from 20 to 85 years in the present study, an age range greater than that of the 3 risk models under study. Moreover, the models used hard clinical endpoints, whereas we used presence of CAD as an endpoint, and, most importantly, they included CAD-free patients, whereas we included only patients undergoing coronary angiography.

The value of newly defined risk factors has yet to be determined in these scoring systems, which usually have different combinations of the same classical risk factors. In general, patients are classified according to their risk factors for primary prevention. The FRS and SCORE scales have underestimated cardiovascular risk in terms of primary outcome, and the development of more accurate models has been desired. This is precisely why the PCRAE model, adopted in the 2013 ACC/AHA guidelines, has been put forward; however, it has also been criticized for overestimation and referral for unnecessary statin treatment, which was called "statinization".[11]

Because the aim of our study was to identify cardiovascular risk factors and to compare risk models for their ability to predict the presence and severity of coronary atherosclerosis, using conventional angiography as the gold standard is undoubtedly valuable. In the literature, the predictive value of risk models has been detected mostly by using coronary calcium scores and intravascular ultrasound (IVUS). The inclusion of the PCRAE risk model in the present study is also important as it supports the often criticized nature of this model, which greatly increases the use of statins compared to widely used conventional risk prediction models, such as FRS and SCORE.

Although studies evaluating the prediction of coronary atherosclerosis by risk scoring systems are limited,[12] coronary anatomy in these studies is mostly assessed by computed tomographic coronary calcium scanning to predict coronary atherosclerosis, and less frequently by IVUS and in small series of patients. Marso et al.,[13] in a multicenter study of 531 patients categorized by the FRS and evaluated by IVUS, showed an increase in plaque volume and thin-cap fibroatheroma in high-risk patients. Similarly, Takeshita et al.,[14] in 217 patients stratified by the FRS in whom coronary plaque volume was investigated by IVUS in non-stenotic left main coronary artery lesions, reported an association of increased atherosclerosis severity with increased cardiovascular risk. Rinehart et al.,[15] used computed tomographic coronary calcium scanning in 375 coronary segments and showed early vessel wall thickening in patients with intermediate to high risk according to the FRS. Ellis et al.[16], in a study of 1000 patients, reported high false positive rates for coronary calcium score assessment in individuals classified as low risk by the FRS, thus

suggesting calcium scoring as a complementary approach to standard risk identification strategies. In the present study (n=414), patients were grouped according to risk category, as assessed by the 3 different risk models, and the Gensini scores were then calculated according to the results of coronary angiography to determine the severity of coronary atherosclerosis in an attempt to determine the correlation between them. This study design had been previously used only by Sayin et al.,[17] and we adapted it to a larger patient population to evaluate risk categorization of patients using SCORE and PCRAE in addition to FRS.

Risk models are valuable tools for risk classification in patients with long-term follow-up of stable CAD and for the evaluation of treatment alternatives. It is important to raise patient awareness of long-term healthy lifestyle by proposing that patients at intermediate risk exercise, eat healthy, and quit smoking, but it is also important to identify and closely follow patients at high risk in order to provide intensive pharmacological treatment and, if necessary, revascularization to reduce cardiovascular risk. Although high-risk patients in current guidelines appear to be the focus of treatment alternatives, undoubtedly early-stage measures to be applied to low- and moderate-risk patients will narrow the high-risk patient population in the future.[18] In practice, predicting the presence and severity of vascular disease is important to establish the treatment strategy. In this respect, the FRS and PCRAE risk models are one step ahead of the SCORE risk model and can be useful tools for guiding invasive and noninvasive diagnostic tests and for determining treatment options.

Limitations

Our study has important limitations. First, the sample size was calculated according to the primary hypothesis of the study. However, the number is underpowered for individual risk factors to predict the presence of severe CAD in subgroup analyses. Second, risk assessment models were not implemented in the population with known CAD, because these patients are already considered a high-risk group. However, since the aim of the study was to compare the differential strengths of the risk scoring systems in patients known to be at high risk, the population selection is considered appropriate. Finally, it is a single center study and the sample consisted only of patients admitted to our hospital, which prevents the generalization of the results.

Conclusion

The commonly used FRS and SCORE risk scoring systems and the new PCRAE risk scoring system have significant differences in terms of their ability to detect high-risk patients. Although the PCRAE system seems to be superior to the others, the high likelihood of having CAD in the present study population should be kept in mind. The PCRAE system has been criticized for its low positive predictive value in the general population, making more people to be on statin treatment. Another important result of this study is that renal insufficiency or reduced eGFR alone were identified as strong predictors of the presence of severe CAD. Therefore, eGFR, which can be easily calculated, is an effective variable to be incorporated into new risk assessment systems.

Author contributions

Conception and design of the research: Gormel S, Barcin C. Acquisition of data: Gormel S. Analysis and interpretation of the data: Gormel S, Barcin C. Statistical analysis: Gormel S, Barcin C. Writing of the manuscript: Gormel S, Barcin C. Critical revision of the manuscript for intellectual content: Barcin C.

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 article is part of the thesis of Doctoral submitted by Suat Gormel, from Gulhane Training and Research Hospital, Ankara – Turkey.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Gata Komutan Bilimsel Yardimciligi under the protocol number 50687469-1491-254-14/1684.4-561. 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

Risk Prediction Systems: One for all or all for Some

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Editorial referring to the article: The Role of Cardiovascular Risk Factors and Risk Scoring Systems in Predicting Coronary Atherosclerosis.

Cardiovascular diseases (CVD) are the main cause of death in Brazil and worldwide, determining an increase in morbidity and disability-adjusted life years (DALYs). The prevalence of CVD increased from 271 million (95% uncertainty interval [UI]: 257–285) in 1990 to 523 million (95% UI: 497–550) in 2019, and the number of deaths steadily grew from 12.1 million (95% UI: 11.4–12.6) in 1990 to 18.6 million (95% UI: 17.1–19.7) in 2019 in the 21 world regions analyzed by the Global Burden of Disease (GBD) 2019 study. The prevalence of CVD is likely to increase in Northern Africa and Western Asia, Central and Southern Asia, Eastern and Southeastern Asia, and Latin America and the Caribbean due to population growth and aging.[1]

Ischemic heart disease (IHD) is part of this heterogeneous group of disorders, in which an acute coronary event is the first manifestation in approximately half of the cases.[2,3] The total number of DALYs due to IHD has risen steadily since 1990, reaching 182 million (95% UI: 170-194) DALYs and 9.14 million (95% UI: 8.40-9.74) deaths in 2019. The GBD 2019 study has estimated 197 million (95% UI: 178-220) prevalent cases of IHD in 2019.[1]

Age-standardized rates for DALYs, deaths, and prevalent cases has declined over this period, indicating that, on average, global increases in IHD have been due to population growth and aging. Age-standardized DALYs due to IHD were highest in Eastern Europe, Central Asia, and the Middle East / Northern Africa. However, for some countries, such as China, age-standardized rates have not declined. Most national health systems will need to address the increasing demand for IHD-related preventive and therapeutic services as these trends continue. Therefore, the ability to recognize asymptomatic individuals with coronary artery disease (CAD) is essential for planning interventions that seek to reduce the individual risk of progressing to a major cardiovascular event, such as myocardial infarction (MI), stroke, or death.

The likelihood of an individual having CAD and, therefore, requiring cardiovascular risk assessment depends on the identification of risk factors and pre-existing comorbidities. The intuitive attribution of risk is often mistaken and can be justified by the complex interaction of different risk factors with the possibility of synergistic pathophysiological action between them.[2,3] Thus, clinical guidelines recommend the use of algorithms based on regression analysis in population studies to improve risk judgment and optimize preventive strategies.

The Brazilian Society of Cardiology recommends through its latest guideline for the prevention of cardiovascular risk (2019) the use of the Global Risk Score (ERG) to help identify asymptomatic individuals with a greater predisposition to CAD.[3] This tool is derived from the "Framingham Heart Study" (FHS), developed in a North American population, which estimates the risk of MI, stroke, heart failure, peripheral vascular failure, or death in 10 years.[4] However, new risk scores are developed in different regions of the world and bring with them innovations and the bases learned from the FHS.

Different geographic regions and their own population characteristics, as well as the transformations they undergo within a timeline, play a fundamental role in the distribution of risk factors and interfere with the positive and negative predictive values of risk scores. Such considerations indicate the need to test and compare the validity of risk scores in different countries and, possibly, within the same country at different times.[5,6] Görmel et al. have exemplified the difference in the predictive value that can be found between the scores when applied to different regions and populations.[7]

Keywords

Coronary atherosclerosis, Coronary artery disease, Risk factors, Cardiovascular diseases, morbidity.

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Clinical research by Görmel et al. has assessed the role of cardiovascular risk factors and risk scoring systems in predicting severe coronary atherosclerosis. Severe CAD was considered when ≥ 1 epicardial artery had a stenotic lesion ≥ 50% or the need for percutaneous or surgical coronary intervention. The study has been carried out in Turkey and included 414 patients (297 men; 61.3 ± 12.3 years) undergoing coronary angiography. The Pooled Cohort Risk Assessment Equation (PCRAE), originating in North America, showed higher positive and negative predictive values to detect severe CAD in high-risk patients than the FHS tool and the Systemic Coronary Risk Evaluation (SCORE), originating in North America and Europe, respectively.[7]

In addition, according to Görmel et al., when patients were classified as having low, intermediate, or high cardiovascular risk, the rate of patients in the high-risk group was significantly different between the PCRAE, the FHS and the SCORE tools (73.4%, 27.5%, and 37.9%, respectively; p <0.001). However, the analysis of subgroups based on individual risk factors could not be considered because of the insufficient sample size. Another important limitation of the study is its single-center nature that hinders generalization of the results.[7]

It is important to note that IHD was responsible for a variable percentage of DALYs in different world regions (Figure 1A-1E). In 2019, in Turkey (Figure 1A), 9.43% (95% II: 7.76% -11.24%) of DALYs were due to IHD, with an annual change of -0.88% between 1990 and 2019. For the United States (Figure 1B), in those same years, the values were 8.09% (95% II: 7.09% -9.17%) and -1.4%; for Western Europe (Figure 1C), 7.22% (95% II: 6.21% -8.19%) and -2.26%; for Brazil (Figure 1E), 5.71% (95% II: 5.07% -6, 34%) and -0.31%; and globally (Figure 1D), 7.19% (95% II: 6.46% -7.95%) and 0.13%, respectively. With such relevant regional variations in mortality and DALYs, it seems difficult to assume that a single risk prediction score would be adequate for different realities, which could justify such different findings by different authors in assessing high-risk patients.[7] In addition, Figure 1 demonstrates the relative importance of noncommunicable diseases (marked in blue) in the regions mentioned above, where those scores were developed and applied.

In conclusion, the prediction of CAD in asymptomatic patients based on risk scores requires validation studies in different populations and, possibly, within the same population at different times. In view of the interest in developing better cardiovascular risk scoring systems, encouraging multicenter research in large sample aggregates can provide better investigation of individual risk factors and their importance for the whole.[8]

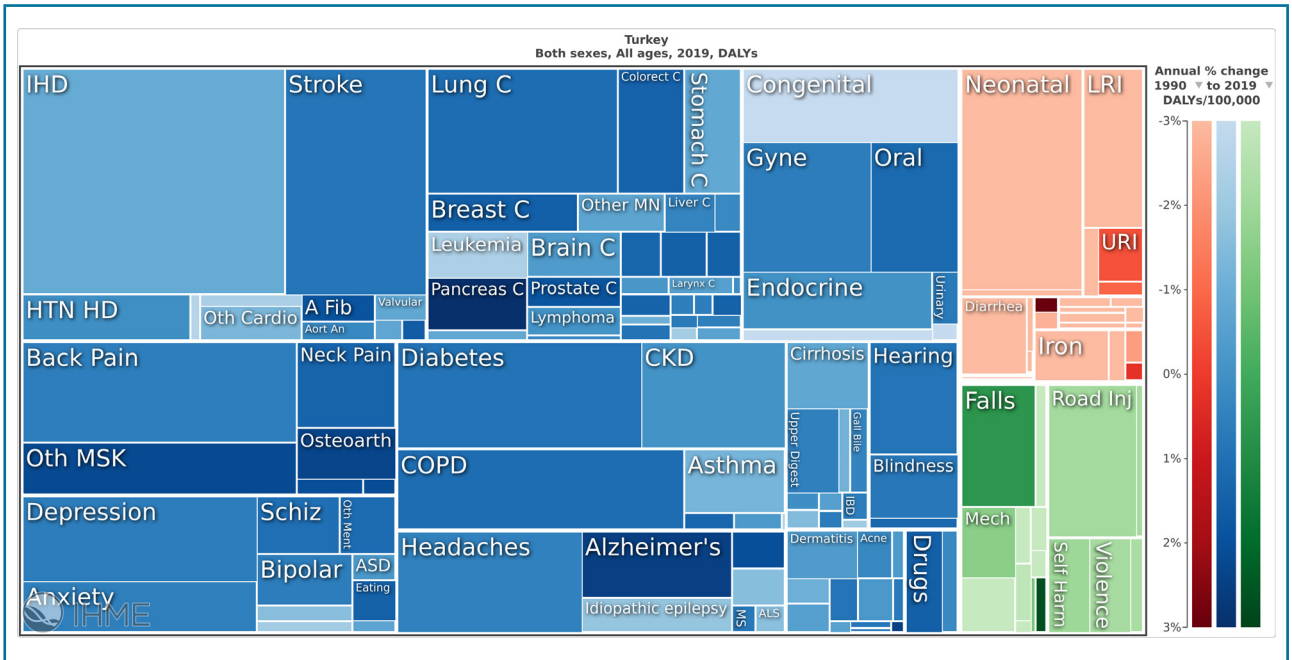

Figure 1A Turkey - 2019 DALYs according to causes and annual percent change from 1990 to 2019, for both sexes, all ages.[9]

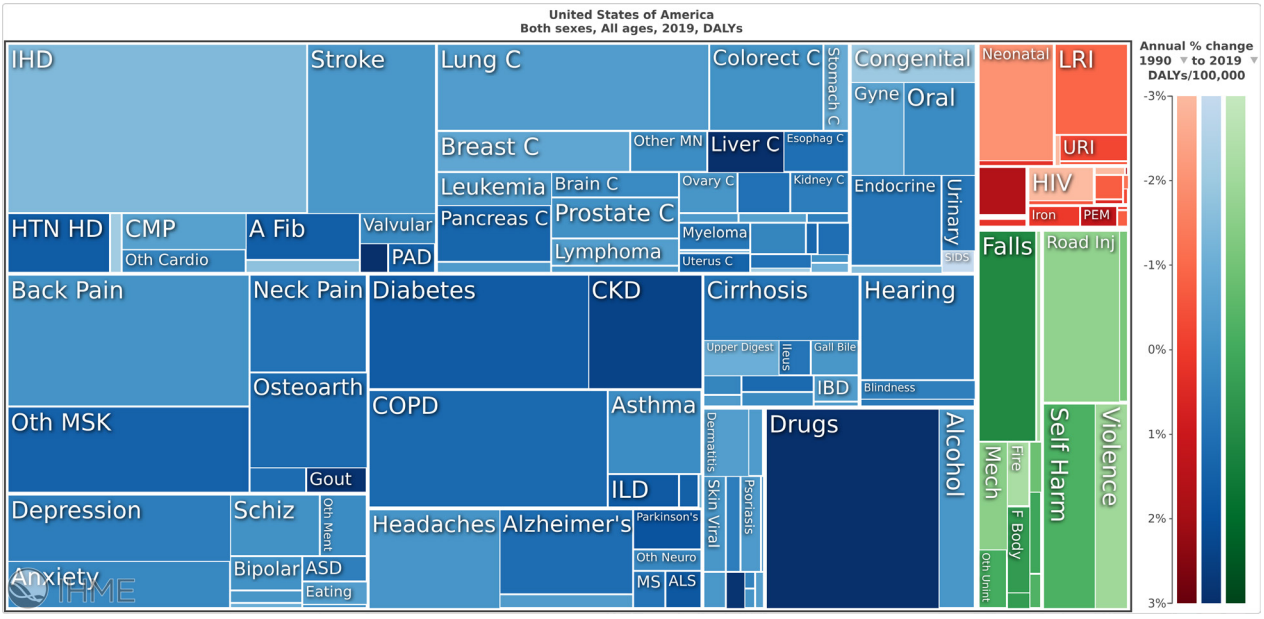

Figure 1B - United States of America / Figure 1C - Western Europe - 2019 DALYs according to causes and annual percent change from 1990 to 2019, for both sexes, all ages.[9]

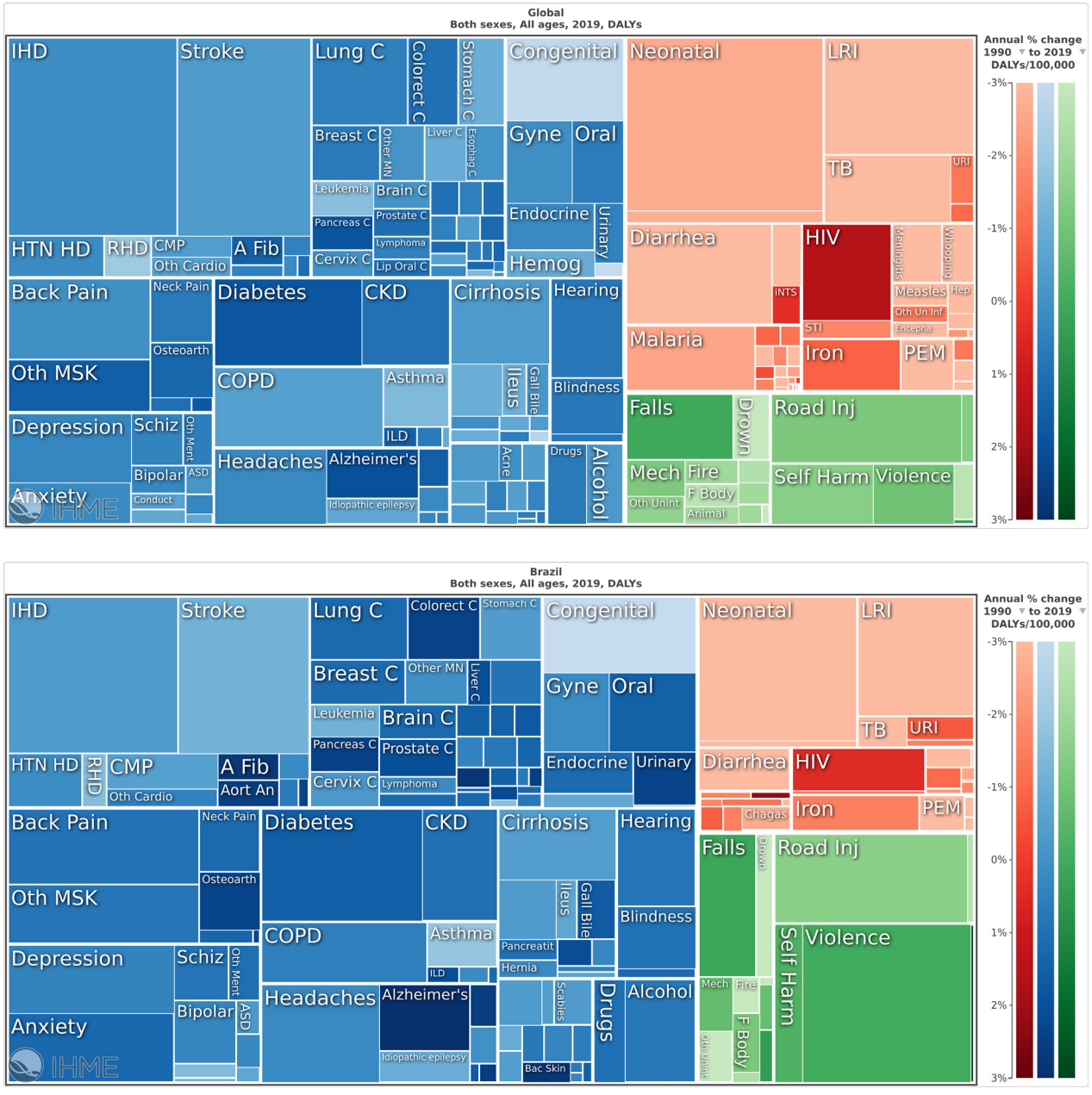

Figure 1D - Global / Figure 1E - Brazil - 2019 DALYs according to causes and annual percent change from 1990 to 2019, for both sexes, all ages.[9]

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ORIGINAL ARTICLE

Effects of Inspiratory Muscle Training Using an Electronic Device on Patients Undergoing Cardiac Surgery: A Randomized Controlled Trial

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Abstract

Background: Cardiac surgery causes pathophysiological changes that favor the occurrence of pulmonary and functional complications.

Objective: To investigate the effects of inspiratory muscle training (IMT) with an electronic device on patients undergoing cardiac surgery.

Methods: A randomized controlled trial was conducted with 30 adult patients undergoing elective cardiac surgery. A control group (CG) received conventional physical therapy care, and an intervention group (IG) received IMT using the POWERbreathe K5® electronic device. Two daily sessions of physical therapy were performed at the intensive care unit and one daily session at the ward until the sixth postoperative day. The following variables were measured preoperatively and on the sixth postoperative day, in both groups: inspiratory muscle strength, dynamic inspiratory muscle strength, and peak inspiratory flow. Data distribution was evaluated by the Shapiro-Wilk test. Analysis of variance was used, and the results were considered statistically significant when $p < 0.05$.

Results: Maximal inspiratory pressure (71.7 ± 17.1 cmH2O vs 63.3 ± 21.3 cmH2O; p = 0.11], S-index (52.61 ± 18.61 vs 51.08 ± 20.71), and peak inspiratory flow [(2.94 ± 1.09 vs 2.79 ± 1.26)] were maintained in the IG but had a significant reduction in the CG.

Conclusion: IMT performed with an electronic device was effective at maintaining inspiratory muscle strength, dynamic inspiratory muscle strength, and peak inspiratory flow when compared to conventional physical therapy. (Int J Cardiovasc Sci. 2021; 34(1):44-52)

Keywords: Respiratory Tract Diseases/complications; Cardiac Surgery/complications; Breathing Exercises; Muscle Strength; Physiotherapy; Rehabilitation.

Introduction

Cardiopulmonary physical therapy is widely used in prevention and treatment of complications after cardiac surgery.[1] Some strategies can be used to minimize complications, including physical therapy, continuous positive pressure, intermittent positive pressure breathing (IPPB), bi-level positive airway pressure (BiPAP), and respiratory stimulants, all of which have been found to be safe, easy to administer, and very effective for patient recovery in the postoperative period.[2]

Respiratory muscle training has received considerable attention in the field of cardiopulmonary physical therapy because of its direct benefits for respiratory muscles.[3] Within respiratory muscle training, inspiratory muscle training (IMT) has long been administered to some patients, including those with chronic obstructive pulmonary disease, and its reported benefits include increased respiratory muscle strength, improved symptoms of dyspnea, and greater ability to perform physical exercise.[4]

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IMT has also been used in the treatment of chronic heart disease and the control of diastolic and systolic blood pressure.[5] Stroke patients who have undergone IMT have increased ability to perform activities of daily living, improved walking ability, and increased respiratory muscle strength.[6]

Some studies have demonstrated that the use of IMT in the preoperative period of cardiac surgery increases inspiratory muscle strength, decreases the incidence of pulmonary complications, and reduces length of hospital stay.[7,8] IMT has been found to improve tidal volume and vital capacity and reduce the length of stay in the cardiology department following cardiac surgery.[1] The beneficial effects of IMT have also been observed in cases of diaphragm paralysis after cardiac surgery.[9]

At present, some electronic devices are commonly used to perform IMT, such as Threshold®, a flow-independent linear load device,[3] and POWERbreathe®, which can be used for assessment of respiratory training and pulmonary function.[6,10] The POWERbreathe® devices differ from others because they are electronic devices that allow adjusting the load proportionally to the inspiratory flow, i.e., the higher the flow generated by the individual, the greater the resistance, and when the flow decreases, the resistance is reduced. This variation according to flow is important as it provides greater comfort to the patient during training.[11,12]

Additionally, electronic devices provide the possibility of starting training at lower loads, for example 3 cmH_2O, which is of utmost importance, especially in patients with very low maximal inspiratory pressure (MIP) values.[13] However, no studies to date have evaluated IMT using an electronic device in patients undergoing cardiac surgery.

Therefore, the objective of this study was to investigate the effects of IMT on respiratory muscle strength, dynamic inspiratory muscle strength, and peak inspiratory flow (PIF) using an electronic device in patients undergoing cardiac surgery.

Methods

This randomized clinical trial was performed in the Department of Cardiac Surgery at the *Hospital Universitário da Universidade Federal do Maranhão*, São Luís-Maranhão, Brazil.

Patients

The study population consisted of a convenience sample of 30 consecutive adult patients who underwent elective cardiac surgery Coronary artery bypass grafting (CABG), valve replacement, or CABG + valve replacement) from June 2016 to February 2017 and who were admitted to the Cardiology Intensive Care Unit (CICU) at Hospital Universitário da Universidade Federal do Maranhão (HUUFMA) in this period.

Patients with preexisting pulmonary or neurological diseases described on medical records or who did not agree to participate in the study were not included. Those who died in the preoperative period or who developed postoperative pulmonary or neurological complications that prevented the evaluations, and those requiring prolonged mechanical ventilation (> 24 hours) or noninvasive mechanical ventilation for more than 4 hours per day were excluded.

Measurements

The patients were informed about the study in the preoperative period. Those who agreed to participate and met the inclusion criteria signed an informed consent form. The enrolled patients completed an evaluation that included the following items:

Identification: included demographic data (name, sex, place of birth, occupation), anthropometric data (weight, height, body mass index, waist-hip ratio), clinical diagnosis, and personal medical history.

Manovacuometry: a digital respiratory pressure meter (MVD300, Globalmed, Porto Alegre, Brazil) was used to determine respiratory muscle strength based on MIP, according to recommendations of the American Thoracic Society and the European Respiratory Society for evaluation of the respiratory function.[14]

Mortality risk: included InsCor, a risk score used to predict mortality in patients undergoing heart surgery by analyzing several variables, including age (> 70 years); sex (female); associated surgery (CABG + valve replacement); recent infarction (< 90 days); reoperation; aortic valve repair; tricuspid valve repair; creatinine (> 2 mg/dL); ejection fraction (<30%); and preoperative events such as use of intra-aortic balloons, cardiogenic shock, tachycardia or ventricular fibrillation, orotracheal intubation, acute renal failure, use of inotropic drugs, and cardiac massage. Each of these variables had specific scores, which were summed to classify the patient into one of three categories: low risk (0–3 points), moderate risk (4–7 points), or high risk (> 8 points), as defined by Mejía et al.[15]

Inspiratory muscle dynamics: was measured using the POWERbreathe K5® electronic device (POWERbreathe International Ltd., Warwickshire, England). Dynamic inspiratory muscle strength (S-index) and PIF were assessed according to Lee et al.[6] and Minahan et al.[16]

Protocols

Patients were randomized by a simple drawing, after CICU admission, and divided into a control group (CG), which received conventional physical therapy care, and an intervention group (IG), which received IMT in addition to conventional care.

