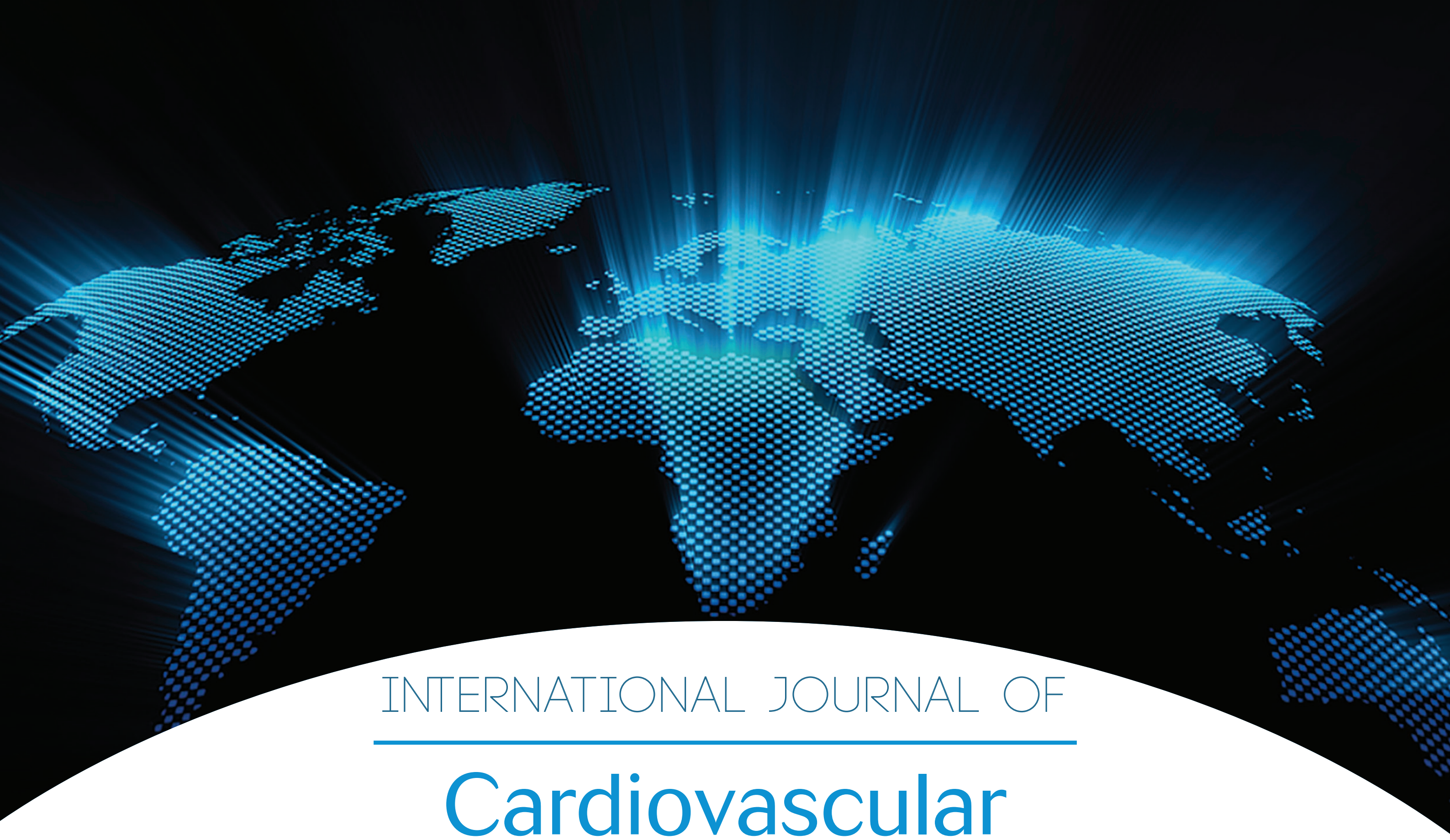

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SPECIAL ISSUE

Guest Editor:
Claudio Gil Soares de Araújo, MD, PhD

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SUMARY

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EDITORIAL

Physical Activity, Exercise and Sport: A Five-Star Path for a Better Cardiovascular Health

Claudio Gil Soares de Araújo[1] and Claudio Tinoco Mesquita[2]

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Exercise is not optional: It is essential.
Herman Pontzer

Why we must exercise? Although this question has many answers, many other questions arise from it. Which are the benefits of exercising? How much exercise is good for health? Is high-intensity exercise better than moderate-intensity exercise? Are there risks in exercising? What to do if someone does not like to exercise? Do cardiologists know the literature on exercise and heart? These are sounding questions that should be covered to understand the real need of exercising.

Why is the International Journal of Cardiovascular Sciences having a special thematic issue on exercise and cardiovascular health? Indeed, searching PubMed for the keywords "heart" and "(exercise OR physical activity OR sport) AND heart", the proportion of papers on exercise and heart were only 1% until mid-60's, with a fast increase to around 7 to 8% in mid-80's and thereafter, although there was a significant increase in the absolute number of publications, close to 5,000 papers/year in 2018 (Figure 1).