Patients initiated IMT 6 hours after extubation, usually on the first postoperative day. In the CICU, the patients remained in semi-Fowler's position at 45º[17] or, if possible, were placed on a chair with their feet flat on the floor and their back against the back of the chair for support (Figure 1). The seated position was also used in patients who were hospitalized but not in the CICU.[5] In both situations, patients were instructed to exhale calmly, followed by a maximal forced inspiration to total lung capacity using a mouthpiece and a nasal clip as an aid to prevent air leaks.[17]

IMT was performed in two daily sessions during the patients' stay in the CICU. Other hospitalized patients performed only one daily session. The patients underwent 30 respiratory cycles using a MIP load of 30% on the first postoperative day.[18] A new evaluation was performed to redefine the MIP load on the third postoperative day.[19]

The conventional physical therapy protocol for both groups was provided as recommended by Mendes and Borghi-Silva,[20] with the following instructions: adequate posture, deep inspiration, protection of the chest, stimulation of the return of functional activities, encouragement to cough, pulmonary re-expansion techniques, diaphragmatic breathing, timed breathing exercises, active range-of-motion exercises involving the limbs, active-assistive or active range-of-motion exercises (depending on each patient's condition) involving the elbows, shoulders, hips, and knees, early removal from the bed and from sedation, reduced ambulation (according to each patient's condition), and oxygen therapy, when necessary.

Inspiratory muscle strength, inspiratory muscle dynamics, and PIF were reassessed on the sixth postoperative day, and the data were compared. All patients received the same analgesia protocol with intravenous morphine (2–5 mg every 4 hours).

Interventions were performed by junior and senior physiotherapists. However, baseline and outcome assessments were conducted by a blinded senior physiotherapist.

Figure 1 – Participant in semi-Fowler's position undergoing an IMT session on the first postoperative day.

Statistical Analysis

The collected data were analyzed using Stata/SE software, version 12.1 (Statacorp, College Station, Texas, USA). The Shapiro-Wilk test was used to assess the normality of the groups. Quantitative variables with normal distribution are presented as mean and standard deviation, while continuous variables with non-normal distribution are described as median and interquartile range. Their differences were determined using paired and unpaired Student's t-test and Mann-Whitney test. Categorical variables are presented as absolute numbers and percentages, and their association was assessed using Fisher's exact test. The results were considered statistically significant when $p < 0.05$.

Results

The 30 patients included in the study had a mean age of 59.2 ± 13.1 years and were divided into two groups, as shown in Figure 1. Other demographic and clinical variables are detailed in Table 1. None of the analyzed variables differed significantly between the two groups, indicating that the sample was homogeneous. There were no significant differences in surgical data, mechanical ventilation duration, length of CICU stay, and length of hospital stay between the two groups (Table 2).

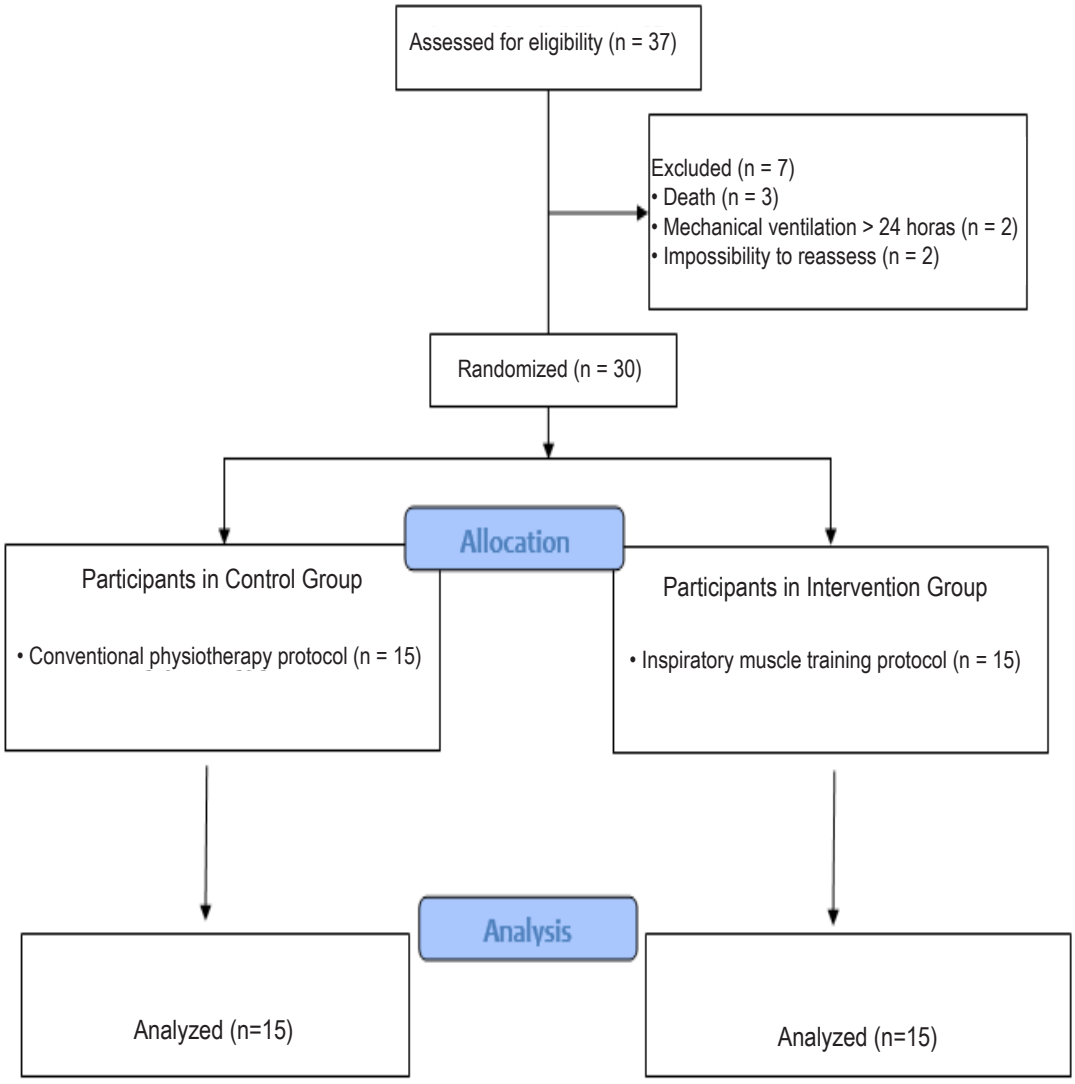

Figure 2 – Study flowchart.

Table 1 - Demographic and clinical data of patients undergoing cardiac surgery.

Variables	Control (n = 15)	Intervention (n = 15)	p
Gender			0.99[a]
Male	12	11	
Female	3	4	
Age (years)	59.7 ± 13.1	61.5 ± 12.3	0.70[b]
BMI (kg/m²)	25.0 ± 3.4	25.7 ± 3.0	0.54[b]
WHR	0.98 ± 0.06	0.98 ± 0.06	0.72[b]
Comorbidities			
Hypertension	10	11	0.99[a]
Smoking	4	9	0.14[a]
Diabetes mellitus	9	6	0.47[a]
Dyslipidemia	4	4	0.99[a]
AMI	3	7	0.15[a]
Chronic renal failure	2	1	0.99[a]
Ejection fraction			
Reduced (< 40%)	2	2	0.99[a]
Mid-range (40-49%)	2	1	
Preserved (> 50%)	11	12	
InsCor			
Low risk	12	9	0.21[a]
Medium risk	2	6	
High risk	1	0	
Surgery			
CABG	9	8	0.99[a]
Valve	5	6	
CABG + valve	1	1	

BMI: body mass index; WHR: waist-hip ratio; AMI: acute myocardial infarction; InsCor: mortality risk in cardiac surgery; CABG: coronary artery bypass grafting. [a]Fisher's exact test. [b]Unpaired Student's t-test.

Table 2 - Surgical data, mechanical ventilation duration, and length of CICU and hospital stay, per group, in patients undergoing cardiac surgery

Variables	Control (n = 15)	Intervention (n = 15)	p
Pump time (minutes)	96 (69.5; 111.5)	110 (90.5; 119)	0.30[a]
Cross-clamp time (minutes)	68 (51; 87.5)	87 (76; 99.5)	0.11[a]
Surgery time (minutes)	202 (184.5; 255)	210 (201.5; 269)	0.33[a]
MV duration (hours)	10.5 ± 7.1	9.5 ± 5.9	0.66[b]
CICU stay (days)	4.0 ± 1.9	3.8 ± 1.3	0.73[b]
Hospital stay (days)	13.1 ± 5.8	13.4 ± 7.4	0.89[b]

MV: mechanical ventilation; CICU: cardiology intensive care unit. [a]Mann-Whitney test. [b]Unpaired Student's t-test.

Manovacuometry

MIP differed significantly only in the CG ($p < 0.007$) but remained unchanged in the IG ($p < 0.11$) when comparing preoperative and sixth postoperative day assessments (Table 3).

S-index Evaluation

The S-index was significantly decreased in the CG ($p < 0.001$) but remained unchanged in the IG; there was no significant intergroup difference in this variable. PIF was significantly decreased only in the CG (Table 4).

Discussion

The present study determined the effect of IMT using an electronic device on patients undergoing cardiac surgery. Respiratory muscle strength and inspiratory muscle dynamics were analyzed.

Studies show that patients undergoing cardiac surgery have a high risk of postoperative pulmonary complications such as pneumonia, atelectasis, bronchospasm, prolonged mechanical ventilation, and acute respiratory failure.[21,22] The incidence of these complications may reach up to 87%, as found by Ortiz et al.[23]

Respiratory muscle strength is compromised after cardiac surgery and may take up to 6 weeks to reverse.[24,25] Some factors, including anesthesia and surgery, have been associated with a decrease in this parameter.[26] IMT has been reported to serve as an option for minimizing these losses,[8,27,28,29] and our study corroborated this finding. Patients who received IMT had similar MIP values in the preoperative and postoperative periods of cardiac surgery.[8,28,29]

Therefore, IMT may be an important strategy for minimizing respiratory muscle weakness due to cardiac surgery.[28] Hulzelbos et al.[30] reported that maintaining or increasing respiratory muscle strength is important to reduce the effects of pulmonary complications and has even decreased the length of hospital stay.

Table 3 - Comparison of maximal inspiratory pressure between study groups

	Control (n =15)	Intervention (n = 15)	p
MIP (cmH_2O)			
Preoperative	80.2 ± 33.7	71.7 ± 17.1	0.35
POD 6	56.5 ± 20.4	63.3 ± 21.3	0.53
p	0.007	0.11	

MIP: maximal inspiratory pressure; POD: postoperative day. Data showed as mean ± standard deviation. Paired Student's t-test (intragroup) and unpaired Student's t-test (intergroup).

Table 4 - Comparison of inspiratory muscle dynamics between study groups

	Control (n = 15)	Intervention (n = 15)	p
S-index (cmH_2O)			
Preoperative	50.71 ± 24.34	52.61 ± 18.61	0.95
POD 6	34.51 ± 16.62	51.08 ± 20.71	0.04
p	< 0.0001	0.79	
PIF (L/s)			
Preoperative	2.81 ± 1.40	2.94 ± 1.09	0.96
POD 6	1.86 ± 1.00	2.79 ± 1.26	0.03
p	< 0.0001	0.69	

POD: postoperative day; PIF: peak inspiratory flow. Data showed as mean ± standard deviation. Paired Student's t-test (intragroup) and unpaired Student's t-test (intergroup).

Cordeiro et al.[28] evaluated 50 patients divided into two groups. One group underwent IMT using the Threshold® device twice a day, with 3 sets of 10 repetitions, and the other group received only conventional ICU care, both until hospital discharge. The authors observed that the Threshold® group maintained its MIP values when compared to the other group. This is consistent with the results of this study, in which training lasted only until the sixth day.

The literature has emphasized the importance of performing IMT in the preoperative period. Some systematic reviews and meta-analyses show that when started in this period, IMT helps maintaining MIP, reduces the risk of postoperative complications, and decreases the length of hospital stay.[8,22] In this study, we investigated the effects of IMT only on inspiratory muscle strength.

IMT can be performed with linear pressure resistors such as Threshold®, which has been on the market for a long time and has already shown its effectiveness for gaining respiratory muscle strength. Recently, electronic load-adjusting devices such as the POWERbreathe K-series® (K1-K5) have been used. These devices adjust to the load imposed on respiratory muscles in proportion to the flow; the higher the flow, the greater the resistance, so the flow decreases the resistance, also providing greater comfort to the patient.[31,32]

In another study, Charususin et al.[33] used IMT with POWERbreathe® associated with pulmonary rehabilitation in patients with chronic obstructive pulmonary disease who had respiratory muscle weakness. At the end of the study, they observed increased endurance and improved dyspnea sensation in the patients.

The S-index can be measured using the POWERbreathe K-series® and is used to assess dynamic inspiratory muscle strength.[29] While MIP is obtained by maximal static inspiratory effort, the S-index is measured during a dynamic unobstructed inspiratory maneuver. Moreover, when MIP cannot be used to measure inspiratory muscle strength, the S-index appears to be a reliable alternative assessment.[11] However, no studies to date have provided reference ranges for this variable. Minahan et al.[11,29] reported that S-index values could not be compared to MIP values obtained using respiratory pressure meters.

In the present study, the group that received IMT maintained their baseline S-index and PIF in the postoperative period; in the control group, these values were lower in the postoperative period. This effect may be due to IMT because clinical and surgical variables were homogeneous in the study groups.

PIF measure has been associated with respiratory muscle strength.[34] Nemopuceno et al.,[17] when analyzing 10 individuals who underwent IMT twice a day for a period of 4 weeks after prolonged hospitalization, observed that these patients had increased PIF at the end of training. Weiner et al.[35] found that patients who underwent IMT presented a significant increase in MIP and PIF. These authors observed that inspiratory muscle strength played an essential role in the generation of PIF. However, no studies to date have provided reference ranges for this parameter.

Study Limitations

To our knowledge, this is the first study to investigate the effects of IMT on cardiac surgery patients using a new electronic device until the 6th postoperative day. However, there are limitations regarding the small number of patients and the number of training sessions (only six). Most studies with IMT after cardiac surgery perform training until hospital discharge. Another limitation of the present study was the non-reevaluation of inspiratory muscle strength (MIP and S-index) and PIF on the day of discharge, so that there was a comparison with the sixth postoperative day values. For these reasons, further randomized controlled trials with larger samples are needed to compare their results with those of the present study.

Conclusion

IMT performed with an electronic device was found to be effective at maintaining inspiratory muscle strength, dynamic inspiratory muscle strength, and PIF when compared to conventional physical therapy.

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Author Contributions

Conception and design of the research: Fortes JVS. Acquisition of data: Fortes JVS, Borges MGB, Marques MJS, Oliveira RL, Rodrigues LR, Castro EM. Analysis and interpretation of the data: Borges MGB, Borges DL. Statistical analysis: Borges DL. Writing of the manuscript: Fortes JVS. Critical revision of the manuscript for intellectual content: Esquivel MS, Borges DL.

Potential Conflict of Interest

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

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Study Association

This study is part of the conclusion work of a multiprofessional residency in health by the authors: João Vyctor Silva Fortes, Mayara Gabrielle Barbosa Borges, Maria Jhany da Silva Marques, Rafaella Lima Oliveira, Liana da Rocha Rodrigues, Érica Miranda de Castro, Mateus Souza Esquivel, Daniel Lago Borges.

Ethics Approval and Consent to Participate

The study was approved by the Brazilian Registry of Clinical Trials (REBEC) (identification no. RBR-8SWGC3) and by the Research Ethics Committee at our institution (Consolidated Opinion no. 1.573.419), as recommended by Brazilian National Board of Health (CNS) Resolution no. 466/12.

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ORIGINAL ARTICLE

Door-to-balloon Time in Cardiovascular Emergency Care in a Hospital of Northern Brazil

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Abstract

Background: The use of an adequate door-to-balloon time (≤ 90 minutes) is crucial in improving the quality of care provided to patients with ST-segment elevation myocardial infarction (STEMI).

Objective: To determine the door-to-balloon time in the management of STEMI patients in a cardiovascular emergency department in a hospital of northern Brazil.

Methods: This was a cross-sectional study based on review of medical records. A total of 109 patients with STEMI admitted to the emergency department of a referral cardiology hospital in Pará State, Brazil, between May 2017 and December 2017. Correlations of the door-to-balloon time with length of hospital stay and mortality rate were assessed, as well as whether the time components of the door-to-balloon time affected the delay in performing primary percutaneous coronary intervention. Quantitative variables were analyzed by Spearman correlation and the G test was used for categorical variables. A $p<0.05$ was set as statistically significant.

Results: Median door-to-balloon time was 104 minutes. No significant correlation was found between door-to-balloon time and length of hospital stay or deaths, but significant correlations were found between door-to-balloon time and door-to-ECG time ($p<0.001$) and ECG-to-activation (of an interventional cardiologist) time ($p<0.001$).

Conclusion: The door-to-balloon time was longer the recommended and was not correlated with the length of hospital stay or in-hospital mortality. Door-to-ECG time and ECG-to-activation time contributed to the delay in performing the primary percutaneous coronary intervention. (Int J Cardiovasc Sci. 2021; 34(1):53-59)

Keywords: Myocardial Infarction; Angioplasty, Balloon, Coronary; Admitting Department, Hospital; Time to Treatment; Quality Indicators; Health Care.

Introduction

Primary percutaneous coronary intervention (PCI) is the safest strategy for the treatment of ST-segment elevation myocardial infarction (STEMI).[1] According to the Brazilian Society of Cardiology (SBC) and the American Heart Association guidelines, the time from arrival at the initial hospital to the time of the first balloon inflation during primary PCI, defined as door-to-balloon time, should be within 90 minutes.[2]

In Brazil, adherence to health care guidelines by healthcare centers is still lower than expected,[3] resulting in a suboptimal performance of these services, compromising the quality of care and safety of patients.[2,4] Current scientific evidence indicates that adherence to good clinical practice guidelines leads to better performance, reducing morbidity and mortality, length of hospital stay, and costs with STEMI patients, in addition to improve patients' safety and satisfaction.[5-7]

Door-to-balloon time has been used worldwide as an indicator of quality of care, helping to monitor the achievement of aims and goals of health care,[3-5] foster the strengthening of analytical capacity of the teams involved

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in the management of patients with STEMI and make it as close to ideal as possible.[8]

Therefore, the present study aimed to measure door-to-balloon time and correlate it to the number of deaths and length of hospital stay. We also evaluated whether time intervals of the door-to-balloon time influence on delayed primary reperfusion (wire crossing) at the emergency department of a cardiology hospital in the State of Pará, Brazil.

Methods

This was a cross sectional cohort study based on review of medical records. Patients of both sexes, aged ≥ 18 years, with confirmed diagnosis of STEMI were included. All patients had undergone reperfusion within 12 hours after precordial pain and were hospitalized at the emergency department of Gaspar Viana General Hospital Foundation (FHCGV) between May and December 2017. The HCGV is a referral center for heart disease in Pará, Brazil, and the only public hospital for medium and highly complex heart diseases, heading the health care line of myocardial infarction patients among the 144 cities of the state. A total of 109 patients were included in the study.

The following data and variables were systematically collected: age, sex, ethnicity, geographic origin, risk factors, length of hospital stay, number of deaths, and door-to-balloon time and its components.

Since May 2017, to monitor the quality of care provided to STEMI patients in FHCGV, door-to-balloon time and its component times have been prospectively measured using a checklist completed by the staff. The following times were measured: door-to-ECG time (Δt1), time between the electrocardiography test (ECG) and activation of an interventional cardiologist (Δt2) (ECG-to-activation time), time for patient preparation (activation-to-patient preparation) (Δt3), time between patient preparation and beginning of reperfusion (Δt4), time between beginning of reperfusion and balloon inflation (Δt5), time between activation and arrival of an interventional cardiologist at the cath laboratory (Δt6) (Figure 1).

Data collection was conducted after the study was approved by the Ethics Committee of the FHCGV (approval number 2.527.630).

Outcome Measures

Door-to-balloon time was described as a numerical variable and defined as a primary outcome. The proportion of patients with adequate door-to-balloon time (≤ 90 minutes), and the components (Δt) of the door-to-balloon time were registered as secondary outcomes.

Door-to-balloon time was defined as the time from patient's arrival at the hospital to the time of mechanical reperfusion of the culprit coronary artery. The first balloon inflation during the primary PCI. "Door" was defined as the time of registration of the patient in the emergency department. "Balloon" was defined as the exact time of mechanical reperfusion of the coronary artery during PCI, determined by the interventional cardiologist.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 22. Continuous variables with normal distribution were described as mean and standard deviation and

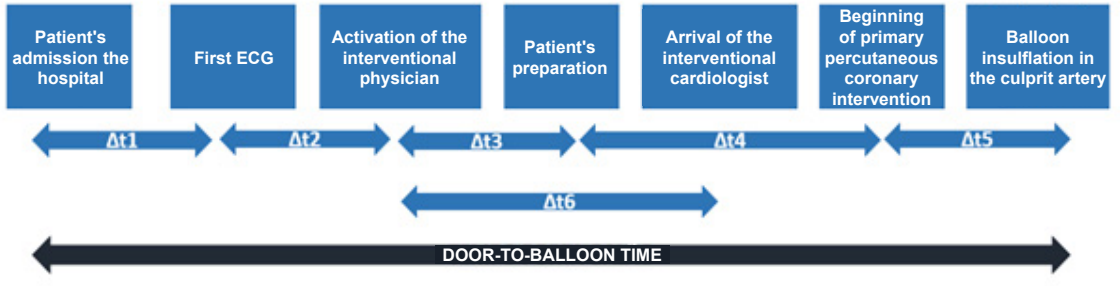

Figure 1 – Representation of the events in the management of patients with acute myocardial infarction with ST-segment elevation, the door-to-balloon time and its components (Δt)

those without a normal distribution were described as median and interquartile range. Normality of data distribution was verified using the Kolmogorov-Smirnov test. Associations between variables were assessed by Spearman correlation (for quantitative variables) and the G-test for categorical variables. The G-test was chosen as it makes no assumptions about the size of the classes. The level of significance was set at 5%.

Results

Characteristics of the Sample

Most patients (78.9%) were male; 64.2% self-identified as "pardo". Mean age was 61 ± 10.88 years and 69.7% came from the metropolitan area of the city of Belem, Brazil. Among the risk factors for acute myocardial infarction, 63.3% of patients were hypertensive, and 53.2% of the sample were smokers. Mean time from symptom onset to hospital arrival was approximately 6 ± 3.116 horas. In 48.4% of the cases, there was lesion of the anterior wall. In-hospital mortality was 8.3% and mean length of hospital stay was 7.77 ± 11.94 days. Other clinical characteristics are listed in Table 1.

Mean and median door-to-balloon time was 115 ± 55.3 minutes and 104 minutes, respectively. Time components of the door-to-balloon time are described in Table 2.

Median door-to-balloon time was 121 minutes and 78 minutes for those cases where door-to-balloon time was > 90 minutes (62.4%) and ≤ 90 minutes (37.6%), respectively (Figure 2).

Both door-to-ECG time (Δt1) and ECG-to-activation time (Δt2) were significantly correlated (p<0.001) with door-to-balloon time. No statistical correlation was found between door-to-balloon time and length of hospital stay or in-hospital mortality.

Table 1 – Characteristics of the sample

Variables	N = 109
Sociodemographic data	
Age (years)	61.11 ± 10.879
Male sex	86 (78.9%)
Pardo ethnicity	70(64.2%)
Metropolitan area of Belem (origin)	76(69.7%)
Risk factors	
Arterial hypertension	69 (63.3%)
Smoking	58 (53.2%)
Alcohol consumption	46 (42.2%)
Diabetes mellitus	32 (29.6%)
Infarction presentation	
Symptom duration on admission (hours)	6 ± 3.116
Anterior wall infarction	49 (45%)
Anterior descending artery occlusion	54 (49.5%)
Right coronary artery occlusion	41 (37.6%)
Circumflex artery occlusion	10 (9.2%)
Deaths	9 (8.3%.)
Length of hospital stay (days)	7.77 ± 11.94)

Source: Division of medical and statistical support of Gaspar Viana General Hospital Foundation, between May and December 2017. Data presented as mean ± standard deviation or number (percentage)

Discussion

In the present study, most patients with STEMI were male. According to current evidence, cardiovascular diseases are more prevalent in men than women.[1,3] In addition, men tend to seek medical care less often than

Table 2 – Door-to-balloon time and its components in the management of patients with acute myocardial infarction with ST-segment elevation. Time in minutes, presented as median and interquartile range (IQR) (n=109)

Time intervals	Median (IQR)
Door-to-balloon time	104 (18 – 133)
Door-to-ECG time (Δt1)	11 (5 – 18)
ECG-to-activation time (Δt2)	10 (5 – 18)
Activation-to-patient preparation time (Δt3)	10 (5 – 15)
Patient preparation-to-PCI initiation time (Δt4)	15 (0 – 45)
PCI initiation-to-balloon time (Δt5)	20 (0 – 30)
Activation-to-arrival of the interventional cardiologist (Δt6)	25 (0 – 38)

Source: Statistical database of the Cardiology Department of Gaspar Viana General Hospital Foundation between May and December, 2017. PCI: percutaneous coronary intervention

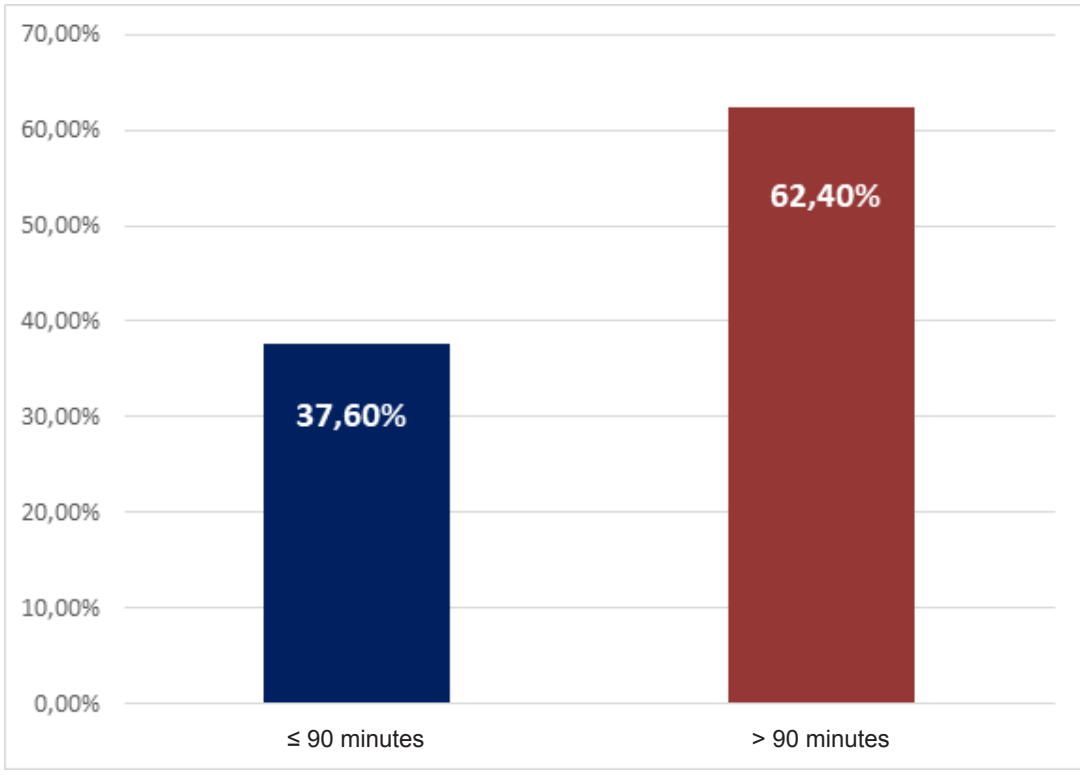

Figure 2 – Distribution of patients according to Door-to-Balloon Time> or ≤ 90 minutes, Belém-Pará, 2018 (n = 109)
Source: authors. 2018.