The World Health Organization (WHO) recommends that adults aged from 18 to 64 years should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity.[1] According to the WHO, insufficient regular exercise, also called hypokinesia, has been identified as the fourth leading risk factor for global mortality.[2] Indeed, hypokinesia is likely the most prevalent chronic health disorder around the world, affecting a significant amount of individuals of all ages and both sexes. Recent data from the United States suggested that approximately 80% of their population of adolescents and adults are insufficiently active.[3]

A WHO report comparing levels of insufficient activity in 168 countries brought some bad news to our country: 1) 47% of the Brazilian population is sedentary, 2) between 2001, and 2016, the levels of insufficient activity increased more than 15% in Brazil, and 3) women in Brazil and in Latin America have the highest levels of insufficient physical activity in the world.[4] The most recent data from Brazil, reported by Vigitel,[5] a long-term project supported by the Brazilian Ministry of Health, indicated that only 37% of our adults – 43.4% of men and 31.5% of women – living in our capitals met the WHO recommendations of a minimal of 150 minutes of medium-intensity exercise or 75 minutes of high-intensity exercise, in average, per week. In reverse order, these data mean that 63% of Brazilian adults are hypokinetic! However, it is even more alarming considering that only 23.3% of those older than 65 years of age are physically active. In this age group, the incidence of chronic diseases, including those of cardiovascular origin, which

Keywords

Exercise Test, Exercise; Athletes; Cardiac Rehabilitation; Sports, Cardiovascular Diseases.

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are known to be potentially prevented and treated by exercise, exponentially increases. In addition, with the recent proposal of the 2018 US Federal Physical Activity Guidelines[3] suggesting a minimum of 60 minutes of moderate-to-vigorous physical activity daily to children aged between 6 and 17 years old and the increase the minimum dose from 150 minutes to 300 minutes a week of moderate-intensity, or 75 minutes to 150 minutes a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity for adults, it can be expected that the percentage of individuals achieving these new standards will probably decrease.

One of the most relevant health status indicators is the individual's level of physical fitness.[6] Physical fitness includes aerobic and non-aerobic components, and the latter involves muscle strength/power, flexibility, balance and body composition. There is a strong association between lack of regular exercise and poor levels of physical fitness. Based on solid data from important cohort studies, it is well-established that aerobic fitness is inversely and strongly related, in a dose-dependent manner, with higher rates of cardiovascular, cancer and all-cause mortality.[7,8] More recent observational data have also indicated that low levels of non-aerobic or musculoskeletal fitness are also strongly associated with poor survival in the following six years.[9]

This outstanding thematic issue of the International Journal of Cardiovascular Sciences, fully dedicated to exercise/sport and cardiovascular health, brings together 16 other contributions including original articles, review articles, viewpoints, one case report and one special communication, written by a highly qualified team of 78 authors (16 foreigners) from seven different countries.

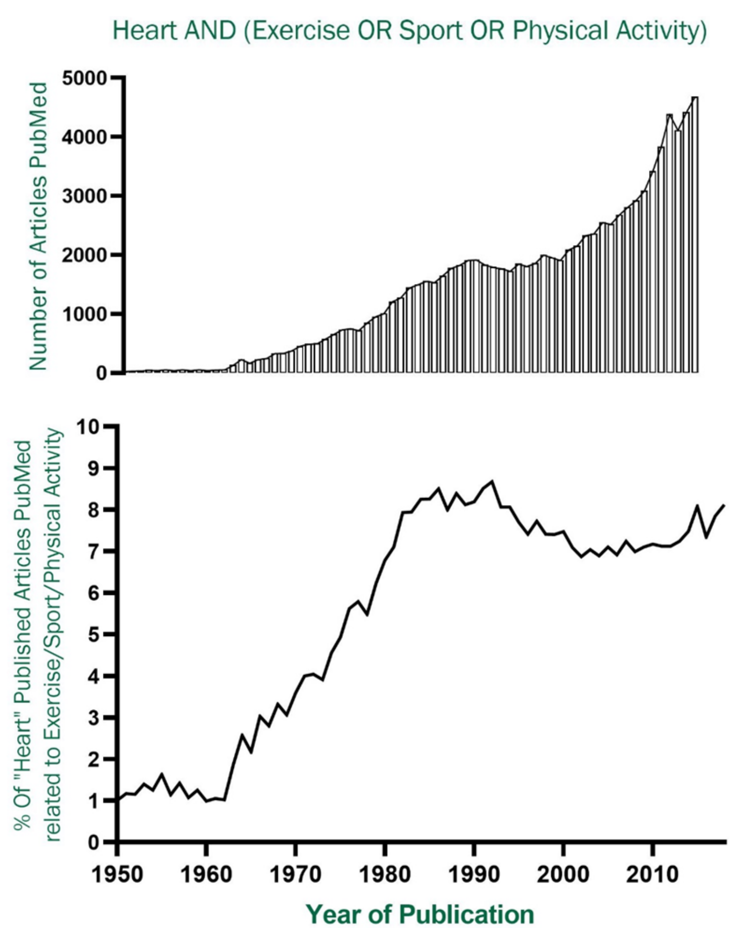

Figure 1 - Number of articles (upper panel) and percentage of them as related to the term "heart" (lower panel) that were indexed by PubMed per year using the combining terms "heart (data extracted from PubMed).

The thematic issue opens with a special communication written by Dr. Ricardo Stein to honor a true icon of Exercise Physiology and Cardiology, Prof. Jorge Pinto Ribeiro, a brilliant cardiologist and sport/exercise physician who passed away some years ago. Then, two viewpoints, the first[10] presenting an innovative format of questions (posed by the leading author) & answers, with participation of distinguished experts in the field from Austria, Brazil, Canada, Finland, Germany and United States, and the second with Dr. Aaron Baggish, from the Massachusetts General Hospital, as the leading author.[11] This very intriguing paper[11] describes a clinical case of a master athlete with coronary artery disease that suffered a cardiac event during a marathon and brings to the discussion some issues about eligibility for sport participation and shared-decision making.