Table 3 – Correlation between door-to-balloon time and its components (n=109)

Components of the door-to-balloon time	Spearman correlation coefficient	p-value*
Door-to-ECG time (Δt1)	0.535	< 0.001
ECG-to-activation time (Δt2)	0.521	< 0.001
Activation-to-patient preparation time (Δt3)	-0.005	0.961
Patient preparation-to-PCI initiation time (Δt4)	0.130	0.209
PCI initiation-to-balloon time (Δt5)	0.168	0.103
Activation-to-arrival of the interventional cardiologist (Δt6)	0.085	0.385

*Source: Statistical database of the Cardiology Department of Gaspar Viana General Hospital Foundation between May and December 2017. PCI: percutaneous coronary intervention; * Spearman correlation*

women, due to greater difficulty in identifying and facing possible health problems, in accepting changes in lifestyle and talking about problems. Therefore, in general, instead of seeking preventive medical services, men go to the doctor when disease is already established and there is little chance of recovery, leading to irreversible changes in health and quality of life.[9,10]

Age of the study population ranged from 60 to 69 years, with mean of 61 ± 10.88 years. Studies have shown that this is the age range of patients who suffer an acute myocardial infarction, due to development of atherosclerotic plaque on the coronary artery wall. Development of early fibroatheroma starts in adolescence and second decade of life and continues throughout life. Advanced atheroma occurs in individuals older than 55 years of age. At this stage, a thin fibrous cap, formed by the activity of proteolytic enzymes, may rupture, exposing the thrombogenic arterial wall, leading to thrombosis.[11]

Hypertension, smoking, alcohol consumption and diabetes mellitus were identified as risk factors for acute myocardial infarction. This is in line with the results reported by a regional study by Costa,[12] showing that 71.6% of patients with acute myocardial infarction had hypertension, 71.5% were smokers or ex-smokers, and 45.5% had diabetes mellitus. Also, in a nationwide study on STEMI patients by Wang et al.,[3] the main modifiable risk factors identified were hypertension (78.8%), dyslipidemia (57.9%) and diabetes mellitus (37.5%), among others.

Modifiable risk factors such as systemic arterial hypertension, diabetes mellitus, smoking habit, dyslipidemia, obesity, alcohol consumption and psychosocial distress are more common in individuals with lower socioeconomic status; among the indicators of socioeconomic status, educational attainment is the one with the best correlation with the frequency and severity of cardiovascular risk factors.[13]

Door-to-balloon time was longer than the recommended (90 minutes) in 62.4% of the cases. In a multicenter study conducted in public and private hospitals in Brazil, Wang et al.,[3] found that 64.04% of 633 patients with STEMI showed a door-to-balloon time longer than 90 minutes. Dharma et al.,[14] in a study carried out in Jakarta, Indonesia, reported that 51.3% of 263 STEMI patients had an inadequate door-to-balloon time. These findings emphasize the difficulty in achieving a satisfactory door-to-balloon time in the management of STEMI patients.

More successful results in door-to-balloon time were detected in studies performed in centers where this parameter has been studied for a longer time, as in the United States, Europe and Asia.[5,15,16] More challenging targets such as a door-to-balloon time shorter than 60 minutes[17] were achieved by some authors such as Mentias et al.,[18] who reported a median door-to-balloon time of 38 minutes.

Different from other Brazilian studies,[4,11] the present study did not show the relationship of door-to-balloon with length of hospital stay and mortality rate. For example, Moreira et al.,[4] investigated the correlation of hospital costs and other variables with the door-to-balloon time (n=141 patients) and did not find any significant difference in the mean length of hospital stay or clinical outcomes between the groups with a door-to-balloon time longer than 90 minutes and those with a door-to-balloon time shorter than 90 minutes. Santos et al.,[19] evaluated the quality of care provided to patients with acute coronary syndrome (ACS) at the emergency department and did not find an association between the quality indicators for ACS (including the door-to-balloon time), and occurrence of complications or death. However, different findings have been reported in international studies, indicating that a reduction in the door-to-balloon time reduces the length of hospital stay, the risk of in-hospital mortality, and even post-discharge mortality at 30 days, one year and three years.[7,16,18,20,21]

Regarding other component times of the door-to-balloon time that may have influenced the primary outcome, door-to-ECG time ($\Delta t1$) and ECG-to-activation time ($\Delta t2$) showed a significant correlation ($p<0.001$) with door-to-balloon time. These two intervals represent the first in-hospital stages of care provided to STEMI patients, and in our sample, they contributed to the delay in primary mechanical reperfusion. Some studies have pointed out that delays in emergency services are associated with difficulties related to the staff, equipment and facility, impaired communication in the hospital setting, and lack of priority care.[5,8,22]

Campos et al.,[5] showed a reduction in door-to-balloon time from 144 minutes to 70 minutes after implementation of a communication code, a 24-hor screening protocol and presence of a cardiologist at the emergency department of the hospital. Also, pre-hospital electrocardiogram, improvement in the communication between the emergency staff and interventional cardiologists and use of technology in patient data transmission, early activation and direct transfer to the cath laboratory result in a significant reduction in the door-to-balloon time.[23-26]

This study put the time-to-door time on view; however, its limitation was the fact that it was a one-center study, which limits the generalization of the results.

Conclusions

In our study, door-to-balloon time in the management of STEMI patients was longer than recommended. We did not find a correlation of the door-to-balloon time with the length of hospital stay or in-hospital mortality rate. Door-to-ECG time and ECG-to-activation of a cardiologist contributed to a delay in mechanical reperfusion. These findings indicate the need for monitoring the time components of the door-to-balloon time in the management of STEMI patients in order to reduce the obstacles to a timely coronary intervention by PCI. In this way, proper measures can be implemented to achieve an adequate door-to-balloon time, according to current guidelines on STEMI, thereby promoting a high quality of care to these patients.

Author Contributions

Conception and design of the research: Amoras TSG, Menezes CR, Zaninotto CV. Acquisition of data: Amoras TSG Analysis and interpretation of the data: Amoras TSG, Menezes CR, Zaninotto CV, Rodrigues TB, Tavares RS. Statistical analysis: Amoras TSG, Menezes CR. Writing of the manuscript: Amoras TSG, Menezes CR, Zaninotto CV, Rodrigues TB, Tavares RS. Critical revision of the manuscript for intellectual content: Amoras TSG, Menezes CR, Zaninotto CV, Rodrigues TB, Tavares RS.

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 article is part of the thesis of master submitted by Tárcio Sadraque Gomes Amoras, from *Universidade do Estado do Pará* and *Fundação Hospital de Clínicas Gaspar Vianna.*

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the *Fundação Hospital de Clínicas Gaspar Vianna* under the protocol number 82951718.3.0000.0016. 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

Correlation between Surgical Risk Scales with Respiratory Muscle Strength and Functional Independence in Patients Submitted to Coronary Artery Bypass Grafting

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Abstract

Background: The European Heart Surgery Risk Assessment System (EuroSCORE) and InsCor have been used to predict complications of cardiac surgery. However, their application to predict lung function and functionality is still uncertain.

Objective: To correlate surgical risk scales with functional independence and pulmonary function in patients undergoing coronary artery bypass grafting.

Methods: This was a prospective cohort study. In the preoperative period, the two surgical scales were applied, the maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), and peak expiratory flow (PEF) were measured, and functionality was assessed using the functional independence measure (FIM). On the seventh postoperative day, the pulmonary function and functionality variables were reevaluated, compared with the preoperative values (delta) and correlated with the risk scales. Correlations of pulmonary function, functional independence and muscle strength variables with the surgical scales were made by Pearson correlation test. The significance level adopted was 5%.

Results: Thirty-one patients were studied; most were male (77%), with a mean age of 56±8 years. Mean EuroSCORE was 2.3±0.5 and mean InsCOR was 1.2±0.5. MIP, MEP, and PEF reduced 30% ($p<0.001$), 33% ($p<0.001$) and 10% ($p=0.23$), respectively. The EuroSCORE correlated with MIP (r-0.78; $p = 0.02$) and FIM (r-0.79; $p <0.01$), and the InsCor correlated with MIP (r-0.77), MEP (r-0.73) and MIF (r-0.89; $p=0.02$).

Conclusion: The EuroSCORE showed a strong negative correlation with MIP and FIM, while InsCor had a strong negative correlation with MIP, MEP and FIM. (Int J Cardiovasc Sci. 2021; 34(1):60-66)

Keywords: Cardiovascular Diseases/mortality; Risk Assessment; Myocardial Revascularization; Pre-Operative Care; Postoperative Care; Respiratory Pressures; Physical Therapy Speciality; Muscle Stremght.

Introduction

Cardiovascular diseases are the leading cause of death in the world. In Brazil, they represent about 30% of the number of deaths. Coronary artery bypass grafting (CABG) is the most common surgical procedure used to treat coronary heart disease, with a high probability of improving ventricular function, reducing symptoms and improving patients' prognosis.[1] The main complications of CABG are related to comorbidities that affect respiratory function, such as chronic obstructive pulmonary disease, pulmonary congestion and prolonged mechanical ventilation, in addition to systemic infections, diabetes mellitus, renal failure and hemodynamic stability.[1,2]

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Functionality may be altered in patients undergoing myocardial revascularization , due to the immobility and complexity of the procedure, such as degree of sedation, cardiopulmonary bypass (CPB), preoperative pulmonary and cardiac functions and mobility restriction in case of admission to the intensive care unit (ICU).[2,3]

Risk scales such as the European System for Cardiac Operative Risk Evaluation (EuroSCORE) and the InsCor in cardiac surgeries are shown to be simple and objective indices to predict operative mortality. In both scores, the preoperative evaluation offers the advantage of patients' stratification, allowing better intraoperative and postoperative planning, with similar performance and accuracy. However, these scores do not provide information about pulmonary function, since the EuroSCORE only evaluates previous chronic lung diseases and pulmonary hypertension, and the InsCor does not provide pulmonary function indices.[4-7]

The functional independence measure (FIM) is a measurement tool used that can be used in these patients to assess functionality, analyzing some of its aspects including self-care, sphincter control, locomotion, cognition, bed transfer and communication.[8]

In addition, to obtain effective treatment, a careful and efficient preoperative evaluation is essential, analyzing patient's pulmonary function, considering the tendency decreased lung volumes and capacities. It is also important to pay attention to possible risks and complications, and properly advise the patient about the procedure, including the extubation process.[9]

Although these scales are validated, there is still no evidence on their possible use to predict the worsening of peripheral and respiratory muscle strength, functionality and pulmonary function of the patient. This would allow the use of these two scales in the preoperative period to identify individuals who would need different care, becoming a tool for individualization of care. The present study aims to correlate surgical risk scales with functional independence measure (FIM) and pulmonary function parameters in patients undergoing CABG.

Material and Methods

This was a prospective cohort study conducted from January 2018 to April 2019, at the intensive care unit (ICU) of Instituto Nobre de Cardiologia, a referral center for cardiovascular care in the City of Feira de Santana, state of Bahia. This study was approved by the Research Ethics Committee of Faculdade Nobre (approval number 2.490.540), and all participating patients signed an informed consent form.

Eligibility criteria

Adult patients of both sexes and over 18 years old, who underwent elective CABG surgery via sternotomy and cardiopulmonary bypass were included in the study. Exclusion criteria were patients with cognitive impairment or neurological and locomotor disorders, previous neurological disease, lower limb amputation (which could affect functionality and quality of life), those who stayed in the ICU for more than three days, readmission to the ICU prior to post-discharge evaluation, death, change in the surgical treatment plan, rescheduling of the date of the procedure and history of smoking or chronic lung disease. The reason for excluding patients who stayed more than three days in the ICU is that they could have had surgery-related complications and represent a bias for future data analysis.

Study protocol

Muscle strength of the patients was assessed preoperatively using the Medical Research Council (MRC) framework. Respiratory muscle strength and pulmonary function was assessed by measuring maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), and peak expiratory flow (PEF). The surgical risk was assessed using the EuroSCORE and InsCor. On the day after these tests, patients were referred to the operating room and subsequently to the ICU. During this period, they were managed according to standard practices of each department, including breathing exercises such as deep or sustained maximal inspiration, lying-to-sit transfer, active kinesiotherapy, orthostatic training, steady gait, ambulation and sitting in an armchair. When postoperative stability was achieved, patients were discharged from the ICU transferred to the wards, where they continued to be followed through the physical therapy protocol of the hospital.

On the seventh postoperative day, they were reassessed for MRC, FIM, MIP, MEP and PEF; the variation (delta) of these variables between the two moments was calculated and correlated with the surgical risk scales applied preoperatively.

Measuring instruments

FIM measured the ability of individuals to perform daily activities, as well as their cognitive ability. Activities related to personal care, sphincter control, mobility, communication, and social cognition were scored from 1 (total dependence) to 7 (complete independence), with a maximum value of 126 points.[11]

The MRC scale tests muscular strength, with application of manual resistance on patient in dorsal, ventral, lateral and sitting positions. Both left and right sides are tested to reduce the influence of dominance and possible asymmetrical involvement of the muscle groups: shoulder abductors, elbow flexors, wrist extensors, hip flexors, knee flexors and ankle dorsiflexors. The MRC scale ranges from 0 to 5 where 0 indicates that there is no visible muscle contraction and 5 indicates a normal strength, with a maximum score of 60.[12]

For assessment of the MIP, using a mask, patients were instructed to breathe out completely (near the residual volume), followed by a maximal inspiration. To determine the MEP, a maximum expiration was performed using an analogue manovacuometer (Indumed®, São Paulo, Brazil). Three to six measurements were taken, avoiding variations of up to 10%, considering the highest value for analysis.[13] PEF was assessed using a Mini Wright® peak flow meter; participants were asked to blow as vigorously as possible. Three to six trials were performed, with a pause of about 10 seconds between repetitions; values were measured in L/min.[14]

The EuroSCORE is a risk-stratification tool used to evaluate risk of death specifically after cardiac surgery. This scale was constructed based on data collected from 128 centers in eight European countries. It system evaluated 68 preoperative and 29 operative risk factors, that could influence hospital mortality. It also identified 17 real risk factors related to the patient, the heart, and the surgery itself. For each factor, in a univariate analysis, a score was assigned, classifying the patients into three groups, according to the risk obtained, *i.e.*, low, medium or high. It is an easy-to-use tool, and its web-accessibility has greatly contributed to the popularization of its use.[15]

The InsCor is a EuroSCORE-derived risk score that assesses local parameters and has flagged 10 risk factors related to patients undergoing cardiac surgery. Variables such as age around 70 years, female sex, myocardial revascularization with valve repair, recent infarction <90 days, reoperation, surgical treatment of the aortic and tricuspid valves, creatinine> 2mg / dL, ejection fraction <30% and at least one of the following events prior to surgery: intra-aortic balloon, cardiogenic shock, tachycardia, ventricular fibrillation, orotracheal intubation, acute renal failure, inotropic drug use and cardiac massage.[16]

Data analysis

For data analysis, the SPSS 20.0 program was used. Normality was assessed by the Shapiro-Wilk test. Continuous data were expressed as mean and standard deviation and categorical data as absolute value and percentage. Pre- and postoperative values were evaluated by the paired Student's t-test. To correlate the values of pulmonary function, functional independence and muscle strength with the surgical scales, the Pearson test was used. This test was used due to the normality of the sample. The significance level adopted in the statistical analysis was 5%.

Results

Fifty-nine patients hospitalized for myocardial revascularization surgery were included in the study. Of these, 28 were excluded because of an ICU longer than three days (n=14), death (n=2), change in the in the surgical treatment plan (n=1), rescheduling of the date of the procedure (n=1), refusal to attend data collection (7th POD) (n=4) and patients discharged before the 7th POD (n=6) (Figure 1).

Therefore, 31 patients were evaluated, 24 (77%) male and with a mean age of 56 ± 8 years. Mean EuroSCORE was 2.3 ± 0.5 and mean InsCor score 1.2 ± 0.5. Other clinical and surgical data are described in Table 1.

All variables related to respiratory muscle strength and pulmonary function was decreased on the seventh POD compared with the preoperative period. The MIP, the MEP and PEF reduced by 30%, 33% and 10%, respectively. In addition, we observed a decrease of 6% in FIM and 5% in MRC (Table 2).

When we correlated the delta of pulmonary function, functionality and peripheral muscle strength with the cardiac risk scales, we found that EuroSCORE had a strong negative correlation with MIP and FIM, while InsCor had a significant positive correlation with MIP, MEP and FIM (Table 3).

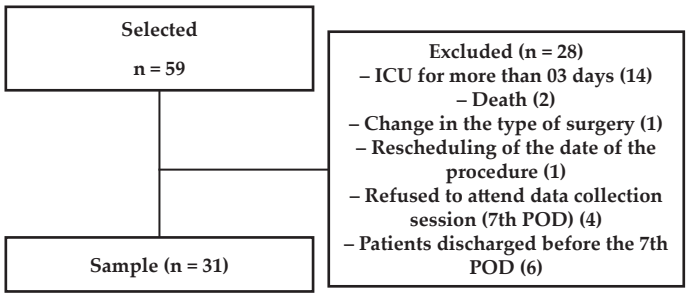

Figure 1 – Flowchart representative of sample loss and individuals research participants.
ICU: intensive care unit; POD: postoperative day

Table 1 – Clinical data of patients (n=31) undergoing coronary artery bypass grafting

Variables	Values (in number and percentage or mean and standard deviation)
Gender	
Male	24 (77%)
Female	7 (23%)
Age (years)	56 ± 8
BMI (kg/m²)	27 ± 4
CPB time (min)	85 ± 10
MV time (hours)	6 ± 4
Number of drains	2.3 ± 0.4
Number of grafts	2.3 ± 0.5
EuroSCORE	2.3 ± 0.5
InsCor	1.2 ± 0.5

BMI: Body mass index; CPB: cardiopulmonary bypass; MV: mechanical ventilation; EuroSCORE: European System for Cardiac Operative Risk Evaluation

Table 2 – Respiratory and peripheral muscle strength, pulmonary function and functionality behavior of patients undergoing coronary artery bypass grafting

Variable	Preoperative	7th POD	p[a]	Δ
MIP (cmH_2O)	111 ± 10	78 ± 11	<0.01	33 ± 10
MEP (cmH_2O)	105 ± 13	70 ± 12	<0.01	35 ± 12
PEF (L/min)	381 ± 20	344 ± 22	0.23	37 ± 21
FIM	125 ± 2	118 ± 3	<0.01	7 ± 2
MRC	59 ± 1	56 ± 2	0.54	3 ± 2

a. Paired Student's t-test; POD: postoperative day; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; PEF: peak expiratory flow; FIM: functional independence measure; MRC: Medical Research Council

Table 3 – Correlation between pulmonary function variables and surgical risk scales of patients undergoing coronary artery bypass grafting

	EuroSCORE		InsCor	
Variable	**r***	**P**	**r***	**P**
Δ MIP	- 0.78	0.02	- 0.77	0.07
Δ MEP	- 0.22	0.53	- 0.73	0.01
Δ PEF	- 0.45	0.24	- 0.04	0.92
Δ FIM	- 0.79	0.01	- 0.89	0.02
Δ MRC	- 0.12	0.55	- 0.34	0.48

** Pearson Test; EuroSCORE: European System for Cardiac Operative Risk Evaluation; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; PEF: peak expiratory flow; FIM: functional independence measure; MRC: Medical Research Council*

Discussion

In the present the study, we found that the EuroSCORE had a strong negative correlation with MIP and FIM, while InsCor had a significant negative correlation with MIP, MEP and FIM.

There was a reduction in all variables related to pulmonary function when compared to the preoperative period. MIP had a 30% decline on the seventh postoperative day, corroborating with Schnaideret et al.,[16] who also showed a reduction in MIP. We obtained a reduction in MEP value of 33% and in PEF of 10% when compared with preoperative values.

On the other hand, Annoni et al.[17] observed a significant increase in MEP and PEF, which may have been correlated with the small sample size, and collaboration and learning of patients to perform the tests, since they were evaluated daily from the first postoperative period until the day of discharge.

This study also corroborated the research conducted by Cordeiro et al.,[10] proving the existence of a positive relationship between a cardiac risk scale and functionality in patients undergoing cardiac surgery. Patients at higher pre-surgery risk experienced worsening of functionality.

It is possible to identify a reduction in muscle strength in patients after surgery, which may be related to several factors related to the surgery itself. Guedes et al.[18] described that thoracic surgical incisions generate a reduction in respiratory muscle strength, as they affect muscle integrity, directly changing its postoperative function and increasing the length of hospital stay. Changes may occur due to dysfunction of the respiratory muscles and nerves resulting from the incision or due to changes in respiratory mechanics,[19] confirming the findings of our study.

Cordeiro et al.[3] reported that cardiac surgeries can cause systemic changes, given the complexity of the procedure: degree of sedation, CPB time, preoperative pulmonary and cardiac functions, which may influence the degree of functionality of these patients, besides mobility restriction due to ICU admission. As expected, there was a decline in functionality, as studies indicate the relationship of preoperative risk with worsening of functionality.[4,10]

Fonseca et al.[20] pointed out that during the postoperative period, there is a need for pain and anxiety control. The authors mentioned that, in a study conducted by nurses in a hospital specializing in cardiology, it was identified that these factors motivate the administration of sedative and analgesic drugs, with consequent depression of the level of consciousness, increasing hospitalization time. These findings coincide with our results, leading to the hypothesis that the longer a person takes sedative drugs, the later will the functional independence be recovered.

In addition to these findings, Pardeans et al.[21] reported that myocardial revascularization surgery and high surgical risk are associated with reduced exercise capacity for the surgical procedure. This may be related to the worsening of ventilatory muscle strength and pulmonary function, as observed in our study.

Another explanation for the decline in the variables presented in this study is sarcopenia.[22] Many of our sample were elderly, which alone contributes to reduction of muscle mass and worsening of cardiac systolic function.

The development of tools that can predict outcomes is of fundamental importance to this population. Ivanov et al.[23] evaluated the use of preoperative pulmonary function testing to stratify the risk of patients undergoing cardiothoracic surgery and did not recommend its routine use due to its low sensitivity. This result reinforces the findings of our study, suggesting the need for a new assessment instrument.

Limitations of our study include the small sample size, lack of sample calculation, and insufficient data such as surgery time, medication use and pain scale, that could improve the interpretation of our results.

Conclusion

It was concluded that EuroSCORE had a strong negative correlation with MIP and FIM, while InsCor had a negative correlation with MIP, MEP and FIM. Given these results, it is evident that the both scales provided knowledge of the risks during surgery and detected the decline in the level of independence and pulmonary function of patients undergoing coronary artery bypass grafting. Further studies should be conducted, stratifying patients at higher risk of such decline, to implement specific interventions.

Author contributions

Conception and design of the research: Cordeiro ALL, Brito A, Almeida G, Jesus L, Oliveira F, Silva J. Acquisition of data: Brito A, Almeida G, Jesus L, Oliveira F, Silva J. Analysis and interpretation of the data: Cordeiro ALL. Statistical analysis: Cordeiro ALL. Writing of the manuscript: Cordeiro ALL, Brito A, Almeida G, Jesus L, Oliveira F, Silva J. Critical revision of the manuscript for intellectual content: Guimarães A, Barros R.

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 *Faculdade Nobre* under the protocol number 2.490.540/2018. 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

Risk Stratification in Chest Pain: Impact on the Diagnosis of Acute Coronary Syndrome

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Abstract

Background: The implementation of institutional protocols in the emergency department (ED) for risk stratification in patients with chest pain has been recommended.

Objective: To assess the sensitivity, specificity and predictive value of an institutional risk stratification protocol for chest pain suggestive of acute coronary syndrome (ACS).

Method: Cross-sectional study conducted based on the computerized records of patients treated with the use of a chest pain protocol adapted from the Manchester protocol. The level of risk was stratified by applying five colors representing the respective levels. Each color represents a level of severity and a maximum waiting time for receiving medical care. Red and orange were considered to be high priority, while patients with yellow, green or blue indications were considered to represent a low priority. To compare the type of diagnosis and the classification of priority for receiving care, the Pearson's chi-square test was used, considering a significance level of $p< 0.05$ for all tests.

Results: The records of 1,074 patients admitted to the cardiology ED were analyzed. Men (54%), with a mean age of 60 ± 15 years, with complaints of chest pain (44%) of moderate intensity (80%) were predominant the study. Of these patients, 19% were classified as high priority, while 81% were considered to represent a low priority. ACS was confirmed in 23% of the patients, with 34% of them being classified as high priority and 66% as low priority. The sensitivity of the risk stratification protocol for chest pain was 33.7% and the specificity was 86.0%, with a positive and negative predictive value of 41.7% and 81.3%, respectively.

Conclusion: The Institutional risk stratification protocol for chest pain suggestive of ACS presented satisfactory specificity and a low degree of sensitivity. (Int J Cardiovasc Sci. 2021; 34(1):67-73)

Keywords: Chest Pain; Acute Coronary Syndrome; Risk Factors; Risk Assessment; Sensitivity and Specifity; Emergency Medical Services.

Introduction

Chest pain is mentioned as one of the main complaints reported by patients admitted to the Emergency Department (ED). The demand for providing care to patients with cardiac chest pain is related to the significant impact that heart diseases have on the world population, as they are considered to be the leading cause of death in Brazil and worldwide.[1]

In order to meet this demand, a triage scale was created, in these departments, based on the guidelines established by the National Humanization Policy (*PNH - Política Nacional de Humanização*) and QualiSUS. These determinations include the implementation of a patient classification screening and/or triage service in the ED,[2] pursuant to the law published by the Ministry of Health under Ordinance GM/MS No. 2048/2002.[3]

In general, applying scales/protocols that stratify the risk across five levels has been recommended, as this offers improved creditability, validity and reliability in the assessment of the patient's clinical status.[4,5] Institutional protocols can be developed using the

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expertise of the healthcare practitioners of the institution. Besides, there is a recommendation from the Ministry of Health indicating that flowcharts should be structured based on those found in the literature and adapted to the service profile and its context in terms of the respective healthcare network.[6]

When receiving patients with chest pain in the ED, the health care professional responsible for patient screening should be aware of the referenced clinical signs and symptoms. An appropriate clinical examination and early diagnosis assist in the classification of the respective risk for patients with acute coronary syndrome (ACS), making healthcare faster.[7] Although chest pain is indicative of priority, aspects such as intense patient flow, delays in performing the supplemental exams and delays in obtaining a definitive diagnosis directly influence the promptness and accuracy of the care provided.

Based on this context, this study aimed to assess the sensitivity, specificity and predictive value of an institutional risk stratification protocol for chest pain suggestive of ACS.

Methods

Study Design and Population

This is a cross-sectional study conducted with patients consecutively treated for complaints of chest pain in a cardiology ED in southern Brazil, from October to December 2017. Patients admitted to the ED with a confirmed diagnosis of ST-Segment Elevation Acute Myocardial Infarction (STEMI), referred from other institutions or by ambulance transport, were excluded.

Scenario

The study was conducted based on the computerized records completed by the healthcare team at the time of admission. The ED provides public and/or private care to an average of 1,800 patients/month. Whereby, 18-20% of these patients have complaints involving chest pain. The respective Hemodynamics Laboratory is available 24 hours a day for myocardial reperfusion cases.

Logistics of the Service Protocol

The chest pain protocol used in the Institution's ED (Figure 1) is developed based on the Manchester protocol[8] and on the recommendations of the Welcome with Risk Classification of the National Humanization Program of the SUS (Brazilian Unified Health System).[2] This protocol has been in force since June 2013.

During the triage screening process, a nurse performs the triage oriented towards the main complaint, in which the patient is asked about signs and symptoms, onset, personal history, medications used and allergies. Airway patency, the presence of ventilation and pulse, as well as the identification of conditions that imply imminent risk of death are also assessed. Patients who present with the complaint of chest pain are referred for an electrocardiogram (ECG). Afterwards, the medical team assesses the patient and the indicated therapy is implemented.

The risk stratification is represented by five color-coded levels. Each color represents a severity level and a maximum waiting time for receiving medical care (Figure 2). In this study, red (immediate) and orange (very urgent) were considered to be high priority, while patients with yellow (urgent), green (standard) or blue (non-urgent) indications were considered to represent a low priority. Based on the recommendations of the American Heart Association,[9] this protocol was defined as being positive when the patient was classified as a high priority.

Confirmation of the diagnosis of ACS was performed according to the International Classification of Diseases (ICD) recorded at the end of the consultation. The medical diagnoses were divided into two groups: ACS (STEMI, NSTEMI and Unstable Angina); and Other Diagnoses (Unspecified Chest Pain, Arrhythmias, Systemic Arterial Hypertension, Aortic Dissection, among others). In addition to the ACS diagnosis and flowchart data, clinical and demographic data were collected.

Data Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 22.0, considering a significance level of $p < 0.05$ for all tests. Continuous variables were expressed as mean and standard deviation. Categorical variables were described as absolute numbers (n) and percentages (%).To compare the type of diagnosis and the classification of priority for receiving care, the Pearson's chi-square test was used. To verify the normality of the data the Kolmogorov-Smirnov test was used.

For sample calculation, the sensitivity, specificity, positive predictive value (PPV) and negative predictive

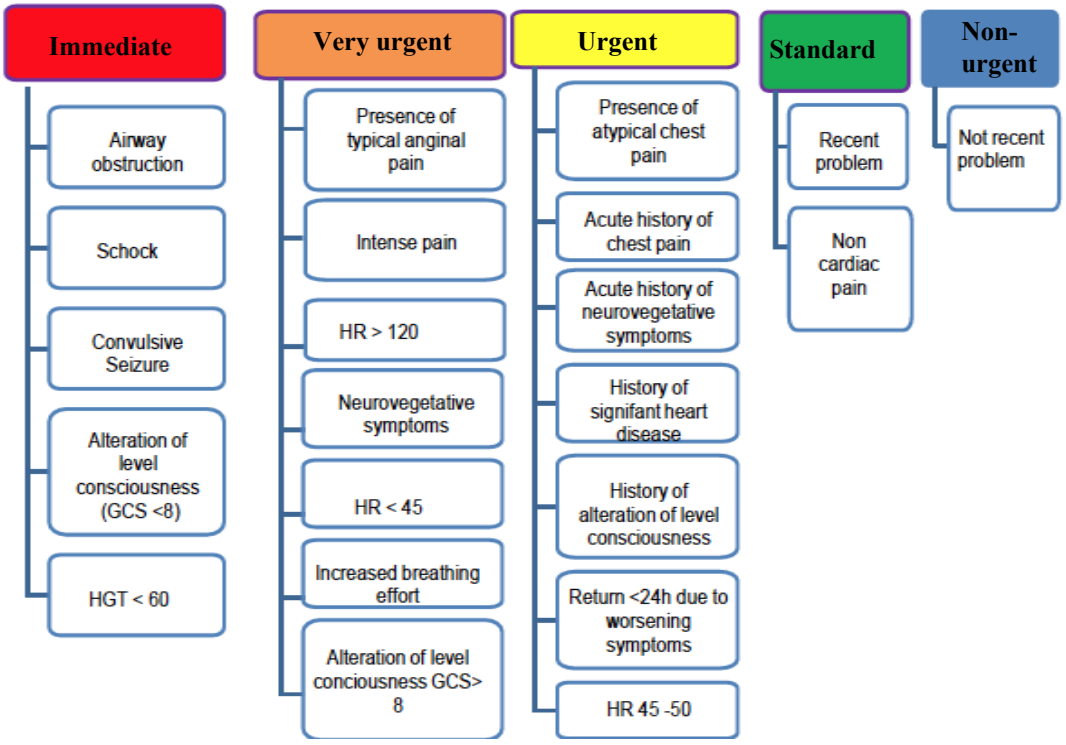

Figure 1 – The chest pain protocol chart used in the Institution's ED.
GCS: Glasgow Coma Scale; HGT: Hemoglobin Test; HR: Heart rate.

Priority	Color	Severity	Target Time to Treat (minutes)	Risk stratification (Priority)	ACS Diagnosis	Other diagnosis
I	Red	Immediate	0	High	True Positive ACS +	False positive ACS -
II	Orange	Very urgent	10			
III	Yellow	Urgent	60			
IV	Green	Standard	120	Low	False negative ACS +	True negative ACS
V	Blue	Non-urgent	360			

ACS: Acute Coronary Syndrome; STEMI: ST-Elevation Myocardial Infarction; NSTEMI: Non-ST-elevation myocardial infarction.

Figure 2. Priorities for receiving care of the Institutional Protocol for Chest Pain and classification of true positives and true negatives, false positives and false negatives, related to the diagnosis of ACS (STEMI AND NSTEMI) and the appropriate prioritization with the protocol for chest pain.

value (NPV) for chest pain suggestive of ACS were assessed in relation to the chest pain protocol. Based in the study conducted by Lunet,[10] for each estimate a confidence interval of 95% was considered, with an absolute error of 9% and sensitivity of 87%. Sample size calculation resulted in a total of 1,061 patients.

Ethical Aspects

The project was approved by the institution's Research Ethics Committee, under number CAAE80458917.1.000.5333, in accordance with Resolution 466/12 of the National Health Council (*Conselho Nacional de Saúde*).

Results

The computerized records of 1,074 patients screened in a cardiology ED were analyzed using the chest pain protocol. Men (54%), with a mean age of 60 ± 15 years, with complaints of acute chest pain (44%), of moderate intensity (80%) were predominant in the study. Among all patients treated, 19% were classified as being a high priority and 81% as low priority for receiving care (Table 1).

The diagnosis of ACS was confirmed in 23% of the patients, with 34% being classified as high priority for receiving care and 66% as low priority (Table 2).

Table 1 – Clinical and demographic characteristics of the study sample (n = 1,074).

Characteristics assessed	Total n (%) (n=1074)	High priority n (%) (n = 199)	Low Priority n (%) (n = 875)	p
Male Gender	582 (54.2)	112 (56.3)	470 (53.7)	0.512
Age (years)*				0.165
18-40	129 (12.0)	15 (7.5)	114 (13.0)	
41-60	411 (38.3)	76 (38.2)	335 (38.3)	
61-80	432 (40.2)	87 (43.7)	345 (39.4)	
81-97	102 (9.5)	21 (10.6)	81 (9.3)	
ED hours of service				0.065
8:01 AM to 2:00 PM	439 (40.9)	67 (33.7)	372 (42.5)	
2:01 PM: to 8:00 PM	355 (33.1)	76 (38.2)	279 (31.9)	
8:00 PM to 8:00 AM	280 (26.1)	56 (28.1)	224 (25.6)	
Pain scale				< 0.001
1-4 Light	23 (2.1)	1 (0.5)	22 (2.5)	
5-7 Moderate	857 (79.8)	7 (3.5)	850 (97.1)	
8-10 Intense	194 (18.1)	191 (96.0)	3 (0.3)	
Determining Factor				<0.001
History Acute of chest pain	477 (44.4)	0 (0)	477 (54.5)	
History of significant heart disease	322 (30.0)	4 (2.0)	318 (36.3)	
Intense pain	190 (17.7)	187 (94.0)	3 (0.3)	
Final diagnosis				<0.001
STEMI	54 (5.0)	37 (18.6)	17 (1.9)	
NSTEMI or UA	192 (17.9)	46 (23.1)	146 (16.7)	
Other	828 (77.1)	116 (58.3)	712 (81.4)	

Data expressed as absolute (n) and relative (%) frequencies. P-values for Pearson's Chi-square test. ED: Emergency Department; STEMI: ST-Segment Elevation Acute Myocardial Infarction; NSTEMI: Non-ST-elevation myocardial infarction; UA: Unstable Angina.

Table 2 – Confirmed ACS and priority for receiving care (n = 1,074).

Priority	Diagnosis		Total of those classified for each priority level
	ACS n (%)	Other n (%)	
High	83 (33.7)	116 (14.0)	199
Low	163 (66.2)	712 (85.9)	875
Total classified for each diagnosis	246	828	1074

ACS: Acute Coronary Syndrome (STEMI, NSTEMI and Unstable Angina); High priority (red and orange); Low priority (yellow, green and blue).

The estimated sensitivity of the risk stratification protocol for chest pain was 33.7% (95% CI: 27.9-40.3) for identifying patients with ACS, and the specificity was 86.0% (95% CI: 83.3-88.2), with a positive and negative predictive value of 41.7% (95% CI: 34.8-48.9) and 81.3% (95% CI: 78.5-83.8), respectively (Table 3).

Discussion

This study found that the patients treated at this ED are predominantly male, aged between 40 and 60 years. These findings resemble previous studies with similar populations.[11] However, the comparison of the priority groups regarding these two variables did not reveal statistically significant differences, thus corroborating the results of another study.[12]

Data in the literature[13] indicate that the elderly and women often manifest dyspnea as the main complaint in the presence of a myocardial infarction, because the absence of chest pain is often evident or not sufficiently assessed. However, this population, which is most vulnerable to atypical manifestations of AMI, should be assessed individually.[14] A previous study on screening using the Manchester protocol showed that advanced age might be a factor associated with misclassifications regarding the prognosis of patients with AMI.[14]

Table 3 – Estimates for the institutional protocol in the risk stratification of patients with chest pain in relation to the medical diagnosis of ACS.

Tests	Values (%)	CI = 95%
Sensitivity	33.7	27.9-40.1
Specificity	85.9	83.3 - 88.2
PPV	41.7	34.8 - 48.9
NPV	81.3	78.5-83.8
Prevalence	22.9	20.4-25.5

PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval.

Chest pain has a multifactorial etiology, including, but not limited to, thoracic, abdominal and psychosomatic pathologies. Although there are numerous diseases that cause chest pain, those originating from the cardiovascular system are of greatest concern due to the higher risk of mortality and the need for hospitalizations and investigations,[15] which may represent 5%-20% of all admissions to emergency rooms. Chest pain analysis, in this case series, was measured using the pain rule[8] at the time of screening and risk classification, with a "high priority" being indicated when patients said that they had severe pain. Accurate assessment of pain during reception is critical for the classification to be at the appropriate level of priority. In this sense, some key points such as the established culture, verbal demonstration and expressions of pain, behavioral changes and the type of injury or trauma should be considered.[16]

Most of the population was classified as representing a low priority for receiving care, based on the determining factors chosen, such as "acute history of chest pain", characterized by pain occurring in the last 24 hours, but not present at the time, and "history of significant heart disease." In addition to typical chest pain (pain, discomfort, burning or pressing sensation located in the precordial or retrosternal region that may radiate to the left shoulder or upper limb, right arm, neck or jaw), the patient may also have atypical complaints (malaise, indigestion, weakness or just sweating).

Thus, pathologies of the heart, aorta, lungs, mediastinum, ribcage, esophagus, stomach, gallbladder, pancreas and nervous system can produce symptoms with chest discomfort and are part of a broad differential diagnosis[17] This variability in the presentation of chest pain is a constant challenge for the healthcare team in ERs.

In the present study, the medical diagnoses of NSTEMI or unstable angina were most prominent, which may in part be attributed to the fact that patients who arrived at the hospital by ambulance with a confirmed diagnosis of STEMI were excluded. There is a tendency towards greater misclassification of patients with NSTEMI and unstable angina due to the less severe and atypical clinical presentations.[18] This hypothesis is corroborated by a previous study conducted in an ED with a similar population, where approximately 44% of those with ACS received a low priority classification based on the Manchester Triage Scale.[11] Furthermore, another important fact is that patients who arrive after being referred by an outpatient clinic have a reduced diagnostic accuracy in the triage screening compared to patients that arrive by ambulance.[19]

This study aimed at assessing the sensitivity, specificity and predictive value of an institutional risk stratification protocol for chest pain suggestive of ACS. Our findings showed a high specificity and low sensitivity in the classification of these patients in the ED. These results may reflect the demand of patients seeking for ED services, as well as the variability in the conditions under which chest pain may manifest.

The low sensitivity in terms of classifying individuals with a complaint suggestive of ACS may be associated with the difficulty faced by healthcare practitioners in performing this classification, considering the heterogeneity of the clinical presentation of chest pain. A study showed that, given the frequency of chest pain complaints in the ED, the variety of possible causes related to it, the potential severity of some of these and the higher prevalence of benign conditions may reduce the degree of suspicion of more serious causes by the less attentive emergency room worker, culminating in misclassifications, with the waiting time being longer than recommended.[20]

In a study conducted on the sensitivity of the Manchester protocol in ACS, the authors have found that data on atypical manifestations of ACS may decrease the sensitivity of the protocol in question. This may incorrectly indicate the selection of other flowcharts or determining factors, thus underestimating the classification of patients with chest pain.[14] Another European study evaluated the performance of the Manchester protocol in three hospitals, in which the sensitivity analyses were 47%, 72% and 87%. The specificity results presented values of 94%, 87% and 84%.[10] Whereby, similar to the present study, in the first institution, they attributed low sensitivity to the variability in the presentation of pain, while 20% of the patients with chest pain received an underestimated classification.

Alternative approaches that aim at reducing this negative impact of low sensitivity are necessary to improve the quality of care. For example, the systematic training of professionals working on protocols and clinical assessments; the incorporation of feasible and low-cost complementary exams; in addition to continuous evaluations of the results related to the new established strategies.[21]

The PPV observed in this study (41.7%; 95% CI: 34.8-48.9) was satisfactory compared to the study of Leite et al. (16%; CI 95%: 10-25)17, as this study also evaluated patients with any presentation of ACS.

This study has certain limitations: 1) the data were collected from medical records and the recorded information was not always complete; 2) the external applicability may be compromised, because it is a local study conducted at a single institution specialized in cardiology.

Conclusion

The specificity of the institutional risk stratification protocol for chest pain suggestive of ACS presented satisfactory values. However, the sensitivity found was low, which is possibly associated with an underestimated classification, being strongly linked to the heterogeneity of the clinical presentation of chest pain. The use of protocols in clinical practice is indicated because they contribute in providing indicators of the quality of the health care provided. These tools must be reviewed frequently and refined by management models.

Author Contributions

Conception and design of the research: Reis APP, Ruschel KB, Fagundes JE, Belli KC. Acquisition of data: Reis APP. Analysis and interpretation of the data: Fagundes JE, Ruschel KB, Belli KC. Writing of the manuscript: Reis APP, Fagundes JE. Critical revision of the manuscript for intellectual content: Ruschel KB, Saffi MAL, Moraes MAP.

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 *Instituto de Cardiologia do Estado do Rio Grande do Sul* under the protocol number CAAE80458917.1.000.5333. 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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REVIEW ARTICLE

Aromatherapy in Patients with Cardiovascular Diseases: A Systematic Review

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Abstract

Background: Aromatherapy consists in the use of volatile aromatic compounds of plant essential oils. Application methods include massage, baths, and mainly inhalation. Lavender essential oil is considered the most effective treatment for emotional disorders, such as stress and anxiety, due to its anxiolytic and sedative agents, which are known to interfere with physiological cardiovascular reactions.

Objectives: To investigate the effects of aromatherapy using lavender essential oil on hemodynamic responses and emotional aspects of patients with cardiovascular diseases.

Methods: A systematic review was conducted using Embase, Bireme, MEDLINE, PEDro, and Scopus electronic databases. Randomized clinical trials that evaluated hemodynamic and emotional outcomes using interventions with lavender essential oil in patients with cardiovascular diseases were selected. Of 539 studies initially identified, 51 were read in full and only 5 were eligible for inclusion.

Results: Reductions were demonstrated in hemodynamic responses, such as systolic and diastolic blood pressure, mean arterial pressure, and heart rate, as well as a decrease in anxiety, depression, stress, and fatigue compared with the control group. Statistical significance was set at $p<0.05$.

Conclusion: Aromatherapy with the use of lavender essential oil provided benefits to hemodynamic parameters, such as anxiety, stress, depression, and fatigue levels, in patients with cardiovascular diseases. (Int J Cardiovasc Sci. 2021; 34(1):74-80)

Keywords: Cardiovascular Diseases; Aromatherapy; Systematic Review; Anxiety; Lavandula; Hemodynamics.

Introduction

Cardiovascular diseases have the highest incidence of morbidity and mortality in the world. According to the World Health Organization (WHO), they caused approximately 17.9 million deaths in 2016, accounting for 31% of all causes of death worldwide.[1] Stress and anxiety seem to destabilize cardiovascular regulation, adversely affecting the autonomic and neuroendocrine pathways and, consequently, cardiovascular parameters and tissue perfusion.[2,3] Recently, Ma et al.,[4] observed that negative emotions can increase systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and cortisol levels, whereas positive emotions can decrease SBP and HR.

In this context, complementary therapies to control stress and anxiety have been studied, and integrative practices have shown to be promising resources in promoting health to patients with chronic diseases, including cardiovascular disease.[5] In Brazil, a decision by the National Policy and Integrative and Complementary Practice (PNPIC) was approved within the scope of

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the Brazilian public unified health system (SUS), and Ordinance No. 702 published on March 21, 2018, added 12 new practices, including aromatherapy, which consists in the use of essential oils extracted from aromatic plants[6] and is commonly administered by inhalation or massage.[7]

Lavender, with the scientific name of *Lavandula*, has been presented as a relevant substrate in the practice of aromatherapy. Its oil is extracted from its flower, and the main chemical compounds are *linalool* and *linalyl acetate*.[8,9] These compounds are rapidly absorbed by the skin and detected in the bloodstream after topical application, reaching peak levels in approximately 19 to 20 minutes after application.[8,10] Inhalation starts in the nose, where there is a chain of chemoreceptor olfactory neurons. Stimuli are conducted from the olfactory bulb, taking information to the cerebral cortex, hypothalamus, and hippocampus, connecting to the limbic system.[5,11] Because of its anxiolytic and sedative properties, the *Lavandula* Officinalis species is recognized for its effective treatment of stress and anxiety.[10-12]

The purpose of this review was to investigate the effects of the use of lavender essential oil on hemodynamic responses and emotional aspects in patients with cardiovascular diseases.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[13] The research question was developed using the PICO strategy, where participants (P) were patients with cardiovascular diseases, the intervention (I) was aromatherapy with the use of lavender essential oil, the comparison (C) was randomized controlled studies, and the outcome (O) was hemodynamic and emotional responses to the intervention. Question: What are the effects of aromatherapy with lavender essential oil on hemodynamic response and emotional aspects in patients with cardiovascular diseases?

Eligibility Criteria for Study Design

The inclusion criteria applied in the present review are shown in Table 1. The primary outcome was the analysis of hemodynamic responses, such as SBP, DBP, HR, and respiratory rate (RR). Secondary outcomes included emotional responses, such as anxiety, stress, fatigue, and depression.

Table 1 - Inclusion Criteria

Study Design
- Randomized Clinical Trials

Participants
- Both sexes with cardiovascular disease

Intervention
- Use of lavender essential oil
- Application of aromatherapy with inhalation and massage
- Measurement of hemodynamic parameters
- Measurement of emotional responses

Results Measured
- Intervention of aromatherapy versus hemodynamic responses
- Intervention of aromatherapy versus emotional factors

Comparison
- Intervention of aromatherapy with inhalation versus control
- Intervention of aromatherapy with massage versus control

Data Sources

The search was performed in May 2020, with no publication date restrictions, using the following 5 databases: Medical Literature Analysis and Retrieval System Online (MEDLINE), Virtual Health Library (Bireme), Physiotherapy Evidence Database (PEDro), Embase, and Scopus.

Search Strategy

The search strategy used MeSH or DeCs terms, combined by the Boolean operators "AND" and "OR", as well as other descriptors with similar concepts: *aromatherapy and Lavandula, and heart or hemodynamics or cardiovascular diseases*.

Study Selection and Data Extraction

Two reviewers screened titles and abstracts independently. Potentially relevant studies were retrieved for full-text reading. After reading the full text, all studies that met the inclusion criteria were selected for review. Any disagreement in the studies would be resolved by consulting a third reviewer for arbitration, which was not necessary.

Quality Assessment

The Cochrane Collaboration's tool was used for assessing methodological quality and risk of bias. This tool has 7 domains: 1. Generation of the Random

Allocation Sequence; 2. Allocation Concealment; 3. Blinding of Participants and Health Professionals; 4. Blinding of Outcome Assessors; 5. Incomplete Outcome Data; 6. Selective Outcome Reporting; and 7. Other Sources of Bias.[14] Each domain was characterized according to the risk of bias of the studies. The assessment was performed independently by 2 reviewers (LSL and FCM).

Results

Of 539 articles initially identified through the search strategy, 213 were from MEDLINE, 113 from Bireme, 10 from Embase, and 203 from Scopus. No studies were identified in the PEDro database. A total of 80 articles were excluded because they were duplicates and 408 after reviewing titles and abstracts, resulting in a set of 51 articles for full-text reading. After independent analysis by the reviewers, 46 were excluded for not meeting the inclusion criteria (Table 1), resulting in 5 studies included in our systematic review. A flowchart of the study selection process is shown in Figure 1.

All 5 studies used aromatherapy with lavender essential oil in patients with cardiovascular diseases.[12,15-18] The studies were published from 1992 to 2020. The sample size ranged from 60 to 135 patients,[15,17] and the mean age was 60 to 73 years.[16,17] Three studies[12,15,16] included participants of both sexes, and 2 studies[17,18] included only women. Regarding the participants, 2 studies[12,15] selected patients who underwent coronary artery bypass graft surgery, 1 study[16] assessed patients with coronary artery bypass graft preoperatively, and 2 studies[17,18] evaluated a sample of women with acute coronary syndrome.

Three studies[12,15,16] administered the intervention by inhalation and 2 studies[17,18] applied massage associated

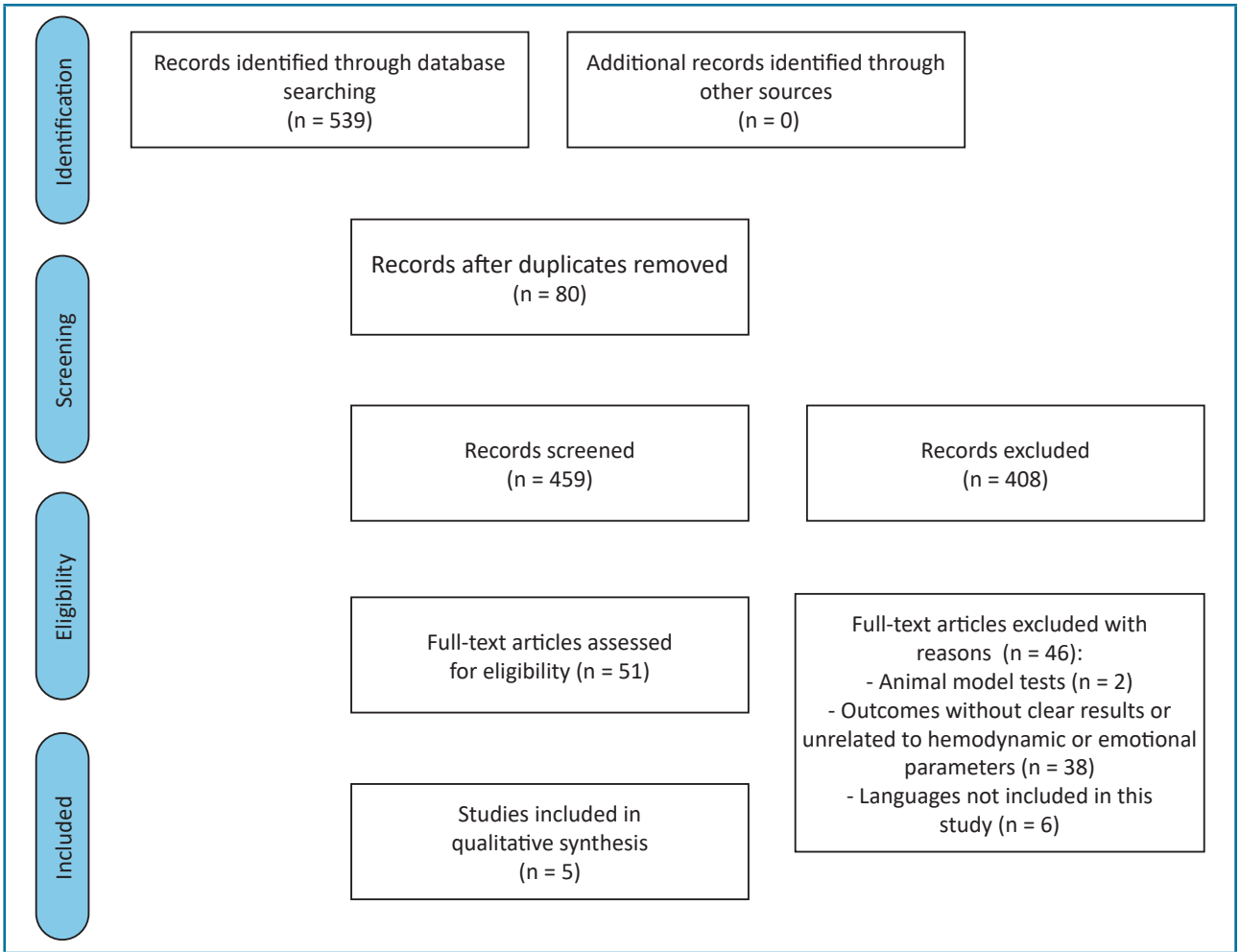

Figure 1 – Flowchart of the study selection process

with reflexology (technique that stimulates different points on the feet). In 4 studies,[12,15-17] intervention lasted for 20 minutes; 1 study[18] did not report total intervention duration. All studies included in this review used a control group. Two studies[12,16] completed the intervention on days 2 and 3 after surgery. The other 3 studies[16-18] completed the intervention in 1 day.