Moving to original papers, there are a total of seven studies that range from relevant aspects of cardiopulmonary exercise testing, an area where Brazilian researchers have made important contributions to the literature, to a timely systematic review and meta-analysis of the effect of regular physical activity on the incidence of atrial fibrillation.[12] The readers will certainly find new and high quality scientific information. Two of these papers make very useful and practical contributions to those working with exercise in their daily practice. In one of these, the authors discuss the proposal and validation of a simple questionnaire for estimating aerobic fitness,[13] and the second one proposes aerobic reference standards derived from a large sample of Brazilian adults.

Then, six review papers are being published in this issue. Authored by Dr. Rachel Lampert from Yale University (United States), the first review study presents the results of the analysis of updated data, derived from an important registry, on sports participation for athletes using implantable cardiac defibrillators, and also discusses the issue of shared-decision making.[14] The second paper presents very practical information for cardiologists who see healthy and unhealthy athletes and practitioners, about the use of wrist monitors and smartphone apps to measure exercise heart rate. Other important topics are covered in three non-systematic reviews and include: sex differences in sudden death during sports and exercise, impact of exercise training on cardiovascular and autonomic responses and the role of exercise training in the management of erectile dysfunction.[15]

Last but not least, the table of contents of this thematic issue ends with a very interesting case report from Portugal, describing a young man who suffered a cardiac arrest during a handball game and relevant aspects of pre-participation assessment and in-field emergency medical services.

Since all the contents of this thematic issue are open access and freely downloadable from the journal's website and from SciELO platform, we believe that many professionals will have the opportunity to acquire or review relevant and practical knowledge and updated concepts about exercise and cardiology. Consequently, not only patients, but the professionals themselves, as well as their families and friends may be benefited from these data, which strongly encourage, based on scientific evidence, the use of physical activity, exercise and sport as a five-star path for a better cardiovascular and general health for the Brazilian population.

Don't wait any longer, it is time to move!

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BRIEF COMMUNICATION

Jorge Pinto Ribeiro: a True Icon of Exercise Physiology and Cardiology

Ricardo Stein
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The initiative to make an edition dedicated to a certain area of knowledge in a scientific journal is always a major challenge full of hard work. Original articles, reviews and / or special cases in the field are expected and the best experts in the subject are those that the editor hopes to be able to count. This edition of the International Journal of Cardiology Science, headed by Dr. Claúdio Gil Soares de Araújo, is focused on physical exercise and its pages contain different articles on the matter. Probably, I was invited to contribute because I work and publish in the sports and exercise cardiology field, besides the fact that I am the Associate-Editor for exercise and rehabilitation of the *Arquivos Brasileiros de Cardiologia*. By the way, when the invitation letter arrived, I immediately accepted it, but wondered what my ideal contribution might be. Thus, over five days I glimpsed different possibilities, until one early morning, while running an insight came: Jorge Pinto Ribeiro!!! Nothing is fairer to remember than a professor and scientist with more than 150 publications, at least half of them in the exercise physiology/cardiology area. So, with the support of the International Journal of Cardiology Science Editors I was able to go through a few lines with a sense of affection and sadness, as long as many years have passed since this cardiology "giant" passed way. It is amazing to mention that, despite the hiatus of more than 6 years since his death, he continues to publish: at least three articles with his name can be found at Pubmed in the year 2018... and two[1,2] in this Edition!!! Well, but who was the Jorge Pinto Ribeiro I met? The differential started with the name. At least for me an affirmative name. A name that always sounded strong, announcing that behind these 17 letters, Jorge Pinto Ribeiro, came a winner. No, actually, he was a champion. A champion at home, at work, at leisure, a blessed champion with unified qualities in a rare individual, a true winner. A man who was always offering the hand to help others on their achievements. Yes, he was the owner of this name, a person who at the height of his 57 years, in the distant year of 2012, left us. Indeed, after a Herculean fight against a rare disease, the flame of his intense and successful life was extinguished. Actually, his early departure left an enormous emptiness and deep longing in relatives, friends, colleagues, students and patients. However, we who know him well always remember his energy, his production, his life as a husband, father, brother, doctor, teacher... as a friend!!! Is evident, he was a man who lived the life. In short, as a brilliant cardiologist and one of the most talented scientists in exercise physiology/cardiology ever, Jorge Pinto Ribeiro certainly is reading the International Journal of Cardiology Science pages delighted and smiling.

Ricardo "Pinto Ribeiro" Stein

Keywords

Exercise/physiology; Sports/trends; Cardiac Rehabilitation/trends; Exercise Therapy.

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VIEWPOINT

Exercise, Sports & Cardiovascular Health: Relevant Questions and Answers

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Introduction

Currently, it is quite common for a clinical cardiologist to be questioned about exercise and sports, topics that are rarely discussed during formal medical education. In this regard, there is a clear need to access high-quality data and evidence-based information to give patients and family members the best advice.

Aiming to present the state-of-the art scientific information on the topic, we have invited several experts from different countries, all of them "knowledge-producers" in exercise and sports cardiology, to contribute with their expertise by answering specific and relevant questions in the matter. The answers were limited to about 250 words and they were asked to preferentially refer to their own publications.

This is an innovative type of scientific paper – questions & answers (Q&A) format -, in which all contributors are listed as coauthors in the paper, but for each one of the answers the responder is clearly identified.