Five studies[12,15-18] evaluated hemodynamic responses such as SBP, DBP, HR, and RR. Two studies[17,18] included mean arterial pressure (MAP). Besides hemodynamic parameters, 1 study[18] evaluated SaO_2 and 2 studies[12,15] evaluated body temperature. Regarding emotional aspects, 2 studies evaluated only the level of anxiety,[12,16] 1 study[18] evaluated anxiety and depression levels, 1 study evaluated fatigue levels,[17] and 1 study investigated stress.[15] A p-value <0.05 was considered significant in all studies. The characteristics of the included studies are shown in Table 2.

In the study by Seifi et al.,[12] there were no statistically significant reductions in HR and RR or in anxiety levels; however, a difference in SBP and DBP was observed on the third day of intervention (30 minutes after intervention) between the aromatherapy and control groups.

Bikmoradi et al.,[15] reported different levels of stress between the aromatherapy and control groups 3 days after surgery. Regarding hemodynamic variables, there were no differences in relevant statistics, and the results were presented with the confidence interval.

Rajai et al.,[16] observed reduced levels of anxiety after intervention in the aromatherapy group; however, no significant reduction was observed in stress. Regarding hemodynamic responses, a reduction in HR was observed after intervention in the aromatherapy group compared with the control group.

Bahrami et al.,[17] reported a decrease in fatigue levels from severe to moderate and considered it a good intervention for the management of fatigue. They also showed a reduction in SBP, MAP, and HR compared with the control group.

In a second study, Bahrami et al.,[18] observed a significant reduction in anxiety and depression levels in the aromatherapy group compared with the control group. Regarding hemodynamic parameters, there were significant reductions in SBP, DBP, MAP, and HR.

Regarding study quality, all studies included in this review showed an appropriate design and carefully assessed the processes of randomization and group allocation, most of them presenting a blind assessment of the results to reduce the risk of bias. In the included studies, there were difficulties in keeping participants blind to the application of scent and massage, but there was no risk of bias due to the allocation of intervention in either group. The studies reported the outcomes as complete outcome data or reported the losses to follow-up.

Discussion

This review demonstrated that the topic of cardiovascular response to aromatherapy has not been fully explored, as there are only a few studies with a design that supports the use of aromatherapy with lavender essential oil as a therapeutic resource in the control of hemodynamic responses and emotional aspects in patients with cardiovascular diseases. Nevertheless, the evidence presented in this review shows the relevant effects of lavender essential oil use on hemodynamic responses, such as SBP, DBP, MAP, and HR, as well as on the reduction of stress, anxiety, and fatigue, when compared with control groups.[19,20]

In a study using a rabbit model, Koto et al., [21] found that linalyl acetate produces progressive effects during vascular contraction by observing the relaxation of the carotid artery and showed that linalyl acetate is the main component of lavender. However, some opposing studies pointed out linalool as the most relevant active substance.[8,9,11] This can be attributed to the different botanical species of *Lavandula* and its variations, since they are directly influenced by the location and the climate where they are cultivated, and this influences the chemical structure of the essential oil.[8] Studies included in this review did not mention the *lanvandula* species used in the interventions.

The use of lavender essential oil triggered some cardiovascular responses, and these responses are attributed to the emotional effects of lavender and may be associated with reduced levels of stress and anxiety, which regulate mood and emotion by stimulating the limbic system.[5,10] This hypothesis is supported by the findings of Koulivand et al., [8] who reported that lavender causes therapeutic effects by activating the limbic system, stimulating emotions, and activating the amygdala and the hippocampus, responsible for behavior and memory. This is in line with the results of the present review which showed a reduction in anxiety, stress, and fatigue.

Hosseni et al.,[19] reported that aromatherapy has effects on SBP, in addition to the effects on HR reduction. A reasonable explanation could be that described by

Table 2 – Characteristics of the studies included in the review

Study	Participants	Evaluation	Intervention	Results	Quality	Level of Significance
Seifi et al.[12] (2014)	n = 60 Age: 65 years Sex: 42M,18F Post cardiac surgery	Vital signs (SBP, DBP, HR, RR) and anxiety (*Questionnaire of Spielberger*). Measured in the 2 groups on the 3rd day after surgery, before and after intervention (30 min)	2 drops of lavender oil inside the O2 mask. Control: 2 drops of distilled water inside the O2 mask Both 20 min.	SBP 30 min (0.66±13.7 mm Hg x 8,1±11.0 mm Hg) DBP: 30 min (0.26±10.1 mm Hg x 4.6±9.9 mm Hg) HR (4.13±21.7 bpm x 2.46±7.8 bpm) RR (0.70±6.31 bpm x 0.60±6.07 bpm) Anxiety (41.5±6.18 x 41.3±3.65)	Low risk	p < 0.05
Bikmoradi et al.[15] (2015)	n = 60, Age: 65 years Sex: 42M,18F Post cardiac surgery	Vital signs (SBP, DBP, HR, RR) and mental stress (Questionnaire DASS-21). Measured in the 2nd group on the 3rd day after surgery, before and after intervention (30 min)	2 drops of lavender oil inside the O2 mask. Control: 2 drops of distilled water inside the O2 mask Both 20 min.	SBP (115.13 mm Hg x 130.63 mm Hg) DBP (72.63 mm Hg x 79.87 mm Hg) HC (82.33 bpm x 85.16 bpm) RR (24.10 bpm x 24.20 bpm) Mental stress (7.70 x 7.03)	Low risk	p < 0.05
Rajai et al.[16] (2016)	n = 60, Age: 60-69 years Sex: 44M,16F Preop cardiac surgery	Vital signs (SBP, DBP, HR, RR) mental stress and anxiety (Questionnaire-DASS-21). Measures before and 5 min after intervention in both groups.	2 drops of lavender oil in cotton in a 10ml jar at 5cm from the nose. For 20 min. Control: breath room air.	SBP (127.20±21.56 mm Hg x 126.96±18.15 mm Hg) DBP (76.80±10.65 mm Hg x 77.06±7.67 mm Hg) HR (84.63±10.41 bpm x 78.83±9.23 bpm) RR (19.30±2.40 bpm x 19.83±2.80 bpm) Mental stress (9.30±4.59 x 8.63±4.16) Anxiety (9.13±4.55 x 6.63±3.95)	Undefined risk	p < 0.05
Bahrami et al.[17] (2017)	n = 135 Age: 72 years Sex: 0M,135F Acute coronary syndrome	Vital signs (SBP, DBP, MAP, HR, RR) e fatigue (*The Rohten Fatigue Scale*). Measured before and after intervention in the 3 groups.	Reflexology with 10 drops of lavender oil on the feet. Reflexology: application of technique. Both 20 min. Control: usual care of the unit.	SBP (126.89±19.15 mmHg x 117.78±10.76 mm Hg) DBP (76.20±12.23 mm Hg x 73.13±8.65) MAP (93.78±16.42 mm Hg x 85.60±7.18 mm Hg) HR (15.18±3.64 bpm x 16.69±2.29 bpm) RR (79.96±8.96 bpm x 76.53±11.19 bpm) Fatigue 16 (35.6%) x 0 (0%)	Low risk	p < 0,05
Bahrami et al.[18] (2017)	n = 90 Age: 73 years Sex: 0M, 90F Acute coronary syndrome	Vital signs (SBP, DBP, MAP, HR, RR) anxiety and depression (*Hospital anxiety and depression scale*). Measured 1 min before and after intervention in the 3 groups.	Reflexology with 6 drops of lavender oil on the feet. Reflexology: technique application. Control: usual care of the unit. No total time of intervention	BPS (126.89±19.15 mm Hg x 118.31±10.03 mm Hg) DBP (76.20±12.23 mm Hg x 71.19±6.50 mm Hg) MAP (93.78±16.42 mm Hg x 85.60±7.18 mm Hg) HR (79.47±9.22 bpm x 74.82±11.74 bpm) RR (14.16±2.89 bpm x 16.27±2.03 bpm) Anxiety (11.07±3.19 x 8.04±4.71) Depression (11.11±3.42 x 8.04±4.71)	Low risk	p < 0.05

BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure, MAP: mean arterial pressure; HR: heart rate in beats per minute (bpm); RR: respiratory rate in breaths per minute (bpm).

Henz et al.,[10] in which they state that the action of linalool in reducing SBP could be related to the effects of sympathetic deactivation of the autonomic nervous system. This hypothesis can be supported by the studies of Rajai et al.,[16] and Bahrami et al.,[18] who found a reduction in HR in the aromatherapy intervention groups. Also, the reduction in anxiety levels observed by Rajai et al.,[16] and Bahrami et al.,[18] may be attributed to the anxiolytic and sedative effects of linalool on the autonomic nervous system as a parasympathetic mimetic effect.[20] Koulivand et al.,[8] demonstrated similar anxiolytic action in an animal experiment comparing linalool with chlordiazepoxide.

Shiina et al.,[20] and Bikmoradi et al.,[15] observed significant reductions in cortisol levels, whereas Bahrami et al., [18] showed significant reductions in the levels of anxiety and depression, which were justified by the relaxing effects of lavender on the autonomic nervous system. Hosseni et al.,[19] reported that anxiety increases cortisol and adrenaline levels, generating a stress response in the body. Bahrami et al.,[17] in their first study, assessed fatigue levels and found a reduction from severe to moderate after aromatherapy.

In both studies conducted by Bahrami et al.,[17,18] foot massage was used as an intervention resource. In this respect, the authors reported that topical massage is absorbed by the skin and stimulates the olfactory system, affecting the limbic system and stimulating the parasympathetic nervous system. Consequently, there is a stabilization of metabolic and physiological parameters, leading to relaxation. Henz et al.,[10] reported that the absorption of linalool through massage could be psychologically more relaxing than inhalation.

A limitation of this study is that, although most of the included studies have an adequate design and low risk of bias, there is a small number of studies on this topic. Also, differences in the application protocols and the heterogeneity of the study populations made it impossible to pool data for meta-analysis.

Conclusion

This systematic review showed that aromatherapy using lavender essential oil has beneficial effects on hemodynamic parameters. Despite the scarce evidence, aromatherapy appears to control the levels of anxiety, stress, depression, and fatigue in patients with cardiovascular diseases. However, there remains a gap in knowledge and more evidence is needed on the use of aromatherapy and its effects on cardiovascular diseases. Further research on the effects of aromatherapy with lavender essential oil in the treatment of patients with cardiovascular diseases is required to explain the physiological mechanisms involved in the results found in this review and to support the clinical practice of aromatherapy as a complementary activity that determines the improvement of health and quality of life in patients with cardiovascular diseases.

Author Contributions

Conception and design of the research: Lopes LS, Tinoco EM, Chermont S. Acquisition of data: Lopes LS, Modesto F. Analysis and interpretation of the data: Lopes LS, Bündchen DC, Quintão M, Chermont S. Statistical analysis: Lopes LS, Bündchen DC, Chermont S. Writing of the manuscript: Lopes LS, Tinoco EM, Chermont S. Critical revision of the manuscript for intellectual content: Lopes LS, Bündchen DC, Quintão M, Modesto F, Tinoco EM, Chermont S.

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REVIEW ARTICLE

Transcatheter Interatrial Shunts for the Treatment of Heart Failure with Preserved Ejection Fraction

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome, which accounts for about 50% of patients with heart failure (HF). The morbidity and mortality associated with HFpEF is similar to HFrEF. Clinical trials to date have failed to show a benefit of medical therapy for HFpEF, which may due to lack of uniform phenotypes and heterogeneous population. In addition, medical therapy proven for HFrEF may not address the pathophysiologic basis for HFpEF. Left atrial remodeling and dysfunction is central to HFpEF and accounts for secondary pulmonary hypertension and pulmonary vascular congestion that frequently occurs with exertion. Interatrial shunts represent a novel treatment modality for HFpEF. These shunts allow for left atrial decongestion and a reduction in pulmonary venous hypertension during exercise leading to improvements in hemodynamics, functional status and quality of life. Trials to date have demonstrated safety and short-term efficacy of these devices for HFpEF. The long-term benefits are currently being evaluated in ongoing trials. If effective, the use of interatrial shunts may be a new therapeutic paradigm for the treatment of HFpEF.

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome, which accounts for about 50% of patients with heart failure (HF), with an estimated prevalence exceeding 5 million people.[1,2] Not only is it associated with poor quality of life, but the mortality and morbidity associated with HFpEF are also similar to those reported for heart failure with reduced ejection fraction (HFrEF).[3] While the management of HFrEF has improved significantly over the last two decades, little or no progress has been made regarding optimal and effective treatment for HFpEF. This lack of evidence-based clinical strategies for the treatment of HFpEF may be due to the diverse phenotypes of HFpEF.[4] While medical therapy has failed to yield clear benefits, there has been interest in device-based therapies, including the creation of interatrial shunts to "unload" the left atrium. This review discusses the diagnosis and pathogenesis of HFpEF, the rationale behind interatrial shunts (IAS) and the current IAS devices under clinical evaluation.

Keywords

Heart Failure; Stroke Volume; Hypertrophy, Left Ventricular; Heart Atria; Transcatheter.

Diagnosis of Heart failure with preserved ejection fraction

Given that HFpEF has several distinct phenotypes and pathophysiological mechanisms, its diagnosis is challenging secondary to the lack of a uniform diagnostic algorithm. Moreover, it is diagnosed primarily by excluding other potential noncardiac causes of symptoms suggestive of HF. The diagnosis does not depend on a single criterion. Furthermore, non-invasive parameters are not consistently reliable for its diagnosis, as abnormalities in diastology may only be revealed on exertion. The current criteria proposed to define HFpEF include: a) clinical signs

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or symptoms of HF; b) evidence of preserved or normal left ventricular ejection fraction (LVEF); and c) evidence of abnormal left ventricular (LV) diastolic dysfunction that can be determined by Doppler echocardiography or cardiac catheterization.[5] Other diagnostic parameters include: left ventricular hypertrophy (LVH), left atrial enlargement, elevated serum natriuretic peptide (NP) levels and history of atrial fibrillation (AF).[6] It is well established that normal NP levels have a very high negative predictive value for excluding HF, but normal NP levels do not exclude HFpEF due to other confounding variables.[7-9] Reddy et al.,[10] have retrospectively derived a composite HFpEF diagnostic score (Table 1), which includes clinical characteristics (age > 60 years, obesity, atrial fibrillation, treatment with ≥ 2 antihypertensive drugs) and echocardiographic measurements [E/e' >9, pulmonary artery systolic pressure (PASP)>35mmHg].[10] However, the gold standard test for confirming HFpEF is invasive right heart catheterization with elevated left ventricular filling pressures: an elevated pulmonary capillary wedge pressure (PCWP) ≥ 15 mmHg at rest or ≥ 25 mmHg during exercise measured by right catheterization.[5]

Pathophysiology of Heart Failure with Preserved Ejection Fraction

HFpEF is a complex entity with many traditional and nontraditional cardiovascular risk factors, such as hypertension (HTN), diabetes mellitus (DM), obesity, renal or pulmonary disease, influencing its pathophysiology.[11] These comorbidities, particularly obesity, induce a systemic proinflammatory state evident from increased circulation of interleukin-6 and tumor necrosis factor alpha (TNF-α). This induces microvascular endothelial cells to produce reactive oxygen species, thus limiting the availability of nitric oxide (NO) for cardiomyocytes. This leads to decreased cGMP production, which decreases protein kinase G and hypophosphorylates the protein titin, thereby inducing concentric left ventricular hypertrophy and stiffness of cardiomyocytes, respectively. This myocardial stiffness and fibrosis cause diastolic myocardial dysfunction, which is the hallmark of HFpEF.[12] Other pathophysiological processes include: increased systemic vascular resistance and arterial stiffness, abnormal ventricular arterial coupling, ventricular dyssynchrony, atrial dysfunction, impaired right ventricular function, pulmonary hypertension, coronary microvascular dysfunction, and chronotropic incompetence.[13] HFpEF is typically characterized by decreased stroke volume and cardiac output. This impaired LV diastolic relaxation leads to elevated left atrial pressure during physical activity, which is deemed the key driver of symptoms in HFpEF.[14]

Left Atrial Remodeling

The decrease in left atrial (LA) function and remodeling is a central pathophysiological phenomenon in HFpEF. Pressure and volume overload can cause left atrial dysfunction at a cellular level. LA remodeling is thought to be due to mechanical stretch, multiple cytokine activation, atrial fibrosis, and cellular apoptosis.[15] Typically in HFpEF, compared to HFrEF, there are lower LA volumes, higher LA

Table 1: Heart Failure with Preserved Ejection Fraction (HFpEF) – Diagnosis

	Clinical Variable	Values	Points
H	**H**eavy	Body Mass Index >30kg/m2	2
	Hypertension	Two or more hypertensive medications	1
F	Atrial **F**ibrillation	Paroxysmal or Persistent	3
P	**P**ulmonary Hypertension	Doppler echocardiographic estimated PA pressures > 35mmHg	1
E	**E**lder	Age > 60 years	1
F	**F**illing Pressures	Doppler Echo E/e' > 9	1
H2FPEF Score			**Sum 0-9**

A low score (0 or 1) excludes HFpEF. A high score (6-9) establishes a diagnosis of HFpEF. An intermediate score (2-5) warrants additional testing.

peak pressures, stiffness, pulsatility, and stress wall variations. High LA stiffness also plays a significant role in increased atrial fibrillation burden. There is also a relationship between LA dysfunction and pulmonary vascular disease, which contributes to right heart failure, most likely due to reduced pulmonary arterial compliance. This decreased compliance can lead to RV to PA uncoupling, which is unmasked with exercise and prevalent in more advanced stages of HFpEF. LA dysfunction in HFpEF is also correlated with mortality among this population.[16]

The "stiff left atrial syndrome" is marked by a non-compliant left atrium and can be seen after cardiac surgeries or after catheter ablation for atrial fibrillation. These patients can develop left atrial diastolic dysfunction and associated pulmonary hypertension. Gibson et al.,[17] demonstrated that severe LA scarring, small LA, diabetes mellitus, OSA, and high LA pressures were predictive of the development of this syndrome in atrial fibrillation patients who underwent catheter ablation.[17] Interestingly, these clinical variables are commonly seen in patients with HFpEF. Case reports document the development of stiff left atrial syndrome after atrial fibrillation ablations, marked by a rise in wedge pressures and prominent v waves during right heart catheterization with exercise.[18] Acute pulmonary vascular congestion may result from an abrupt rise in left atrial pressures.[19] Atrial septostomy can significantly improve symptoms, increase peak VO2, and mitigate RV dysfunction and pulmonary hypertension.[20] Interatrial shunt devices may promote reverse LA remodeling by decreasing pressure and volume overload, thereby decreasing the risk of RV failure and improving mortality in patients with HFpEF.

Failure of Medical Therapy for HFPEF

To date, the pharmacological interventions approved for HFrEF have not shown to improve any outcomes in HFpEF.[21] Angiotensin receptor blockers failed to demonstrate benefit in the CHARM-Preserved trial.[22] Spironolactone did not meet its primary endpoint of death from cardiovascular causes, aborted cardiac arrest, or heart failure hospitalizations in the TOPCAT trial.[23] Inconsistent patient selection and medication administration may have undermined the trial.[24] The PARAGON-HF trial, which compared sacubitril–valsartan with valsartan alone in patients with HFpEF, also failed to meet its primary endpoint of lower heart failure hospitalization rates or cardiovascular death among patients with heart failure and an ejection fraction of 45% or higher.[25] However, there was a suggestion that women may have benefited from sacubitril-valsartan more than men in reducing heart failure hospitalization.[26]

Interatrial Shunting for Heart Failure with Preserved Ejection Fraction

It has been observed that, compared to patients with isolated mitral stenosis, patients with Lutembacher's syndrome (mitral stenosis and congenital atrial septal defect) have less profound symptoms due to LA pressure offloading. In similar contexts, patients with HFpEF have higher filling pressures (at rest and/or with exercise), which drives fluid retention and acute decompensations;[27,28] interatrial shunt devices have been used to reduce left atrial pressure by allowing modest left to right shunting in HFpEF.[29,30] Interatrial pressure gradient regulates flow through the interatrial shunt to relieve left atrial pressure overload. In a cardiovascular simulation model, Kaye et al.,[30] demonstrated that a shunt diameter of 8-9mm lowered wedge pressure without an increase in right atrial or pulmonary artery.[30] The target patient population for such treatment included HF patients with a high-pressure gradient between the left and right atrium without RV dysfunction. Patients with RV dysfunction are not candidates for shunts due to concerns for RV overload and progressive RV failure.

Devices (Table 2)

The Interatrial shunt device (IASD, Corvia Medical) consists of a 19 mm wide nitinol mesh with multiple legs, radiopaque markers and an 8 mm central communication to create the interatrial septal defect.[31,32] The legs of this device are flat on the LA side to minimize the risk of thrombus formation. Dual antiplatelet therapy with aspirin and clopidogrel is recommended for 6 months, followed by lifelong aspirin monotherapy. Patients taking oral anticoagulants are recommended to continue their existing oral anticoagulant therapy after the procedure with endocarditis prophylaxis advised for a minimum of six months after the implantation.[32]

The V-wave device (V-wave Inc) is a tri-leaflet porcine tissue valve on an hourglass shaped device also made of nitinol, encapsulated by expanded

Table 2 – Interatrial Septal Devices

Device	Characteristics	Studies	Notes
IASD® system (Corvia Medical Inc., Tewkesbury, Massachusetts)	8mm ASD Shunt fraction 1.2-1.3	REDUCE LAP- HF and REDUCE LAP-HF I study (phase II trial). Evidence of safety of the IASD with no differences between MACCRE in IASD vs sham.	REDUCE LAP-HF II: Phase III RCT that is currently enrolling.
V-wave Shunt (V-Wave Ltd., Caesarea, Israel)	5 mm unidirectional Nitinol	Initial safety and clinical and hemodynamic benefits in HFrEF and HFpEF	RELIEVE-HF. V Wave to be assessed in both HFrEF and HFpEF
Atrial Flow Regulator (Occlutech, Istanbul, Turkey)	2, 5and 10 mm 4-10 mm	Initial improvement in symptoms, functional class, hemodynamic sand biomarkers in HFrEF and HFpEF.	

ASD: atrial septal device, MACCRE: major adverse cardiac, cerebrovascular and renal events.

polytetrafluoroethylene on the left atrial side with the three porcine pericardial leaflets sutured with Prolene to ensure a 5 mm unidirectional (left to right) shunt.[33,34] The PTFE is designed to improve blood flow and restrict new growth over the device. Following implantation, patients require anticoagulation with warfarin or direct-acting oral anticoagulant (DOAC) for three months and low-dose aspirin indefinitely.[35]

The Atrial Flow Regulator (AFR, Occlutech) is another device made of nitinol mesh and a central hole. There are three waist sizes to suit the atrial septal thickness (2, 5 and 10 mm) and the fenestration diameter varies from 4-10 mm, which was tested in a small pilot study in patients with HFrEF and HFpEF.[31,34,36]

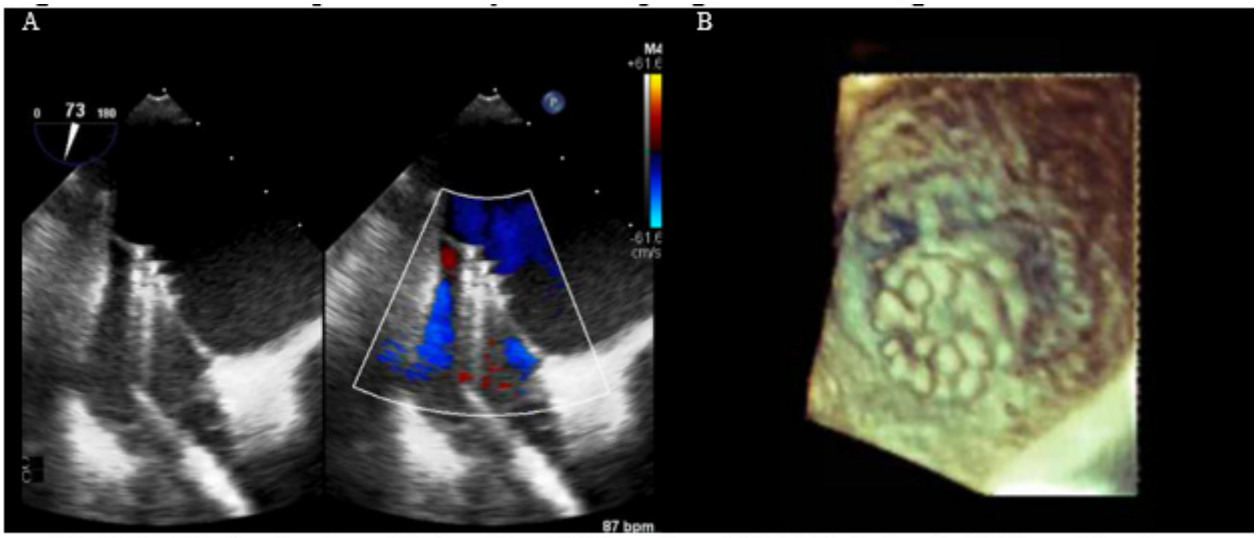
Implantation Technique

For most interatrial devices, implantation is performed under general anesthesia, using transfemoral approach with fluoroscopic and transesophageal or intracardiac echocardiographic (ICE) guidance. Following a transseptal puncture, a 14-16 Fr sheath is advanced into the LA, and each device is deployed with its respective delivery system with balloon pre-dilation recommended for implantation of the AFR device.[36] The left side of the device is initially opened, with the entire system pulled back, ensuring tenting at IAS, followed by deployment of the right side of the device. (Figure 1) The delivery system and guide wire are then removed, and hemostasis is achieved.

Clinical Evidence

The first human experience of IASD (Corvia Medical) was a non-randomized, pilot study by Sondergaard et al.,[32] in 11 patients with LVEF > 45% , baseline PCWP > 15 mm Hg at rest or > 25 mm Hg during exercise, ≥ one hospitalization for heart failure within the past 12 months, or persistent NYHA class III /ambulatory class IV for at least 3 months.[32] The average age of these patients was 71 years, with an average left ventricular ejection fraction (LVEF) of 57%, average PCWP of 19 mm Hg, and median NT-proBNP of 148 pg/mL. Devices were successfully implanted in all but one patient, in whom the insertion of a new device corrected device malposition. There were no device-related complications, such as migration or loss of patency. After 30 days, LV filling pressures were significantly reduced by 5.5 mmHg (28%, 19.7 ± 3.4 vs. 14.2 ± 2.7; P = 0.005), and there were significant improvements in 6MWT distance, quality of life, and NYHA class, with no changes in PAP or RAP. At one year all patients survived and the symptomatic improvement (as measured by NYHA class) was sustained, although some patients required an increase in their daily dose of loop diuretics.

The Reduce Elevated Left Atrial Pressure in Patients



A. IASD device deployed in the interatrial septum. B. IASD device in 3-dimensional imaging.

Figure 1 – Intra-atrial Septal Device by Transesophageal Echocardiogram

with HF (REDUCE LAP-HF) study was a multicenter, prospective, non-randomized, open-label, single-arm study in patients with symptomatic HFpEF (NYHA class II-IV) and elevated PCWP (>15 mm Hg at rest and > 25 mm Hg during exercise).[29,37] A total of 68 patients with symptomatic HFpEF underwent an IASD system II device implantation. The average age of subjects was 69 years, average LVEF of 47%, mean PCWP at rest was 17 mm Hg and median NTproBNP was 377 pg/mL. Overall, the device was successfully implanted in 64 patients. At a six-month follow-up, there was no significant change in PCWP at rest, but a significant drop in PCWP upon exertion was observed. Sustained device patency at 6 months was confirmed by left-to-right shunting. Furthermore, IASD was associated with significant improvements in symptoms, quality of life, and functional status at six months, which were sustained at the 12-month follow-up.[29,38] Kaye et al.,[39] investigated the impact of IASD on HFpEF mortality over a follow up of 739 days. The observed mortality rate of the IASD-treated cohort was 3.4/100 patient-year, representing a 33% reduction in all-cause mortality rates (p = 0.02).[39]

These observations were further validated in a sham-controlled randomized trial, REDUCE LAP-HF I study (Reduce Elevated Left Atrial Pressure in Patients With Heart Failure), which was a phase 2, randomized, parallel-group, blinded multicenter trial in patients with NYHA class III or ambulatory class IV HF. Enrolled patients had an EF ≥40%, exercise PCWP ≥25 mm Hg, and PCWP-right atrial pressure gradient ≥5 mm Hg. Forty-four patients were randomized (1:1) to the IASD system II device placement *versus* a sham procedure (femoral venous access with intracardiac echocardiography, but no IASD placement).[40] Mean age of participants was 70±9 years, and 50% were female. At one-month follow-up, the IASD group resulted in greater reduction in PCWP compared with sham control (P=0.028 accounting for all stages of exercise). Peak PCWP decreased by 3.5±6.4 mm Hg in the treatment group *versus* 0.5±5.0 mm Hg in the control group (P=0.14). There were no major periprocedural complications or adverse cardiac, cerebrovascular, or renal events reported in the IASD group at one month. At one-year follow-up, there was 100% device patency. There were no statistically significant differences in functional class, exercise capacity, HF hospitalization or diuretic use between the two groups at one year, although this may be attributed to the limited sample size (n=44).[41] Despite an increase in right ventricular size, the IASD was not associated with right ventricular dysfunction, and improvements were observed in pulmonary vascular function at rest and during exercise.[42]

The V-wave device was the first IAS device implanted in a patient with HFrEF.[35] Initial experience with this device was reported by Del Trigo et al.,[33] in 10 patients with HFrEF.[33] A single-arm multicenter assessment in 38 patients (30 with HFrEF and 8 with HFpEF) demonstrated no periprocedural mortality, although pericardial tamponade occurred in one patient (2.6%).[43] After 3 and 12 months, improvements in NYHA functional class, QoL, and 6MWT were observed, although there was no significant change in hemodynamic parameters at 12 months. After an extended follow-up of 28 months, ten deaths were reported (of which eight were from cardiovascular causes), and two patients required advanced therapies (one received an LVAD at 15 months and another received transplant at 27 months). All shunts remained patent at three months but, at one year follow-up, 5 out of 36 (14%) were occluded, and another 13 (36%) were stenotic, leading to a shunt stenosis/occlusion rate of 50%.[43] A comparative analysis between patients with patent and occluded shunts suggested significant improvements in hemodynamic parameters and late clinical outcomes, including death, HF hospitalizations and requirement of advanced therapies in those who maintained patency.

The potential cause of stenosis was deemed to be intra-shunt valve deterioration, which prompted development of a newer generation V-wave device. The second-generation valveless V-wave shunt was studied in ten patients, which remained patent at one-year follow-up.[44] The efficacy of this device has been currently evaluated in a large randomized trial.

The AFR-PRELIEVE was a prospective, non-randomized, open-label, multicenter phase 2 pilot study in patients with symptomatic heart failure NYHA Class III /ambulatory class IV and pulmonary capillary wedge pressure (PCWP) ≥15 mmHg at rest or ≥25 mmHg at exercise, irrespective of LVEF. The study included 36 patients, of whom 20 had HFpEF. Implantation success rate and device patency with the left-to-right shunt was 100% at the three-month follow-up.[36] Individual patients from both the HFrEF and HFpEF groups showed improvement in symptoms and surrogate parameters of heart failure, including NYHA class, six-minute walking distance, Kansas City Cardiomyopathy Questionnaire, PCWP and NT-proBNP values. Further evaluation is necessary to determine the long-term benefits of the device in HFPEF.

Future Trials

The REDUCE LAP-HF TRIAL II (NCT03088033) is a sham-controlled, multicenter, prospective phase 3 trial being conducted to evaluate the clinical efficacy and safety of the IASD II for HFpEF patients with elevated left atrial pressure who remain symptomatic despite appropriate medical management. Patients are randomized to IASD II implantation or to control arm and will be followed for five years for "hard" clinical endpoints (cardiovascular death, non-fatal stroke, need for hospitalization because of acutely decompensated HF). A post-market observational registry is also underway that aims to assess the efficacy and safety of the IASD System II and its benefits on quality of life (REDUCE-LAP HF III, NCT03191656).

Reducing Lung Congestion Symptoms in Advanced Heart Failure (RELIEVE-HF, NCT03499236) is a prospective, multicenter, randomized, double-blinded study which aims at providing data on the safety and clinical effectiveness of the V-Wave Interatrial Shunt System in patients with NYHA functional class III or ambulatory class IV HF, irrespective of LVEF. Approximately 400 patients will be randomized to shunt treatment and a non-implant control arm, and the study will be blinded during follow-up for a minimum of 12 months to a maximum of 24 months. All implanted patients will be followed for five years from the time of the study device implantation.

Limitations of this Modality

The results of interatrial shunt devices have been encouraging in small studies; however, there remain concerns regarding its efficacy and safety in clinical practice. Even though there was a notable drop in filling pressures, not all studies demonstrated a significant improvement in mortality. Larger clinical trials will address whether pivotal hemodynamic improvements seen in initial studies will translate to benefits in "hard" clinical endpoints and long-term cardiac remodeling.

In addition, long-term adverse outcomes with these devices – including paradoxical embolus, right ventricular dysfunction, tricuspid regurgitation and pulmonary hypertension – will need to be appraised before adoption in standard clinical practice. While the degree of shunt ratios remain small, with Qp:Qs averaging 1:2 to 1:3, the impact on right atrial function

and potential arrhythmias may be of concern.[45] Optimal long-term antiplatelet regimens for these devices will also need to be determined to maintain patency.

Conclusions and Future Perspectives:

HFpEF carries morbidity and mortality similar to HFrEF, and poses a similar fiscal strain on healthcare.[46] HFpEF remains a clinically ill-defined entity, given its complex etiology and pathogenesis, and therapeutic options are lacking HFpEF due to the heterogeneity in the patient population. Interatrial shunting appears to be a promising option for treating patients with HFpEF. It may prove to be a safe, cost-effective, and feasible therapy for patients who remain symptomatic due to pulmonary congestion and intrinsically elevated left atrial pressure; it may also be considered as a palliative therapy in selected patients with refractory pulmonary hypertension associated with HFpEF. The current devices seem to be safe in the short and midterm, albeit data on their long-term safety and efficacy are lacking. Ongoing studies that include a more significant number of patients and with extended follow-up periods will determine whether this novel approach is a viable treatment modality for HFpEF.

Review Criteria

A search of the PubMed database was performed using the following terms: "interventional therapy heart failure with preserved ejection fraction", "interatrial shunt", "atrial shunting" and "atrial septostomy". Only full-text, peer-reviewed articles published in English were included, predominantly from 2000 to 2020. Bibliographies of the studies identified in the search were also reviewed for additional papers relevant to this topic.

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Writing of the manuscript: Bhardwaj A, Parikh V, Nair A.

Potential Conflict of Interest

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REVIEW ARTICLE

Practical Approach to Acute Coronary Syndrome in Patients with COVID-19

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Abstract

Acute cardiac injury is associated with higher mortality in patients with the novel coronavirus disease-2019 (COVID-19) and the exact etiology can be challenging to diagnose in the emergency setting during the pandemic. From a pathophysiological perspective, SARS-CoV-2 infection is characterized by an overproduction of inflammatory cytokines (IL-6, TNF-alpha) that leads to systemic inflammation and consequent increased risk of acute myocardial infarction (AMI) caused by atheromatous plaque rupture and significant myocardial oxygen supply-demand imbalance. Moreover, SARS-CoV-2 tropism to the renin-angiotensin-aldosterone system through the ACE2 receptor induces myocarditis that may rapidly progress to left ventricular dysfunction and hemodynamic instability. Myocardial inflammation with pericardial involvement, *i.e.*, myopericarditis, can progress to cardiac tamponade and obstructive shock. These cardiovascular complications, which are associated with a worse prognosis and higher mortality, can be associated with clinical manifestations, electrocardiographic changes, and troponin values similar to AMI. Thus, the diagnosis and treatment of patients with acute chest pain and dyspnea admitted to the emergency department is a significant challenge during the COVID-19 pandemic. Here, we provide a review of the literature focusing on a practical approach to acute coronary syndrome patients with confirmed or suspected COVID-19.

Keywords

Acute Coronary Syndrome; Betacoronavirus; COVID-19; Infection; Pandemics; Troponin; Electrocardiography/methods.

Introduction

In December 2019, a new positive-strand RNA virus,[1] belonging to the family *Coronaviridae*, began to circulate in Wuhan, China. The new virus shares characteristics with the SARS-CoV and MERS-CoV, both responsible for epidemics in past decades. It was named SARS-CoV-2, which is the cause of the current pandemic announced by the World Health Organization (WHO) in March 2020. In Brazil, at the end of June 2020, the number of confirmed cases had already surpassed 1,5 million, with 65,000 deaths from the disease.[2] The fatality rate in the country reaches 6.9%, similar to other countries with similar diagnostic approaches.[3] Unlike the other six phylogenetically similar viruses, the etiological agent of coronavirus disease-2019 (COVID-19) is highly infectious, with a basic reproduction number (R0) between 2 and 3.5.[4-6] Moreover, some studies have identified high viremias in patients who do not present any symptoms, emphasizing the relevance and the direct impact of this finding on the global spread of the disease.[7-9]

Acute coronary syndrome is a clinical condition with high prevalence, morbidity, and mortality. Acute chest pain is a usual complaint in the emergency units, with well-defined protocols and differential diagnosis from other (fatal or not) diseases, aiming to establish a rapid and effective treatment. In the current global health crisis, scientific evidence has revealed significant cardiovascular involvement in COVID-19, which makes the management of acute chest pain even more complex

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and challenging in the emergency setting, urging the need for reviewing these protocols. Cardiac involvement in SARS-CoV-2 patients seems to affect mainly those with typical cardiovascular risk factors and to incorporate several pathophysiological mechanisms, such as a direct cardiac injury by the viral cytopathic effect, myocardial injury due to a pro-inflammatory state and systemic inflammation, and decompensation of pre-existing cardiovascular disease.[10-13]

A meta-analysis with 341 patients associated myocardial injury with severe COVID-19 infection since patients with high troponin serum levels required intensive care more often.[14] Myocardial injury is also a predictor of higher mortality in patients with COVID-19. Furthermore, cardiovascular complications such as acute myocardial infarction (AMI) are frequent in these patients and may cause irreversible myocardial damage[15] or even rapidly progress to cardiogenic shock and death.[16,17]

Therefore, it is imperative to understand the main mechanisms involved in the development of myocardial ischemia in SARS-CoV-2 infection, and its diagnosis, to implement appropriate clinical interventions aiming to prevent unfavorable outcomes and possibly permanent sequelae.

Methodology

This study is an extensive scoping review. The bibliographical survey was performed in the PubMed platform using the descriptors "COVID-19", "2019-nCoV", "Myocardial Infarction", "Acute Coronary Syndrome" and "Echocardiography" in the advanced search function. Articles diverging or not related to the main theme, and articles not written in English were excluded from the review. After exclusions, 59 articles were selected and thoroughly reviewed to compose the present study and were cited either directly or via cross-reference.

Discussion

Cardiovascular Risk Factors

Hypertension and diabetes mellitus has been described as the most prevalent comorbidities among individuals with COVID-19, particularly in the more severe forms of the disease requiring hospitalization. On average, 30% and 10% of severe COVID-19 patients are hypertensive and diabetics, respectively,[16] and these conditions are also related to higher mortality in these patients, varying amongst different populations.[18] A meta-analysis including 12 studies demonstrated that the prevalence of diabetes and hypertension in patients with severe COVID-19 was significantly higher compared to those with non-severe forms of the disease (OR: 3.52; 95% CI: 2.65-4.67 and OR: 2.69; 95% CI: 2.16-3.34, respectively). Three studies showed that uncontrolled glucose levels are related to higher severity. However, regarding blood pressure control, the results were controversial.[18]

In a case study performed in New York City, United States with 5,700 patients (mean age of 63 years; 39.7% female), the most frequent comorbidities were hypertension (56.6%), obesity (41.7%), and diabetes mellitus (33.8%).[19] In a meta-analysis with 419 patients (61.8% male, mean age of 55.6 years), the most prevalent comorbidity was hypertension (24.3%), followed by diabetes mellitus (15.2%) and heart disease (6.2%).[20] In general, patients with COVID-19 and hypertension had a higher mortality risk compared to those without hypertension.[21]

It is worth highlighting that patients with hypertension and diabetes, from a pathophysiological perspective, have higher inflammation levels. Therefore, these patients are at higher risk for complications due to immune hyperactivity and severe inflammatory response caused by the SARS-CoV-2 infection, heightening pre-existing endothelial dysfunction and inflammation, leading to more adverse outcomes. It is still unclear if the risk of infection among these patients is greater than in the general population. However, hypertension and diabetes are comorbidities associated with the highest morbidity and mortality among patients with COVID-19.[18] Additionally, chronic cardiovascular disease may become unstable as a consequence of the imbalance between the disease-induced increase of metabolic demand and decrease in cardiac reserve.[22]

Yang et al.,[21] in a retrospective study assessing the effect of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) on clinical parameters and inflammatory profile of 126 patients with pre-existing hypertension and COVID-19, reported that hypertensive patients had higher mortality rates (10.3% vs. 6.4%) and higher incidence of critical illness (18.3% vs. 11.2%) when compared to normotensive patients, but without statistical significance. Moreover, hypertensive patients with COVID-19 showed higher plasma concentrations of ultra-sensitive C-reactive protein (25.4

[4.6-100.8] vs. 12.6 [2.6-53.3]; p=0.024), procalcitonin (0.092 [0.049-0.223] vs. 0.062 [0.035-0.134]; p=0.017), and IL-6 (13.8 [4.8-51.3] vs. 8.2 [1.8-22.8]; p=0.017) in comparison to non-hypertensive patients of the control group. It is possible that patients with COVID-19 and pre-existing hypertension experience a greater increase in inflammatory markers when compared to non-hypertensive patients, developing, therefore, a more exacerbated immune hyperactivity and more pronounced systemic inflammation.[21]

In addition to a pro-inflammatory state at baseline, which *per se* is a risk factor for a severe form of COVID-19, it must be noted that older age is associated with a higher prevalence of hypertension and diabetes than the general population.[22,23] Previous studies revealed that older patients with underlying diseases have a higher likelihood of progressing to a more severe form of the disease. Also, exacerbated immune and inflammatory responses associated with a cytokine storm may have a significant role in the progression of COVID-19 in hypertensive patients since increased IL-6 levels and a higher degree of inflammation were identified in this population.[23-25]

It is still unclear if individuals with diabetes mellitus are more susceptible to COVID-19, but studies have reported a higher risk of unfavorable progression in this group of patients. Huang et al.,[26] in a meta-analysis including 30 retrospective and cohort studies with 6,452 patients, evidenced that diabetes mellitus was associated with unfavorable clinical outcomes (RR 2.38 [1.88,3.03], p<0.001; I^2: 62%), with a subgroup composed of higher mortality (RR 2.12 [1.44, 3.11], p<0.001; I^2: 72%), higher risk of severe COVID-19 (RR 2.45 [1.79, 3.35], p<0.001; I^2: 45%), and higher incidence of ARDS (RR 4.64 [1.86, 11.58], p=0.001; I^2: 9%] in patients with COVID-19. However, diabetes mellitus was not associated with a greater need for hospitalization in intensive care units (RR 1.47 [0.38, 5.67], p=0.57; I^2: 63%, p=0.07).[26]

From a pathophysiological perspective, the relationship between diabetes and higher virulence of SARS-CoV-2 has not been well elucidated in the medical literature. However, authors have postulated that pathophysiological mechanisms, such as: a higher expression of ACE2 favoring viral endocytosis; an increased expression of furin, a type-1 membrane-bound protease belonging to the proprotein convertase subtilisin/kexin class (PCSK), optimizing viral entry and replication; and basal hypercytokinaemia at the expense of IL-6, enhancing the systemic inflammatory state observed in the severe forms of the disease, are all factors potentially responsible for increased risk, virulence, and severity of SARS-CoV-2 infection among patients with diabetes.[27] Moreover, diabetic individuals have a higher risk of respiratory infection due to an impaired immune system response.[27] Thus, it is postulated that ACE2 may have an important role in aggravating COVID-19 infection among patients with diabetes.[26]

Furthermore, it is known that the damage caused by COVID-19 to the cardiovascular system is probably multifactorial, caused by metabolic imbalance, systemic inflammation (cytokine storm), coagulation disorders characterized by a pro-thrombotic state, and direct myocardial injury due to a viral cytopathic effect.[23-25] Several studies have shown that patients with cardiovascular risk factors (advanced age, hypertension, and diabetes) and pre-existing cardiovascular disease (coronary arterial disease, cardiomyopathies, and cerebrovascular disease) have a higher risk of progressing to more severe forms of COVID-19, and are consequently more susceptible to cardiac complications.[10,18,28] Hence, the association between SARS-CoV-2, coronary artery disease, and acute coronary syndromes is most likely related to the ability of these several mechanisms to destabilize previous coronary artery plaques and cause complications.[29,30] Therefore, patients with heart disease present greater susceptibility to viral infection and cardiac complications related to COVID-19.

Pathophysiology

The fourth definition of AMI published by the American Heart Association (AHA), American College of Cardiology (ACC), and European Society of Cardiology (ESC) is characterized by acute myocardial injury associated with clinical, electrocardiographic, and laboratory findings suggestive of ischemia, being classified in five types according to the underlying pathophysiological mechanism.[31]

Individuals with previous cardiovascular disease and cardiovascular risk factors are at higher risk for type 1 AMI and atherothrombosis when infected by the coronavirus.[32] Patients with severe COVID-19 develop cytokine storm with consequent systemic inflammation, which increases the predisposition to thrombosis due to a hypercoagulability state, causing atherosclerotic plaque instability and rupture, coronary thrombosis, and subsequent ischemia and necrosis of the myocardial segment irrigated by the occluded coronary artery.[31,33]

Previous epidemiological studies about influenza have already demonstrated an association between the viral infection and an increased risk for acute coronary syndrome during the first seven days of the disease.[31,33]

Type 2 AMI, characterized by an oxygen supply-demand imbalance, has also been described in patients with SARS-CoV-2 infection with or without previous cardiovascular diseases.[31,32] The pathogenic hypothesis for the correlation between COVID-19 and type 2 AMI derives from the increase of metabolic demand generated by viral infection and the decrease of oxygen supply due to hypoxemia in patients with severe respiratory failure in more advanced stages of the disease.[34] Furthermore, a Chinese study suggests that some proteins in the viral structure of SARS-CoV-2 may bind to the hemoglobin beta chain, reducing the oxygen supply to tissues.[35]

Despite its scarce description in the medical literature, the existence of another type of AMI, the type 4b, should be mentioned. This type is restricted to patients with previous coronary disease who already underwent primary angioplasty, which in the context of SARS-CoV-2 infection, might progress to stent thrombosis and myocardial ischemia.[31] The pathophysiological correlation between AMI type 4b and COVID-19, as previously mentioned, seems to be associated with a hypercoagulability state due to endothelial dysfunction caused by inflammatory hyperactivity and hypercytokinaemia observed in SARS-CoV-2 infection. Also, it is worth reinforcing the chronic pro-inflammatory state of these patients due to coronary artery disease, which exacerbates the expression of cytokines and contributes to the formation of new thrombus.[36]

The Role of Troponin and Electrocardiography

Several studies have demonstrated that myocardial injury, diagnosed by the increase in troponin levels, is associated with higher mortality in patients with COVID-19.[13,37] In a meta-analysis that included 13 studies, patients with acute myocardial injury required more hospitalization in intensive care units (RR 7.945, $p<0.01$) and presented higher mortality (RR 7.95, $p<0.001$).[38] In a retrospective study which analyzed 187 patients hospitalized with COVID-19, serum troponin levels presented a significant positive linear correlation with C-reactive protein and NT-proBNP levels, evidencing an important association between myocardial injury and ventricular stress with systemic inflammation, which is mainly present in the more severe stages of the disease.[39] Therefore, these findings suggest that troponin is an important prognostic marker in patients infected with SARS-CoV-2.[13,38,39]

Infection by SARS-CoV-2 increases the risk of AMI particularly because it induces instability and rupture of pre-existing atherosclerotic plaque and causes significant oxygen supply-demand imbalance in the myocardium.[32] Moreover, there are case reports describing the development of acute myocarditis, due to a likely viral tropism or association with the hypercytokinaemia and systemic inflammation triggered by viral infection, with clinical and laboratory presentations suggestive of AMI, becoming, therefore, an important differential diagnosis in patients with COVID-19.[40]

Due to the significant clinical similarity between myocarditis and acute coronary syndrome, it is vital to determine the pre-test probability through the elucidation of risk factors, physical examination, and complementary exams such as serum troponin dosage and electrocardiography (ECG). Due to their practicality, these exams are feasible to perform in an adverse hospital environment, where the risk of disease transmission is high and complex logistics for invasive exams would otherwise be required.[32,41]

The ECG may be a useful tool to elucidate cardiovascular complications related to COVID-19. Electrocardiographic changes such as convex ST-segment elevation or depression and ischemic T-wave, respecting the anatomic topography of the culprit coronary artery, especially when associated with mirrored reciprocal images in anatomically opposed electrocardiographic leads, corroborate the diagnosis of AMI. However, it does not completely exclude the possibility of a myopericarditis,[41] which usually presents with diffuse ST-segment changes not anatomically correlated with a certain coronary bed, absence of mirrored reciprocal images, and concave morphology.[42,43] Furthermore, there are reports of myocarditis associated with pericardial inflammation with unspecific ECG repolarization abnormalities, presence of alternating QRS amplitude and low voltage, accentuating the importance to investigate concomitant pericardial effusion in these patients.[40]

The fourth global definition of AMI postulates that the diagnosis of atherothrombotic type 1 AMI is established based on the increase or decrease of troponin serum levels, with at least one measurement above the 99th percentile of the upper reference limit in a healthy

population, in association with a compatible clinical state.[31] Nevertheless, it is worth noting that patients with acute myocarditis may also present increased troponin levels besides similar clinical manifestations during hospital admission. Thus, although increased troponin values reflect myocardial injury, it does not indicate the etiology and the underlying pathophysiological mechanism.[31] On the other hand, troponin curve and delta may help to diagnose patients with precordial pain and suspected COVID-19, since myocardial injury associated with ischemia usually reaches its peak in 12-24 hours, while non-ischemic etiologies such as myocarditis present a late peak and a longer plateau.[14,32]

A retrospective study including 6,557 patients assessed ultrasensitive troponin variability in emergency rooms and reported that an absolute delta of 16 ng/L presented a specificity and sensitivity of 94.2% and 83.2% for AMI, respectively, being a significant AMI predictor in patients with basal troponin between 14 and 50 ng/L.[44] This result reinforces that, although the analysis of troponin curve and absolute delta may be useful for the differential diagnosis between AMI and myocarditis in patients with acute precordial pain and suspected COVID-19 in the emergency setting, it does not have the capacity for diagnostic exclusion.

The European Society of Cardiology[45] guidance advocates that mild elevations in troponin serum levels in patients with suspected COVID-19, 2-3 times higher than the upper limit, particularly in older patients with pre-existing cardiovascular disease, do not require a more profound investigation for type I AMI unless the patient has suggestive clinical manifestations or electrocardiographic changes. However, a significant increase (*i.e.* five times the upper limit) indicates a more severe myocardial injury in patients with COVID-19, potentially reflecting cardiac complications such as Takotsubo syndrome, myocarditis, or COVID-19-induced type I AMI. It is noteworthy that due to its prognostic value in patients with COVID-19, major centers have recommended the measurement of serum troponin levels in every patient, with suspected or confirmed COVID-19, with cardiovascular risk factors, established cardiovascular disease, or symptoms indicating a more severe form of the disease.[28]

Nonetheless, in emergency rooms, diagnostic uncertainty may persist even after performing ECG and measurement of serum troponin levels in patients with precordial pain and suspected SARS-CoV-2 infection. In these cases, point-of-care echocardiography may be a useful tool to clarify the diagnosis. Moreover, in the absence of symptoms or electrocardiographic findings suggestive of type I AMI with a significant increase in troponin, an echocardiographic evaluation may be also beneficial to define the underlying cause of cardiac injury.