Keywords

Exercise; Sports; Exercise Movement Techniques; Muscle Strenght; Hypertension; Preventive Health Care; Exercise Therapy.

Exercise should be a lifelong habit: from childhood to the elderly individual

Barry A. Franklin

Q: There is a well-established consensus that regular exercise is beneficial for mental and physical health. It is also well-recognized that regularity of exercise is an important issue. Notwithstanding, most of the interventional physical activity studies are short-term, most of them rarely exceeding months or one year and, indeed, we do not know very much about the effects of lifelong exercise habits. In addition, it is already known that aerobic and non-aerobic (i.e., muscle strength, flexibility, balance) fitness tends to decrease with aging. So, in a clinical practice setting and based on the most recent evidence, what advice should the cardiologist give about the amount and the intensity of regular weekly exercise for his (her) aging patients? Should they maintain, reduce or increase the exercise dose over the decades for maximal clinical benefit?

A: Both regular physical activity (PA) and higher levels of cardiorespiratory fitness (CRF) are associated with a reduced risk of developing hypertension, type 2 diabetes mellitus, atrial fibrillation, chronic kidney disease, heart failure, and cardiovascular events.[1] Each 1-MET increase in exercise capacity is associated

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with a ~15% reduction in mortality in patients with and without cardiovascular disease. Indeed, a recent landmark study reported that the most physically active cohorts of men and women demonstrated 7- to 8-year gains in life expectancy.[2] Increased levels of habitual PA prior to hospitalization for acute coronary syndromes are also associated with better short-term cardiovascular outcomes. In contrast, individuals with low CRF have higher annual health care costs, higher rates of surgical complications, and are more likely to die prematurely than their matched counterparts.

Although arterial dysfunction has been widely considered a marker of age-associated cardiovascular disease, regular aerobic exercise inhibits large artery stiffening and preserves endothelial function. Increased CRF in middle-age is also associated with a lower risk of developing heart failure, regardless of the body mass index.[3]

Vigorous PA (≥ 6 METs) appears to be superior to moderate-intensity exercise (3.0 to 5.9 METs) in promoting health benefits. However, patients should be counseled to augment their CRF by starting with level walking at a 2.4 to 4.8 km/h pace and gradually progress to more vigorous exercise, provided they remain asymptomatic. Aerobic exercise should be complemented with flexibility and resistance training. Although some studies suggest that high intensity interval training (HIIT) elicits greater increases in CRF than moderate intensity training, concerns regarding the safety of HIIT in "at risk" patients suggest that it should be cautiously prescribed.[4] Vigorous PA appears to be superior to moderate-intensity exercise in promoting health benefits.

Cardiorespiratory fitness (CRF) as a prognostic marker for sudden cardiac death and all-cause mortality

Jari Laukkanen

Q: It is already known that high levels of CRF are related to longer life expectancy. On the other hand, sudden cardiac death, always a very dramatic event, is a rare event that is often difficult to be prevented. What do you currently know about the possible influence of a high CRF on the incidence of sudden cardiac death and if there is such influence, what are the most probable mechanisms involved?

A: Sudden cardiac death (SCD) is a devastating event which has a profound effect on the families affected, and it is an ongoing challenge for physicians, healthcare providers and global economies. Previous evidence supports the concept that modulation of risk factors would provide pivotal ways of preventing SCD in the general population.[5] However, measurements of functional capacity, such as CRF, are correlated with risk for SCD. CRF has been suggested as a strong predictor of SCD in the population and considered a vital marker in patient risk assessment.[6] Our study group has recently found early evidence on the association between good CRF and lowered risk of serious ventricular arrhythmias.[7] We have also found that a good CRF may attenuate the risk of SCD in overweight/obese men, suggesting that a good CRF may reduce the risk of SCD in high risk subjects.[8] In our prospective population study,[5] VO_{2peak} yielded only a modest improvement in SCD risk prediction, and there was a slight improvement in the level of discrimination on the top of cardiovascular risk factors and other confounders. However, further evidence is needed to know to which extent the incremental prognostic information offered by the assessment of CRF aids in risk stratification and prevention of SCD.

Changing from low to high CRF improves clinical prognosis

Jari Laukkanen

Q: An adult with high levels of cardiorespiratory (aerobic) fitness tends to live longer and better. CRF is known to depend on both genetic traits and regular exercise pattern. Unfortunately, most of subjects in the world are either sedentary or have insufficient exercise to keep or to get high CRF levels. So, from a practical viewpoint, is it always time to try to adopt an exercise plan to improve CRF levels or is there an age limit for this? If a previously sedentary patient gets to improve the CRF with exercise training, will this have a positive effect on his/her long-term clinical outcomes?

A: Almost all previously sedentary patients are able to improve their CRF with exercise training and benefit from it considering long-term outcomes. We just need to find the most suitable exercise therapy mode for specific patient groups.

CRF is related to the ability to transport oxygen from the lung to the mitochondria during exercise, regardless of the individual's age. It is known that CRF depends on a chain of processes in multiple organs, including pulmonary ventilation, vascular function, left and right ventricular function, the ability of the vasculature to transport blood from the heart to meet the oxygen requirements, the ability of muscle cells to use the oxygen and other essential nutrients delivered by the blood. Indeed, the efficiency of this system is only partly related to aging.[6]

When evaluating existing knowledge in exercise medicine, we need to know the difference in findings derived from observational studies as compared with possible effects of exercise interventions on death, myocardial infarction and stroke.[6] An important question is how physicians should deal with individuals who have low CRF level. Should we carry out diagnostic examinations to find out the possibly underlying early disease stages reducing fitness or should we just prescribe exercise training to improve CRF and possibly reduce the risk of death? When comparing the prognosis of physically active versus inactive individuals to prevent serious adverse events, we should understand that many measurable or immeasurable factors are associated with physical activity level even before the intervention or follow-up was started.