Role of Echocardiography

Echocardiographic assessment may also help in the differential diagnosis between myocarditis and acute coronary syndrome in COVID-19. Transthoracic echocardiography is more likely to detect contractility changes in the ventricular segment perfused by the culprit coronary artery of patients with acute coronary syndrome. On the other hand, the usual finding in myocarditis is diffuse hypokinesia with a reduction in the ejection fraction, maybe associated with a discrete pericardial effusion, although segmental dyskinesia and even a hyperdynamic state may also occur. However, acute myocarditis may also occur with preserved ventricular function without any segmental ventricular contractility changes evidenced by echocardiography. Thus, abnormal electrocardiographic and echocardiographic findings, combined with the patient's clinical manifestations may guide the differential diagnosis and outcome of COVID-19 patients.[33]

The main echocardiographic findings described in the more severe forms of COVID-19 are: (1) hyperdynamic state, represented by an increase in cardiac output and left ventricular ejection fraction with reduced peripheral vascular resistance; (2) stress-induced acute cardiomyopathy, characterized by abnormalities in segmental contraction and left ventricular apical ballooning (Takotsubo cardiomyopathy); (3) right ventricular hypertrophy and acute pulmonary hypertension; and (4) global systolic and/or diastolic dysfunction, caused by severe hypoxia, long-term anoxia and/or systemic inflammation. It is worth noting that circulatory failure in these patients is usually associated with a state of significant ventricular dysfunction and reduced peripheral vascular resistance secondary to concomitant lactic acidosis.[46]

Another significant aspect of the echocardiographic evaluation of these patients is the assessment of pulmonary vascular resistance and the presence of right ventricular dysfunction due to hypoxia, vasospasm of the pulmonary arteries, hypercapnia, and inflammation.[46] This finding may point to the presence of pulmonary thromboembolism (PTE), which is often described in patients with more severe SARS-CoV-2 infection. The presence of echocardiographic findings such as interventricular septum protrusion

towards the left ventricle, right ventricular systolic and/or diastolic dysfunction, changes in pulmonary artery flow, and acute tricuspid valve regurgitation indicate the presence of pulmonary hypertension and right ventricular dysfunction in patients with COVID-19.[46] The association between pneumonia caused by COVID-19 and pulmonary embolism is a challenge for frontline intensive care physicians since the symptoms overlap. Bedside echocardiography may be a useful tool to early detect PTE.[47]

In a study evaluating 120 patients with COVID-19, right ventricular global longitudinal strain (RVGLS) was shown to be a significant predictor of mortality in these patients. Lower RVGLS values were associated with higher serum levels of D-dimer and C-reactive protein, in addition to a higher incidence of ARDS and greater need for mechanical ventilation.[48] It is worth noting that the severe forms of COVID-19 associated with cytokine storm result in systemic inflammation and hypercoagulability. Thus, acute right ventricular dysfunction in patients with COVID-19 may be secondary to an abrupt right ventricular pressure overload caused by increased pulmonary vascular resistance in PTE and/or pulmonary artery vasospasm resulting from severe hypercapnia and/or hypoxemia in patients with severe respiratory failure.[46] Clinically, a suddenly increased dyspnea associated with pleuritic chest pain requires PTE investigation in patients with COVID-19.[46,48]

It is noteworthy that coronary computed tomography angiography and cardiac magnetic resonance imaging (CMR) may be useful to clarify the diagnosis. Regarding magnetic resonance imaging, the presence of interstitial myocardial edema without anatomical correlation, early myocardial gadolinium enhancement (EGE), and multifocal late myocardial enhancement with subepicardial or mesocardial distribution suggest myocarditis. On the other hand, myocardial ischemia presents a subendocardial or transmural distribution, respecting the anatomical topography of the obstructed coronary artery.[49] Furthermore, coronary computed tomography angiography can assess the presence or absence of coronary obstruction in a non-invasive manner, having, however, limitations due to the need for heart rate control and coronary vasodilation during the exam. Thus, since neither CMR nor coronary computed tomography angiography is not very feasible due to the high transmission rate of COVID-19, increased risk of health-care personnel contamination during patient transportation, and prolonged-time of these exams, these tests should be considered in stable patients, as additional diagnostic methods when the diagnosis cannot be established by echocardiography.[37]

Transthoracic echocardiography should ideally be performed in an emergency setting, by point-of-care or dynamic method, as an early assessment method of patients with COVID-19. The method provides hemodynamic evidence to guide clinical management. In critically ill patients, it is recommended a daily echocardiographic evaluation for a strict assessment of the ventricular function and hemodynamic parameters, and guidance of treatment with inotropic and/or circulatory support.[28]

Clinical Approach

During the current pandemic, patients presenting to the emergency department with chest pain, dyspnea, and hyperdynamic state, are highly suspected cases of COVID-19. However, due to its high prevalence, acute coronary syndrome must also be considered as a differential diagnosis.[50] Moreover, in the most severe forms of COVID-19, there are cardiovascular complications such as myocarditis, acute myocardial infarction, and right ventricular overload due to severe pulmonary involvement.[33,41,51]

Thus, clinical reasoning is based on clinical assessment, appropriate propaedeutic, risk stratification, and complementary diagnostic exams (ECG, cardiac enzymes, and bedside echocardiography) (Figure 1), taking into consideration that a diagnostic error in this context has a strong iatrogenic effect regarding the patient – due to the risks of an unnecessary procedure – and the healthcare team – due to the exposure to a potential infection without the appropriate protection and caution.[37]

Several scientific societies and institutions have positioned themselves on the relocation of the scarce medical supplies in face of the increased demand for hospital care and adjustments in the management of acute coronary syndrome during the COVID-19 pandemic.[37,52]

An initial guidance – Catheterization Laboratory Considerations During the Coronavirus (COVID-19) Pandemic: From ACC's Interventional Council and SCAI[52] – proposed the first hospital protocols for the management of AMI in the COVID-19 pandemic. The paper suggests a preference for fibrinolysis over primary percutaneous intervention (PCI) aiming to avoid contamination of healthcare professionals. However, this strategy has generated undesirable results.[53]

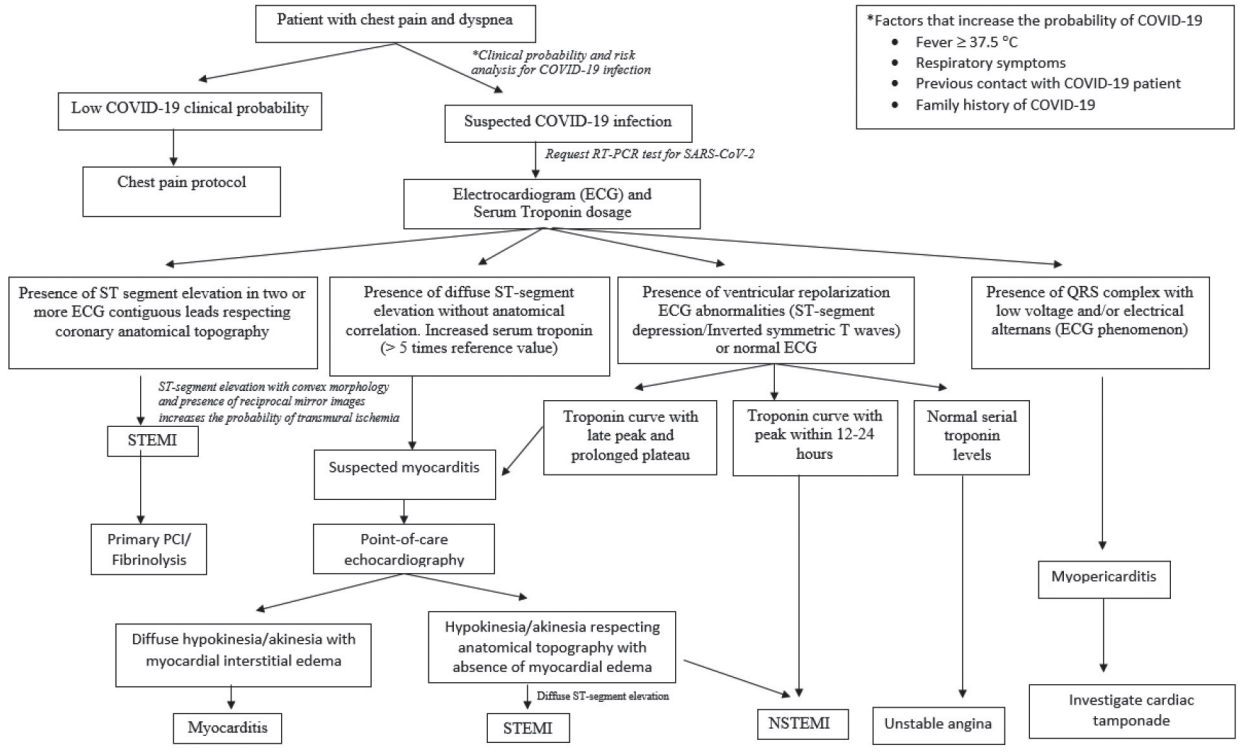

Figure 1 – Flowchart of the clinical approach to patients with chest pain during the coronavirus disease-2019 (COVID-19) pandemic
COVID-19: coronavirus disease-2019; STEMI: acute ST-elevation myocardial infarction; NSTEMI: acute non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention.

A second guidance – Management of Acute Myocardial Infarction During the COVID-19 Pandemic – published by the Society for Cardiovascular Angiography and Interventions (SCAI), American College of Cardiology (ACC), and American College of Emergency Physicians (ACEP) has been used as a foundation for most of the new current protocols. The document proposes that patients should be classified into five distinct groups: definitive diagnosis of acute ST-elevation myocardial infarction (STEMI), possible diagnosis of STEMI, acute non-ST-elevation myocardial infarction (NSTEMI) and unstable angina, patients out of the therapeutic window, and patients in cardiogenic shock/out-of-hospital cardiac arrest.[37] Regardless of the category to which the patient is assigned, a COVID-19 rapid test must be performed if available, to define the patient's infectious state.[37] Furthermore, the adoption of individual protection procedures while providing care to any patient with suggestive symptoms of COVID-19 is imperative, including hemodynamic and other invasive procedures. The guidance on the diagnosis and management of acute coronary syndrome proposed for the COVID-19 pandemic is summarized on Table 1.

It is worth mentioning that this guidance[37] and several other similar institutional protocols,[54] published based on a smaller set of evidence, contrast with those that recommend performing fibrinolysis as a preferable therapeutic strategy to STEMI with primary angioplasty reserved only for patients with contraindications to this pharmacological procedure,[55,56] patients without a confirmed SARS-CoV-2 infection,[57] and AMI patients with hemodynamic and/or electrical instability.[58]

Nevertheless, the request for cardiac catheterization (38% in the United States) during the SARS-CoV-2 pandemic has decreased. This fact may be explained by: 1) reluctance of patients with symptomatic AMI to seek health care due to fear of contracting COVID-19, resulting in a longer therapeutic window; 2) higher frequency of diagnostic errors due to the burden of healthcare logistics; 3) increased use of fibrinolytic therapy as the main therapeutic intervention, due to its presumed safety regarding the risk of SARS-CoV-2 transmission.[59]

Table 1 – Clinical approach to patients with acute coronary syndrome during the coronavirus disease-2019 (COVID-19) pandemic

Category	Diagnosis	Conduct
STEMI	Definitive diagnosis (suggestive ECG + common AMI symptoms)	Primary PCI (if available) or Fibrinolysis and referral to a COVID-19 dedicated cardiac catheterization laboratory Performance of SARS-CoV-2 rapid testing Appropriate individual protection procedures must be rigorously adopted during PCI
STEMI	Possible diagnosis (differential diagnosis: myocarditis)	"Point-of-care" echocardiography If needed: chest X-ray, serial ECG, enzymatic curve, and echocardiography and, in the last instance, coronary computed tomography angiography (inconclusive echocardiography, myocarditis excluded) Confirmed PCI (if available) or Fibrinolysis and referral to a COVID-19 dedicated cardiac catheterization laboratory after a COVID-19 rapid test (absence of a catheterization lab with appropriate door-to-balloon time)
NSTEMI	Differential diagnosis of myocarditis (ECG and enzymes of myocardial necrosis)	GRACE score ≥ 140 or hemodynamic instability: Urgent invasive coronary angiography Confirmed NSTEMI: PCI – percutaneous coronary intervention
UA/ low risk NSTEMI	ECG and enzymes of myocardial necrosis	Clinical management and drug treatment following ACS guidelines. Invasive coronary angiography after controlling the infectious state considering the initial risk stratification
Cardiogenic shock/out-of-hospital CA	a) ECG with ST-elevation + echocardiographic segmental changes	a) Primary PCI
	b) Without ST-elevation + hemodynamic instability	b) Primary PCI
	c) Without ST-elevation in stable patient	c) Supportive treatment: analgesia, oxygen therapy, nitrate, antiplatelet therapy etc.
Out of therapeutic window	ECG changes + markers of myocardial necrosis	Supportive treatment: analgesia, oxygen therapy, nitrate, antiplatelet therapy etc.

STEMI: acute ST-elevation myocardial infarction; NSTEMI: acute non-ST-elevation myocardial infarction; UA: Unstable Angina; AMI: acute myocardial infarction; ECG: electrocardiography; PCI: percutaneous coronary intervention; GRACE (Global Registry of Acute Coronary Events); CA: cardiac arrest

Conclusion

Acute myocardial injury is significantly associated with in-hospital mortality, and a marker of worse prognosis in patients infected with SARS-CoV-2. Risk stratification and assessment of the pre-test probability are essential to improve the diagnostic accuracy of cardiovascular complications of COVID-19, with as accurate as possible differentiation of myocarditis from acute coronary syndrome, careful indication of invasive diagnostic tests, and consequent implementation of appropriate therapies.

Potential Conflict of Interest

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VIEWPOINT

Health Promotion to Reduce Hypertension Patients' Vulnerability to Coronavirus Disease-19 (COVID-19)

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Abstract

Hypertension remains a prominent risk factor for cardiovascular diseases. It is not a coincidence that 23% to 30% of coronavirus disease-19 (COVID-19) confirmed cases are hypertensive patients, and the case-fatality rate of adult COVID-19 cases with hypertension was estimated at 6%. It is important that hypertensive patients be aware of their vulnerability to COVID-19, which may be achieved by a health promotion program in addition to preventive measures.

Introduction

Hypertension is a serious disease that affects more older than younger individuals. The current clinical practice guideline of the American Academy of Pediatrics reports an increasing prevalence of hypertension between the age range of 14 to 19 years, in addition to a high prevalence among adults according to current blood pressure thresholds.[1,2] Parallel in Clinical Practice Guideline.

The young population is also susceptible to coronavirus disease 2019 (COVID-19), an ongoing pandemic. In early July 2020, the death toll from COVID-19 had already hit 517,877, in addition to about 10,710,005 confirmed cases globally. The Americas accounted for half of these numbers, followed by Europe.[3] However, the elderly population is more likely to be affected and become critically ill, with high case-fatality rates.[4] Furthermore, the prevalence of hypertension is alarmingly high worldwide - 31.1%, occurring predominantly among vulnerable individuals.[2] These individuals would be benefited tremendously from adequate protection and individualized health promotion. Although old age cannot be regarded as an independent risk factor of hypertension, it is a congruence of multiple vulnerabilities and poor prognostic determinants.[5]

Coronavirus belongs to the family of severe acute respiratory syndrome (SARS). The relative genome instability of SARS-CoV-2 was indicated by experts in next-generation sequencing experts. A dynamic mutation of the virus was also pointed out, with a high transmission of the virus even among asymptomatic people.[6] The angiotensin-converting enzyme 2 (ACE2) receptor mediates the entry of SARS-CoV-2 into human cells *in vivo* and *in vitro*.[7] The ACE 2 can be found in different parts of the human body – the tongue, nose and throat, and the lower part of the bowel. A substantial amount can also be found in the kidneys, lungs, vessels, and heart, which may explain the occurrence of multiple organ dysfunction in coronavirus patients.[7,8,9]

Hypertensive patients, who additionally use antihypertensive drugs such as angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) may suffer a significant expression of ACE2, due to their opposing effects on the renin-angiotensin system. Hence, these antihypertensive agents seem to play a double edge effect on COVID-19 susceptibility and lung epithelial cells protection. The intense expression of ACE2 was equally noted with other drugs like thiazolidinedione and ibuprofen.[9]

The spike glycoprotein of SARS-CoV-2 binds to ACE2 to enter and infect the cells, multiply its genetic material, and proliferate in a wide range of cells. By using more

Keywords

COVID-19; Betacoronavirus; Hypertension/complications; Antihypertensive Agents; Health Promotion.

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than 80% of angiotensin receptor 2 (AT2) found in 64% of ACE2 in the epithelial cells to colonize the lungs. Coronavirus damages several alveolar epithelial cells, which is aggravated by a poor immune system, which, in turn, also destroys almost the affected cells. This complex mechanism causes the extensive loss of gaseous exchange and shortness of breath. [8, 10]

Although hypertension is growing in low- and middle-income countries, the east and southeast Asia, Europe and North America have a large number of elderly people, and likely high prevalence of hypertension and other comorbidities. [11] In China, studies showed that hypertension was highly prevalent among patients with comorbidities associated with coronavirus disease. Hypertension was present in 17% (17 ± 7, 95% CI 14-22%) of COVID-19 confirmed cases, as reported in an investigation of 46,248 coronavirus patients. Another meticulous research which involved 1,099 of confirmed participants, showed that 23.7% were hypertensive. Clinical data revealed that hypertension was present in 30% of confirmed cases and 48% of patients who died from COVID-19. [12] Due to the fact that hypertension is one of the main comorbidities among elderly patients, and due to the seriousness of coronavirus in about 20% of critical patients, we believe that health promotion programs for hypertensive patients are a reasonable and cheap approach to improve their prognosis.[2,13-15]

The use of ACEI/ARBs for Hypertensive Patients During Coronavirus Outbreak

Current studies show that hypertensive patients are more vulnerable to COVID-19 than any other population. This may be due to the advanced age of most of the hypertensive patients, presence of other comorbidities and deficient immune system. Although antihypertensive drugs such as ACEI and ARBs have been prescribed due to their cardiovascular protection and stroke prevention effect, these drugs appear to exert a twofold effect in the context of COVID-19. The first effect is to raise the susceptibility to SARS-CoV-2 infection by increasing the expression of ACE 2; SARS-CoV-2 has a high affinity and better recognize human ACE2 than SARS-CoV, resulting in increased ability to spread from person to person. [7] The second effect is to protect epithelial cells of the lungs from injury during the severe acute respiratory syndrome (SARS-CoV). Based on these, there is an urgent need to prevent the outbreak propagation by reducing the susceptibility to SARS-CoV-2 infection. Also, there is evidence supporting the administration of recombinant human angiotensin-converting enzyme 2 (rhACE 2) in SARS-CoV-2 infected patients to protect the lungs and heart. [15, 16]

A recent study showed that influenza A (H7N9, H1N1, and H5N1) share with the SARS-CoV-2 the same mechanism of using the ACE2 receptor, and that the use of ACE inhibitors and ARBs was associated with either no effect on the incidence of influenza or a lower incidence, depending on the duration of use. [17]

Although some clinical studies have not recommend discontinuing the use of ARBs and ACEI by hypertensive patients, these medications seem to provide no significant beneficial in critically ill patients with spontaneous breathing activity during acute respiratory distress syndrome. [18]

COVID-19: Health Promotion and Mortality Reduction

Currently, almost the entire global population is in social distancing due to the COVID-19 pandemic. The most vulnerable people must be aware of their susceptibility to the disease, and account for 20% of all coronavirus patients who are at higher risk for severe illness and death. [12] Lockdown was applied as a traditional health promotion strategy to block the outbreak of SARS-CoV-2 and aggressively reduce mortality. However, the lockdown measure has presented lots of negative psychosocial and economic impact on global community. In this context, a health promotion program is a key, cheap, simple strategy to ease these lockdown effects. Health promotion is also the impetus to reduce the morbidity and mortality of hypertensive patients during coronavirus epidemic. Its application during and after lockdown is possible through the workplace, social media, and electronic channels (TV, radio, WhatsApp, YouTube, etc.) and other technological tools (drone-based healthcare delivery). The health promotion strategy for hypertensive patients during pandemic may be conceptualized as a six-stage program and presented as a funnel plot (Figure 1):

(1) Screening for hypertensive patients and identification of anti-hypertensive drugs in use;

(2) Age stratification of hypertensive COVID-19 patients; according to Fei et al., while 23% of patients aged 45-58 years survived, 48% of hypertensive patients aged 63-76 years succumbed;

(3) Evaluation and monitoring of other comorbidities that may affect the immunity of

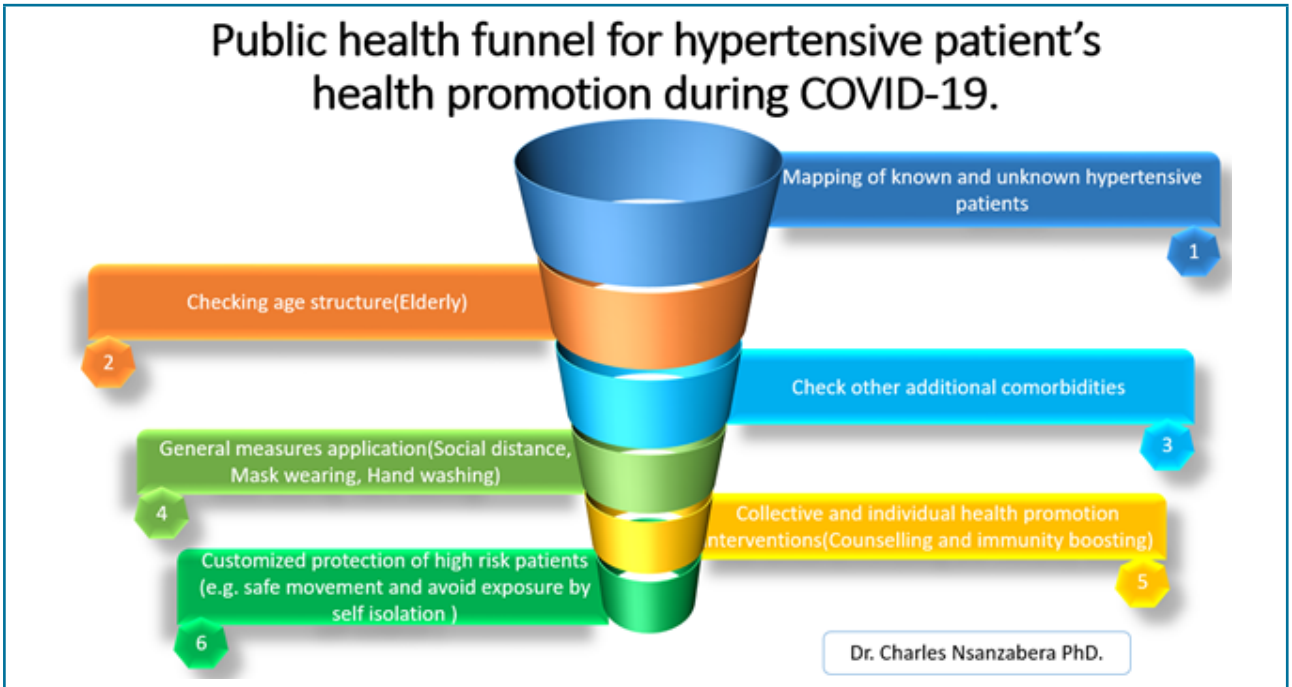

Figure 1 – Public health funnel for hypertensive patient's health promotion during COVID-19.

hypertensive patients like diabetes and other cardiovascular diseases;

(4) Application of general measures in hypertensive groups (local community and workplace) like social distancing, mask-wearing, hand washing and compliance of personal protective equipment for health professionals;

(5) Collective and individual health promotion interventions (awareness, education, counseling, and immunity-boosting mechanism);

(6) Personalized protection of high-risk patients with regards to health status, socioeconomic status and profession; and coronavirus propagation level in the region where the patients are living to ensure safe movement and avoid exposure by quarantine, self-isolation, orientation, and guidance.

Conclusion

Health promotion would primarily support hypertensive patients to understand their vulnerability to COVID-19 and adopt preventive behaviors and guidance obtained via all communication and delivery channels.

We suggest that this health promotion strategy targeting these vulnerable patients with hypertension be adopted by different government and healthcare levels in the countries. We also encourage vulnerable people to safeguard their health and follow protection measures. This could prevent the overcrowding in intensive care units, deaths and other negative impacts of COVID-19, in addition to inform current guidelines on hypertension.

Potential Conflict of Interest

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

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Author Contributions

Conception and design of the research: Nsanzabera C. Acquisition of data: Nsanzabera C. Analysis and interpretation of the data: Nsanzabera C. Writing of the manuscript: Nsanzabera C. Critical revision of the manuscript for intellectual content: Nsanzabera C.

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CASE REPORT

Mitral Valve Replacement with Regent Aortic Valve in Severe Mitral Stenosis

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Introduction

Mitral valve replacement (MVR) in the context of calcification of the mitral valve annulus (<25 millimeters diameter) is challenging, with an increased risk of postoperative complications.[1] Mitral annular calcification is more common in elderly patients due to secondary aging and tissue degeneration. It can also be found in younger patients with connective tissue disorders and inflammatory conditions including the Marfan's syndrome, rheumatoid arthritis, and rheumatic fever.[2] Calcification of the mitral annulus has been associated with arrhythmias, heart block, stenosis, valve insufficiency, bacterial endocarditis, and arterial embolization. Although the condition is not common, calcified mitral annulus may been found in patients requiring surgery for mitral valve dysfunction. However, replacement of a calcified valve is challenging especially because of the difficulty in placing the sutures through the calcified annulus, increasing the risk of leakage, poor positioning and dehiscence.[3,4] For this reason, some studies have suggested the implantation of an aortic mechanical valve (St. Jude Medical prosthesis) in mitral position due to its smaller surface area.[5] Advantages of the St. Jude Medical valve prosthesis over other mechanical prostheses include a reduced sewing cuff size and a reduced frame diameter to allow a greater orifice area for a given annular size. There is limited number of studies on this kind of replacement surgeries, and here we report a case of successful placement of a St. Jude Medical aortic valve prosthesis in a calcified mitral annulus without postoperative complication.

Keywords

Rheumatic Heart Diseases/complications; Hypertrophy, Left Ventricular; Mitral Valve/surgery; Stenosil mitral valve/surgery; Calcinosis/complications; Heart Valve Prosthesis.