CRF is related to reduced health costs

Jonathan Myers

Q: It is widely recognized that a high cardiorespiratory (aerobic) fitness in middle-aged and older men and women is strongly related to many important health outcomes. A substantial amount of years of life and life to years is gained with regular exercise and, as a natural consequence, CRF is improved. Additionally, healthier people tend to use less regular medication and to have lower chances to be hospitalized for chronic diseases. In a time of growing interest in reducing and controlling medical expenses, what is already known about the relationship between CRF and health costs?

A: It is correct that there is a growing body of research on the impact of CRF and health outcomes, and it makes intuitive sense that a fitter individual would have lower healthcare costs. While there has been quite a bit research performed on the impact of physical activity patterns (or more often, corporate wellness programs) on healthcare costs, surprisingly few data are available regarding the association between fitness and healthcare costs. In an era in which there is increasing focus on reducing healthcare costs, it is also surprising that there has been so little attention paid to the potential impact of fitness on costs, given that it so powerfully influences health outcomes.

The effect of fitness on healthcare costs has recently been documented by the Cooper Institute[9] and the Veterans Exercise Testing Study (VETS).[10,11] After controlling for age and the presence of co-morbidities, these studies demonstrate that fitter subjects have markedly lower health care costs compared to those who are less fit. Both groups observed that each 1-MET higher fitness level was associated with approximately 5-7% lower annual costs over lengthy follow-up periods; in the VETS cohort, this represented ≈$1,600 USD lower annual health care costs per higher MET.[11] Much like cardiovascular and all-cause mortality, a small improvement in fitness has a considerable effect on costs. In addition to its effect on health outcomes, improving fitness through regular physical activity should be encouraged for its potential to lower health care costs.

Cardiovascular diseases and indication for exercise training

Claudio Gil Araújo

Q: According to several institutional guidelines, exercise training has been recommended as part of the treatment of patients with coronary artery disease and heart failure. Notwithstanding, it is possible that patients with several other cardiovascular disorders could benefit from exercise training programs. Is it time to extend exercise training prescription as an important therapeutic strategy to cardiovascular disorders other than ischemic heart disease and heart failure?

A: This is 100% true. While there is a large body of evidence showing many relevant benefits of different modalities of exercise training (either alone or in combination with other lifestyle and/or behavioral interventions) for patients with coronary artery disease or heart failure, there are also recent observational studies showing that patients with other cardiovascular diseases – including valve or vascular patients[12] – could also benefit from exercise training. So, for a given patient with a specific cardiovascular disorder, the question would be how to prescribe the most appropriate, individualized exercise program, with a high benefit-risk ratio based on functional assessment results. Competent expertise and knowledge of exercise sciences are basic requirements to prescribe the best, most viable and individually tailored exercise regimen.

Indeed, in the clinical scenario, it is very rare to find a patient to whom all types of exercises would be formally prohibited or contraindicated. Complete avoidance of exercise would always be an exception and it should be restricted to very special cases and often for a very limited period of time.[13]

Non-aerobic fitness as a valuable prognostic marker for all-cause mortality

Claudio Gil Araújo

Q: For several decades, exercise prescription for cardiac patients was primarily based on aerobic exercises, such as slow and brisk walking, running, cycling, swimming and rowing. Other types of exercise were undervalued and hence, poorly quantified. This approach was based on consistent research studies that identified cardiorespiratory (aerobic) fitness as well as regular aerobic exercise as strongly related to favorable healthy outcomes, including better health-related quality of life and all-cause mortality. More recently, several studies have shown that non-aerobic fitness is also very important for health and even possibly associated to survival. Should non-aerobic fitness be regularly assessed during physical examination or clinical evaluation?

A: Recently, the American Heart Association has suggested that the cardiorespiratory (aerobic) fitness, ideally measured by cardiopulmonary exercise testing, should be considered as a clinical vital sign.[1] On the other hand, there are recent data indicating that, especially in older subjects, adequate or above the sex- and age-median values of non-aerobic fitness – muscle strength/power, flexibility, balance and body composition – are strongly associated with all-cause mortality.[14,15]

Some years ago,[15] using the sitting-rising test (SRT) – a simple, reliable and safe assessment tool for simultaneous evaluation of the four non-aerobic components of physical fitness –, we were able to show that low SRT scores (SRT composite scores from 0 to 3) resulted in a five times higher mortality in middle-aged and older subjects in the following six years as compared with good SRT scores (SRT composite scores from 8 to 10). Indeed, among those scoring 10 – able to sit and rise from the floor without showing unsteady performance and without using hand or knee for support –, the all-cause mortality rate was extremely low.[15] More recently, we have presented preliminary results indicating that maximal muscle power relative to body weight, one of the components of both non-aerobic and musculoskeletal fitness, is also strongly related to all-cause mortality.[14]

It is interesting to point out that, when comparing the top and bottom quartiles of data distribution, the relative risks were extremely high (5 to 10 times higher), depending on the variable and sex of the subjects. It is worthwhile to note that these very high relative risks are considerably higher than those usually seen in studies on classical risk factors for coronary disease, such as hypertension, dyslipidemia and family history.