Case

A 49-year-old patient with a history of rheumatic heart disease, diabetes mellitus and dyslipidemia presented with chest pain and exertional dyspnea (New York Heart Association functional class II. The body mass index (BMI) was 30 kg/m^2. A transthoracic echocardiography showed an ejection fraction (EF) of 60% with severe mitral stenosis (mitral valve area 0.5 cm^2, mean gradient 16 mmHg) (Figure 1). There was mild mitral regurgitation, mild valvular aortic stenosis, mild aortic regurgitation, mild concentric left ventricular hypertrophy with arterial hypertension (sPAP=88 mmHg). Moreover, pre-operative coronary angiography showed stenosis of 70-90% of the distal left circumflex artery and first obtuse marginal artery (OM1). Combined MVR and CABG was planned. The patient underwent a MVR with placement of the mechanical St. Jude Medical Regent bileaflet prosthetic valve. After cardiac arrest, CABG was performed on the OM1. The patient had severe calcified and fibrotic mitral valve, not suitable for replacement with a regular mitral mechanical valve. With excision of the diseased valve, the mitral annulus was found to be too small for a 25-mm mechanical prosthesis, and thus, a 19-mm St. Jude Medical Regent prosthesis was chosen. Supra-annular pledgeted sutures were placed circumferentially and the Regent aortic valve was then implanted in the mitral position. After a four-month follow-up, the patient was free of symptoms and the echocardiography showed an EF of 55%, good leaflet motion with acceptable gradient of 4 mmHg, no paravalvular leakage, and sPAP of 55 mmHg (Figure 2). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the ethics committee of the Tehran Heart Center.

Discussion

The number of patients presenting with severely stenotic valve is limited and so are the techniques for

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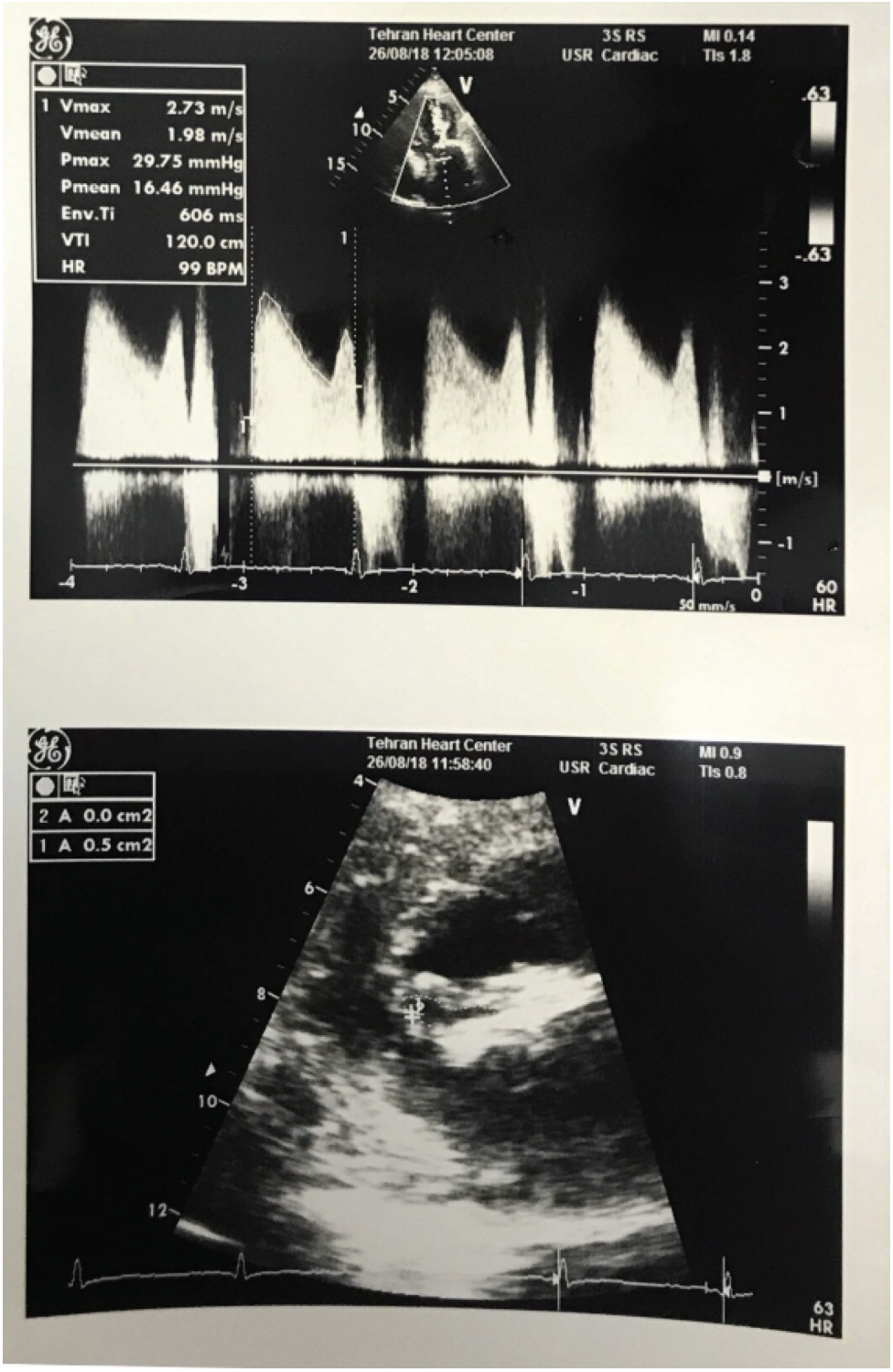

Figure 1 – Upper figure: Echocardiography before mitral valve replacement. Ejection fraction of 60% with severe mitral stenosis (mitral valve area 0.5 cm², mean gradient 16 mmHg). Lower figure: Two-dimensional echocardiography showing mitral valve replacement with a St. Jude Medical Regent aortic prosthesis. Cross-section at the mitral valve, showing a calcified valve with a 0.5 cm² valve area by planimetry.

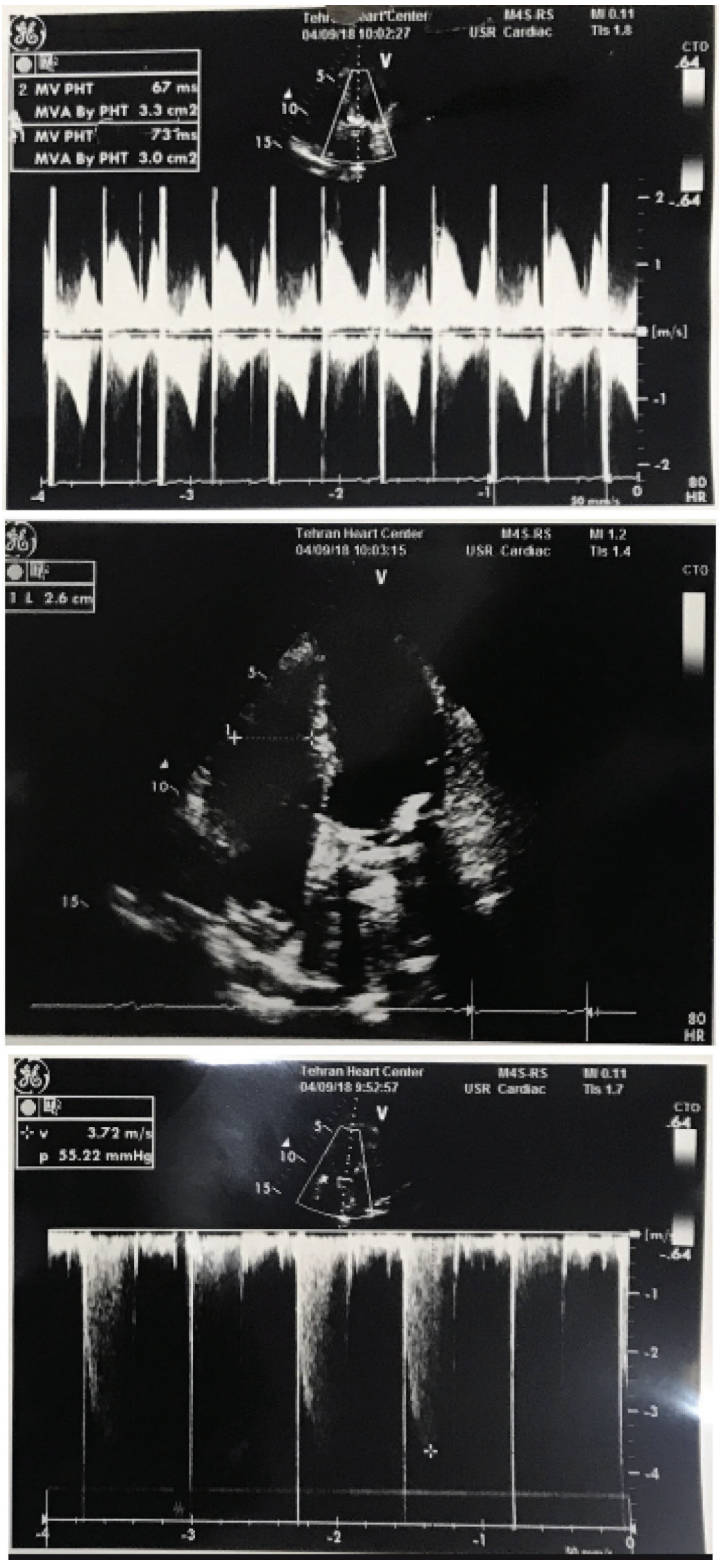

Figure 2 – Echocardiography after mitral valve replacement with a St. Jude Medical Regent aortic prosthesis. Upper figure: mitral flow showing a mitral valve area (PHT) of 3.0 cm², mean gradient of 3.5 mmHg and maximum gradient of 7 mmHg. Middle figure: Two-dimensional echocardiography showing the mechanical prosthesis in the mitral position. Lower figure: tricuspid reflux with a pulmonary artery pressure of 55 mmHg.

repairing this problem including extensive annular debridement and reconstruction. MVR in these patients is technically difficult and is associated with increased risk of mitral annular disruption, ventricular dysfunction, atrioventricular groove rupture, circumflex coronary artery injury, thromboembolic events, left ventricular outflow obstruction and perivalvular leakage.[2,3,5] In the present case, due to the small mitral annular size, a St. Jude Medical Regent 19 was used for MVR. Body surface area was 1.76 cm^2/m^2. On the other hand, effective orifice area (EOA) of the prosthesis was 1.7 cm^2/m^2, so the EOA index would be 0.96 cm^2/m^2. Although a minimum EOA index of 1.2 cm^2/m^2 is recommended to prevent patient prosthetic mismatch,[6] the patient showed a well-seated and normally function valve without mismatch in the follow-up. Barac et al.,[5] reported that, even though the Regent aortic valve is approved by the Food and Drug Administration (FDA) to be placed in the aortic position only, it can also be used in severe stenosis of the mitral valve. In this case, one might expect a low risk of late valve dysfunction, new paravalvular leak or pannus ingrowth. Our results, consistent with the one published by Barac et al.,[5] suggest that this technique can be used as a safe option in small mitral annulus.

Conclusion

Implanting a Regent aortic valve in a small fibrotic or calcified mitral valve annulus is feasible with a minimum risk of technical complications . Certainly, more cases and long-term follow-ups are required to ensure the safety of this procedure.

Author contributions

Conception and design of the research: Tafti SHA, Shirzad M. Acquisition of data: Tafti SHA, Shirzad M. Analysis and interpretation of the data: Yavari N, Landy MG. Writing of the manuscript: Yavari N, Landy MG, Omidi N. Critical revision of the manuscript for intellectual content: Yavari N, Tafti SHA, Landy MG, Shirzad M, Omidi N.

Potential Conflict of Interest

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Sources of Funding

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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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CASE REPORT

Sgarbossa Criteria in Left Bundle Branch Block in a Hypertensive Emergency, a Case Report

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Abstract

Left bundle branch block and hypertensive emergency are very common conditions in clinical cardiovascular and emergency practice. Hypertensive emergency encompasses a spectrum of clinical presentations in which uncontrolled blood pressure leads to progressive end-organ dysfunction. Suspected acute myocardial infarction in the setting of a left bundle branch block presents a unique diagnostic and therapeutic challenge to the clinician. The diagnosis is especially difficult due to electrocardiographic changes caused by altered ventricular depolarization. However, reports on the use of the Sgarbossa's criteria during the management of hypertensive emergency are rare. My current case is a hypertensive emergency patient with acute chest pain and left bundle branch block. Sgarbossa's criteria were initially very weak and, over time, became highly suggestive of acute ST-segment elevation myocardial infarction. Interestingly, chest pain increased as the Sgarbossa's diagnostic criteria were met. Here, we present a case of developing ST-segment elevation myocardial infarction with left bundle branch block that is indicating for thrombolytic therapy. Thrombolytic therapy was strongly indicated because of a higher developing of Sgarbossa criteria scoring. Thus, the higher Sgarbossa criteria scoring in the case was the only indication for thrombolytic. Therefore, how did Sgarbossa criteria developing during the course of the case to indicating the need for thrombolytic therapy?

Keywords

Bundle-Branch Block/complications; Coronary Occlusion/complications; Electrocardiography; Emergency Service Hospital; ST Elevation Myocardial Infarction/complications.

Introduction

Diagnosis of ST-segment elevation myocardial infarction (STEMI) in the setting of a left bundle branch block (LBBB) is difficult.[1] Timely and accurate identification of acute coronary occlusion in the presence of ischemic symptoms is critical for urgent angiography and appropriate reperfusion therapy.[1] Although ST elevation on the ECG is the primary indication for emergency reperfusion therapy,[1] identification of STEMI in the setting of left bundle branch block remains challenging.[1] LBBB is a major confounder for STEMI diagnosis using ECG.[2] Sgarbossa et al.,[2] introduced ECG criteria for detecting STEMI in the presence of LBBB. The criteria are based on concordant ST-segment elevation, discordant ST elevation and anterior ST depression in leads V1-V3, with points assigned for each criterion.[2] In terms of the specificity of the criteria, discordant ST-elevation criterion has been shown to be less useful than the other two criteria.[2] A Sgarbossa score ≥ 3 has been the most commonly used by researchers.[2] Sgarbossa et al. proposed a score of > 3 points in the following criteria for the diagnosis of acute myocardial infarction in the presence of LBBB: (1) concordant ST-segment elevation of 1 mm (0.1 mV) in at least 1 lead (5 points), (2) concordant ST-segment depression of at least 1 mm in leads V1 to V3 (3 points), or (3) excessively discordant ST-segment elevation, defined as greater than or equal to 5 mm of ST-segment elevation when the QRS result is negative (2 points)[3] (Table 1).

A modified Sgarbossa rule[4] has been suggested for the diagnosis of acute myocardial infarction in the presence of LBBB. In this rule, the replacement of the third Sgarbossa

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component (excessively discordant ST-segment elevation as defined by 5 mm of ST-segment elevation in the setting of a negative QRS) with one defined proportionally by ST-segment elevation to S-wave depth (ST/S ratio) was proposed to have better diagnostic utility for STEMI equivalent[1] (Table 1).

Hypertension is an extremely common problem, that affects one billion individuals worldwide,[5] and is responsible for an average 7.1 million deaths annually.[6] Arterial hypertension is the main independent risk factor for the development of cardiovascular disease and cardiovascular mortality in developed and developing countries.[6] Approximately 1% of these patients will develop acute elevations in blood pressure (BP) at some point in their lifetime.[5] Zampaglione et al.,[7] assessed the prevalence of hypertensive crises in an ED for 12 months in Turin, Italy.

An Italian study performed in 1992 showed that hypertensive crises (76% urgencies and 24% emergencies) represented 3% of all the patient visits, but 27% of all medical emergencies.[8] Hypertensive crisis is defined as levels of systolic BP > 180 mmHg and/or levels of diastolic BP > 120 mmHg.[6] Depending on whether there is damage to vital organs or not, we can distinguish between hypertensive emergency and hypertensive urgency.[6] Hypertensive emergencies occur in up to 2% of patients with systemic hypertension.[8] Hypertensive emergencies are life-threatening conditions because their outcome is complicated by acute damage to vital organs, and can be presented with neurological, renal, cardiovascular, microangiopathic and obstetric complications.[6] Hypertensive emergencies include hypertensive encephalopathy, left ventricular relaxation associated with acute myocardial infarction or unstable angina, aortic dissection, subarachnoid hemorrhage, ischemic stroke, and severe pre-eclampsia or eclampsia.[6] Hypertensive urgency is a situation with a severe increase in BP without progressive dysfunction of vital organs. The most common symptoms are headache, dyspnea, nausea, vomiting, epistaxis, and pronounced anxiety.[6]

As therapeutic approach, an immediate BP reduction is required only in patients with acute end-organ damage.[5] Nitroglycerin as a potent venodilator that reduces BP by decreasing preload and cardiac output, and therefore is not acceptable as the first choice for hypertensive emergencies except in patients with acute coronary ischemia.[9]

Case Report

A 53-year-old married heavy-smoker Egyptian male worker presented to the emergency department with acute chest pain, palpitations, rapid breathing, and dizziness. The patient had a recent history of psycho-familial problems. Chest pain had anginal characteristics. The patient used furosemide (40 mg once daily) and captopril (25 mg twice daily) for previous episodes of chest pain and hypertension, respectively. The patient denied any other relevant diseases. Upon examination, the patient appeared irritable, sweaty, anxious, and tachypneic. His vital signs were as follows: BP: 240/140 mmHg, heart rate: 100/minute, body temperature: 36.2°C, respiratory rate: 36/min, initial pulse oximetry: 92%. The patient was admitted to the intensive care unit (ICU) and initially managed with O_2 inhalation using a nasal cannula at a rate of 5 L/min and sublingual isosorbide

Table 1 - The original and the modified Sgarbossa's criteria

Criteria	Description	Score points	Notes
Sgarbossa A	Concordant ST elevation > 1 mm (0.1 mV) in at least 1 lead, in leads with positive QRS	5	
Sgarbossa B	Concordant ST depression ≥ 1mm in V1 - V3	3	
Sgarbossa C	Discordant ST elevation ≥ 5mm , in leads with negative QRS	2	
Modified Sgarbossa C (Smith critreria)	Discordant ST elevation and ST/S ratio ≤ 0.25 [1,3]		Modified Sgarbossa criteria: superior to original Sgarbossa criteria For Dx ACO in LBBB [4]

Dx: diagnosing, ACO: acute coronary occlusion, LBBB: left bundle branch block.

dinitrate tablet (4 mg). The initial emergency ECG tracing showed sinus tachycardia (VR;180 bpm) with LBBB (Figure 1). Of the Sgarbossa criteria, the only ECG finding was discordant ST elevation > 5 mm. Intravenous nitroglycerin (5 μg/min with intermittent titration) and sublingual captopril tablet (25 mg) were given. Serial ECG tracings were taken, with no significant changes within 12 minutes of the first ECG tracing (Figure 2 B). STEMI appeared in high lateral leads (I, aVL) with ST-segment depression in inferior leads (II, III, aVF) (Figure 2 C). Sgarbossa score was 7. Interestingly, chest pain got worse as the other Sgarbossa criteria were met, suggesting the presence of a severe underlying disease. BP was controlled within three hours of admission (140/85 mmHg), after administration of aspirin (four tablets, 75 mg), clopidogrel (four tablets, 75 mg), intravenous streptokinase (1.5 million units over 60 minutes). ECGs were performed within five hours of the first ECG tracing and within two hours of streptokinase infusion. Sgarbossa criteria returned to the initial score (2) (Figure 2 D). Troponin test was positive, and RBS was 223 mg/dl on admission. An echocardiography then revealed anterolateral hypokinesia with ejection fraction of 63%. Unfortunately, coronary angiography report was not available. No other abnormality was found. The patient became free of symptoms after streptokinase infusion and control of BP. The patient continued on captopril tablet (25 mg twice daily), aspirin tablet (75 mg, once daily), clopidogrel tablet (75 mg, once daily), nitroglycerin retard capsule (2.5 mg twice daily), and atorvastatin (40 mg once daily) until discharge on the fifth day.

The main differential diagnoses of the case are non-ST-elevation myocardial infarction and second type myocardial infarction (MI). Type-II MI that is defined as myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply.[10] Presence of a higher Sgarbossa score ruled out this possibility.

Discussion

Highlights:

• The current case was LBBB with subsequently developed acute ST-segment elevation myocardial infarction that was indicating for thrombolytic therapy.

• Both hypertensive emergency and electrocardiographic LBBB pattern were encompassing the serious consequences in the case.

• Serial ECG tracings were showing a graded developing of Sgarbossa criteria of LBBB that is meeting with the diagnosis of acute myocardial infarction. Upgrading of Sgarbossa criteria of LBBB had happened throughout the course of the hypertensive emergency.

• Presence of LBBB, angina, positive troponin, and Sgarbossa score of 7 were indications for the presence of acute ST-segment elevation myocardial infarction.

• The only initial electrocardiographic Sgarbossa criteria were discordant ST elevation > 5mm (score 2). This lonely ECG sign is an insufficient indication for a more serious condition.

• A concordant ST elevation > 1mm in leads (I, aVL) with reciprocal ST depression in inferior leads (II, III, aVF) are specified for a high lateral ST-segment elevation myocardial infarction rather than the extensive anterior infarction.

• Resolving of developed Sgarbossa criteria in LBBB to the initial condition after streptokinase infusion and controlling of blood pressure had occurred.

• The novelty in the case study was the marvelous progression of the LBBB to the acute infarction that is an indication for thrombolytic therapy.

• Unfortunately, there were similar cases for comparison in the past literature.

Conclusion

Resolving of upgrading of Sgarbossa criteria in LBBB to the initial status after streptokinase infusion with controlling of blood pressure will strengthens the role of streptokinase and tight blood pressure control. The current case is considered the first reported case study where up-grading of Sgarbossa criteria for LBBB into acute ST-segment elevation myocardial infarction during the course of hypertensive emergency had happened. Moreover, this case report highlights the importance of adequate and tight controlling for patients of hypertensive emergency with LBBB.

Author contributions

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

Potential Conflict of Interest

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

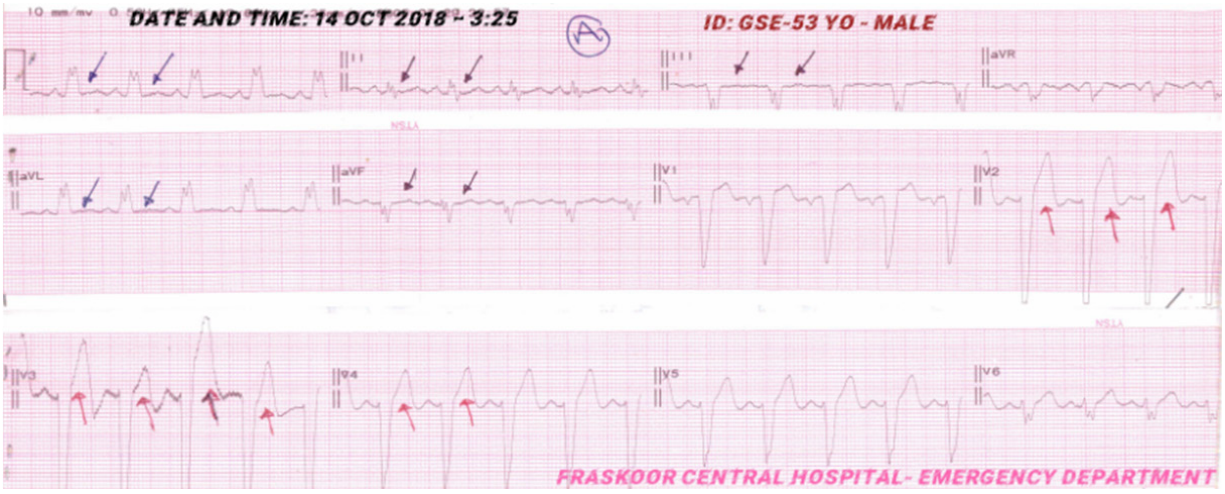

Figure 1A - Electrocardiographic tracing during admission to the emergency room showing sinus tachycardia (VR; 180 bpm) with left bundle branch block. Red arrows indicate discordant ST elevation > 5 mm (V2-4) (one of Sgarbossa criteria), and blue and black arrows indicate no other ST-segment abnormalities.

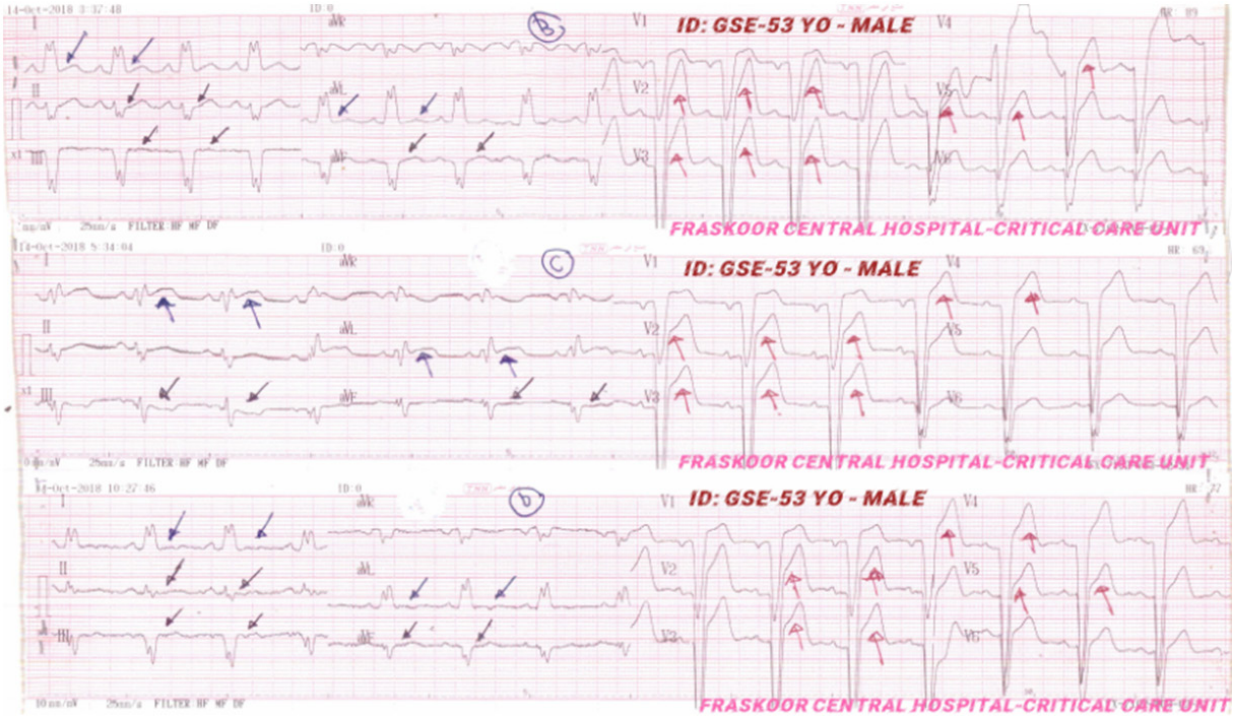

Figure 2 - Initial electrocardiogram (B) performed 12 minutes of admission to the emergency department showing no significant difference compared with A and C; blue arrows indicate concordant ST elevation > 5 mm in high lateral leads (I, aVL), with ST-segment depression in inferior leads (II, III, aVF) (= black arrows). (D) electrocardiogram taken within five hours of the first.

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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 Egyptian Ministry of Health (MOH).

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