In summary, yes, it is time to incorporate the assessment of non-aerobic fitness as a valuable clinical tool in nearly all populations. Perhaps, the recently published sex- and age- reference values for SRT could be useful in this context.[16]

Isometric handgrip training as an important strategy to treat hypertension

Philip J. Millar

Q: Some decades ago, adult hypertensive patients were advised not to carry weights, including grocery bags or their own children or grandchildren, negatively affecting their quality of life. Exercises with a significant isometric (static) component were particularly forbidden. However, several experimental and epidemiological studies have shown that resistance exercises were not so risky and, indeed, could be beneficial for hypertensive patients. Recently, a special exercise protocol called isometric handgrip training (IHT) has been proposed to reduce systolic and diastolic resting blood pressure. Is there good evidence to recommend IHT to treat hypertensive patients and if so, is there any group of patients that will respond more favorably to IHT?

A: Initial fears over completing isometric exercise were related to the potential for increased blood pressure responses and increased risk for a cardiovascular event.[17] However, short duration isometric contractions at low-to-moderate intensities (e.g. 1-2 minutes at 30-50% of maximal voluntary contraction) produce blood pressure responses in line with those observed during dynamic aerobic exercise.[18] Also, submaximal isometric exercise may be associated with a lower rate-pressure product (less myocardial oxygen demand) and a higher diastolic blood pressure response (greater coronary perfusion pressure), which together, would lower the risk of exercise-induced myocardial ischemia compared with a similar-intensity dynamic exercise.[18]

Over the last 25 years, a number of research groups around the globe have shown that submaximal IHT (or isometric leg exercise) can reduce resting blood pressure in both normotensive and hypertensive populations. A recent meta-analysis of 16 randomized control trials found significant reductions in systolic blood pressure (~5 mmHg) and mean arterial pressure (~3 mmHg) – similar reductions to those reported with aerobic exercise training.[19] Reductions in resting blood pressure with IHT seem to be similar between men and women,[19] but whether certain classes of antihypertensive drugs affect IHT efficacy remains unknown. It is also important to note that while IHT may lower resting blood pressure, it is also unclear whether it can modify additional cardiovascular risk factors (e.g. CRF, insulin sensitivity) known to be benefited from aerobic exercise.[18] As a result, the present data supports IHT as an adjuvant exercise-based intervention for hypertensive patients with indications for a similar-intensity dynamic aerobic exercise program.

Exercise and sports competition in hypertensive patients

Josef Niebauer

Q: Until recently, participation in most competitive sport and/or recreational long-distance events (i.e., marathon, triathlons, etc.) was often prohibited for hypertensive patients, even for well-controlled patients. Regarding this very practical and relevant clinical question, where do we stand in 2019? Is it better for hypertensive patients to avoid sports competition, or is it possible to give these patients evidence-based advice and allow them to participate in competitions in a safe way, in terms of risk for cardiovascular events?

A: Current guidelines of the European Society of Cardiology advocate regular physical activity as a class IA recommendation for the prevention and treatment of cardiovascular disease.[20] Nonetheless, competitive athletes with arterial hypertension may be exposed to an increased risk of cardiovascular events. Therefore, timely identification of hypertensive individuals is paramount in the setting of pre-participation screening, in order to implement a healthier lifestyle, appropriate management and follow-up. Therefore, it is not so much a question of whether or not athletes should train for and participate in long-distance sporting events, it is more about identifying and treating arterial hypertension to target levels. Indeed, it is endurance exercise that has been shown to have the most beneficial effects not only in hypertensive subjects, yet another reason to train for and participate in long-distance races, in those whose blood pressure has reached normal values, with or without medication. If drugs are needed, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are the preferred choice as they do not affect exercise capacity and are not on the doping list. However, they shall not be given to females during reproductive years, because of potential adverse fetal/neonatal effects. While eligibility for competitive sports may have to be restricted if target organ damage is present, an athlete with well-controlled blood pressure, having no additional risk factors or target organ damage, is eligible for competition in all sports. Details can be found in Niebauer et al.,[21] there, a figure can be found on sport disciplines divided according to acute physiologic responses (i.e. heart rate and blood pressure) and long-term impact on cardiac output and remodeling, which is very helpful when recommendations on the type of sports have to be given.

Cardiac function and markers after marathon running: the correct interpretation

Jurgen Scharhag

Q: Popular participation in long-distance mass events, such as half-marathon, marathon, road cycling, open-water swimming, IronMan etc, has exponentially increased the number of participants in the recent years. Even more interesting, a larger participation of women and a widening in the age of participants – including adolescents and very old subjects – has also been noted. On the other hand, there are several studies suggesting that cardiac markers of undue stress – both biochemical and functional – are triggered by prolonged exercise on the heart of these participants. Do these cardiac markers have clinical relevance or, placing the question from a different perspective, should the cardiologist request any laboratory and imaging tests after the patient completed a mass, recreational sports event?

A: During the last two decades, an increasing number of scientific examinations on the effects of endurance exercise on modern cardiac biomarkers have been performed. It has been demonstrated that strenuous endurance exercise usually induces mild increases in the cardiac biomarkers troponin (Tn) I and T and brain natriuretic peptide (BNP) and its N-terminal end (NT-proBNP) in obviously healthy male and female athletes of all ages. The increases seem to depend on age, training status, and exercise time and intensity, with higher increases in older and less trained athletes as well as in more intensive and longer exercise bouts. Nevertheless, increases in cardiac biomarkers in cardiovascular healthy athletes are lower than in patients with acute coronary syndromes and cardiac diseases and normalize within two to three days, and therefore are considered as physiologic, corresponding to a release from the cytosol of the cardiomyocyte.[22-26]

However, so far clear cut-off values for Tn and BNP/NTpro-BNP differentiating between physiological and pathological exercise-induced increases in athletes without and with cardiac diseases are still missing. Therefore, exercise-induced increases in cardiac biomarkers can get clinicians into trouble, and it is of utmost importance to take clinical symptoms into consideration and perform additional non-invasive examinations (e.g. ECG, echocardiography) in unclear cases, for not to treat the blood test only.

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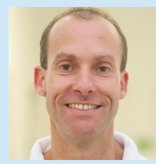

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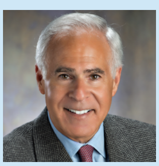

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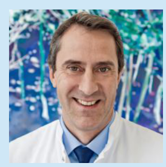

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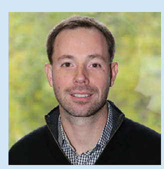

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VIEWPOINT

Invasive Coronary Physiological Assessment in Symptomatic Middle-Aged Endurance Athletes

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Abstract

Despite the health benefits of routine exercise, coronary artery disease (CAD) is common among older competitive athletes and is an important cause of sudden cardiac death. Athletes with suspected or confirmed CAD routinely undergo conventional coronary angiography involving the performance of invasive coronary physiological assessment using the fractional flow reserve (FFR) or the instantaneous-wave free ratio (iFR). Data defining the role of invasive coronary physiological assessment, while robust in general clinical populations, are untested among older competitive athletes with CAD. The paper discusses the challenges and uncertainties surrounding the use of the FFR and iFR in this unique population with an emphasis on the need for future work to better define this approach.

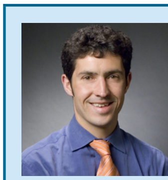
Introduction

Although routine vigorous exercise promotes favorable changes in atherosclerotic vascular risk factors, it cannot provide complete immunity from coronary artery disease (CAD), regardless of its level. CAD is common among older competitive athletes,[1] and is an important cause of sudden cardiac death.[2,3] Effective clinical management of athletes with CAD, much like non-athletic patients, requires a strategy that integrates lifestyle modification, pharmacotherapy, and coronary revascularization. Most athletes with CAD, with diagnosis made by symptoms, abnormal findings during functional testing, or through the increasing use of computed tomography screening will undergo conventional coronary angiography. This method facilitates a definitive determination of coronary anatomy and provides an opportunity for simultaneous percutaneous revascularization.

The decision to perform percutaneous coronary revascularization in competitive athletes depends on medical therapy options and coronary lesion severity. For determination of coronary lesion severity, visual inspection of coronary anatomy has been increasingly associated with invasive coronary physiology analysis, which has emerged as a powerful tool to guide coronary revascularization decisions. Measurement of the fractional flow reserve (FFR), and more recently, the instantaneous-wave free ratio (iFR) to assess the functional significance of angiographically intermediate coronary stenoses have been shown to improve clinical outcomes,[4–7] and has been established as the standard of care for the general population.[8] However, competitive athletes represent a population with unique physiology where these modalities have not been well validated. Thus, application of data derived from non-athletic populations has the potential to lead clinicians astray. This paper examines¬ the use of invasive coronary physiological assessment among athletes with coronary disease, with an emphasis on potential limitations that arise from the absence of physiologic and outcome data derived from this specific population.

Keywords

Athletes; Adult; Circuit Based Exercise/mortality; Physical Fitness; Coronary Artery Disease; Fractional Flow Reserve; Myocardial; Coronary Angiography/methods.



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Clinical case study

A 49-year-old male marathon runner with many years with consistent sub-three hour finish times presents with progressive exertional dyspnea and consequent reductions in his running pace over a 6-month period. He also noted a significant increase in race time in the last marathon three months ago. The atherosclerotic risk factor profile was marked by the presence of dyslipidemia, treated with low-dose statin, and a family history of premature CAD (his father and uncle). He underwent a maximal symptom-limited exercise test with metabolic gas exchange on the treadmill that demonstrated a functional capacity well above the predicted peak value for age/sex (VO_{2peak} = 53.0 ml/kg.min) but experienced the described symptoms. In conjunction with dyspnea, there were 1 to 2-mm horizontal ST-segment depressions across the precordial leads of the exercise ECG, that emerged near peak exercise and resolved completely by 3 minutes of recovery. Transthoracic echocardiography demonstrated mild 4-chamber dilatation, preserved systolic and diastolic left ventricular function, and no significant valvular disease.

He underwent a conventional coronary angiography, which revealed a focal 60-70% stenosis by visual assessment in the proximal left anterior descending artery. The lesion was further characterized by FFR, which yielded a value of 0.82. Based on data from the FAME trials,[4,5] from which an FFR revascularization cut-point of 0.80 was established, intervention was deferred. Despite presenting with angina syndrome and objective evidence of ischemia on functional testing, the patient was advised that his CAD was not "severe enough" to justify an intervention and then clinical treatment with beta-blocker, long-acting nitrate preparation, statin, and aspirin was initiated. As often observed in athletic patients, significant undesirable side effects were caused by the beta-blocker (further reduction in exercise capacity with no improvement of angina), nitrate (post-exertional orthostatic intolerance), and statin (myalgia), leading to treatment noncompliance and discontinuation. He presented again eight months later after being successfully resuscitated from cardiac arrest that occurred 100 meters before the finish line of a large city marathon. Repeat coronary angiography showed no evidence of plaque rupture or new lesions, and stable left anterior descending coronary artery disease both by visual angiography and repeat FFR. After a discussion with the patient about management options, the proximal left anterior descending artery was treated with a drug eluting stent.

Discussion

This case study highlights several areas of clinical uncertainty regarding the use of invasive coronary flow assessment in competitive athletes with atherosclerotic coronary disease. The central uncertainty relates to whether the guideline-supported decision to forgo revascularization based on the FFR data initially obtained from the patient was the appropriate management option. This question cannot be answered by the available clinical trial data and underscores the challenges of applying invasive coronary physiological assessment in patients who were unrepresented in the literature. Clinical cases such as this illustrate the need for future investigations designed to assess the utility of FFR and iFR in athletes.

FFR is a ratio that quantifies the difference between the proximal and distal blood pressure surrounding a focal coronary stenosis during adenosine-induced hyperemia and provides a quantitative assessment of stenosis severity.[9] For example, an FFR of 0.82 obtained across a focal stenosis of the left anterior descending artery indicates an 18 % reduction in blood flow distal to the stenosis under pharmacologically-induced maximal hyperemia. Although the catheter actually measures coronary pressure, the hyperemic conditions are thought to eliminate the effect of the resistance vessels such that the coronary pressure is essentially equivalent to coronary blood flow.[9] The iFR is an increasingly popular alternative as it obviates the need for adenosine-induced hyperemia by assessing the flow gradient during a quiescent period in diastole, when microvasculature resistance is stable, which allows uniform measurements during the resting state.[10] Accordingly, FFR and iFR provide insight into the supply component of the myocardial ischemia supply/demand relationship.

Measurement of FFR or iFR is typically performed when the severity of angiographic lesion cannot be visually determined and the decision to proceed with or to defer revascularization must be made. The use of FFR/iFR in this context relies on clinical cut-points or binary "lines in the sand" which differentiate adequate versus inadequate blood supply. Current recommendations for FFR/iFR cut-points have emerged from careful analysis of clinical trial and registry data,[4–7] with emphasis on hard outcomes including mortality and the need for future revascularization. Specifically, FFR and iFR cut-points have been chosen to represent a lesion severity at which the risk-benefit balance of percutaneous intervention favored intervention rather than conservative management among populations enrolled in these trials. In the case of the pivotal Fractional Flow Reserve Versus Angiography for Multi-Vessel Evaluation (FAME) 1 and FAME 2 trials,[4,5] the study cohorts were predominantly older (median age of about 65 years old) and male and, in the former, all patients had multi-vessel CAD with at least two lesions with > 50% luminal narrowing (Table 1). Both studies demonstrated an improvement in the incidence of major adverse cardiovascular events when using a FFR-guided strategy in stable CAD, FAME 2 being halted prematurely due to the robust early benefit.[4,5] The key iFR studies, the Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization (DEFINE-FLAIR) and Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome (iFR-SWEDEHEART) trials, were comprised of similar population demographics (Table 1). Both studies demonstrated a non-inferiority of iFR compared to the gold standard FFR with respect to major cardiovascular outcomes.[6,7] As is often the case in clinical sports cardiology, it is prudent to consider whether care patterns that have emerged from these clinical trials are universally appropriate for use among competitive athletes.

An important assumption when applying FFR (and iFR) cut-points is that they reflect the ischemic threshold of the population studied, below which coronary supply is insufficient to meet myocardial demands. It is noteworthy that endurance athletes have a unique supply/demand relationship whereby they regularly endure sustained increases in heart rate, blood pressure, and cardiovascular workload during training and competition. In doing so, they far exceed the peak myocardial oxygen demands of the typical study patients that have been enrolled in the FFR/iFR cut-point derivation trials. When considering the high myocardial oxygen consumption and associated neuro-hormonal activation that is present at times of peak performance, it is likely that endurance athletes with focal CAD will experience significant myocardial *demand* ischemia despite FFR (and iFR) values that lie above the traditional cut-points.

Table 1 - A summary of the pivotal trials of invasive hemodynamic assessment

Clinical trial	(n)	Age	% Male	Inclusion / coronary anatomy
FAME 1 (2009)	1005	64.2 +/- 10.2 years (Angiography group) 64.6 +/- 10.3 years (FFR group)	74.0%	Patients with indications for PCI who had stenosis > 50% in at least 2 of 3 major coronary vessels *67.4% had stable angina
FAME 2 (2018)	888	63.5 +/- 9.4 years (PCI group) 63.9 +/- 9.6 years (Medical therapy group)	78.2%	Patients with stable angina in whom PCI was being considered with at least one functionally significant stenosis as determined by FFR ≤ 0.80
DEFINE-FLAIR (2017)	2492	65.5 +/- 10.8 years (iFR group) 65.2 +/- 10.6 years (FFR group)	75.9%	Patients with stable angina or ACS who had an indication for physiologically guided assessment of a coronary lesion (40 to 70% stenosis on visual assessment) *80.2% had stable angina
iFR-SWEDEHEART (2017)	2037	67.6 +/- 9.6 years (iFR group) 67.4 +/- 9.2 years (FFR group)	74.7%	Patients with stable angina or ACS who had an indication for physiologically guided assessment of a coronary lesion (40 to 80% stenosis on visual assessment) *62.1% had stable angina

FFR: fractional flow reserve; iRF: instantaneous-wave free ratio PCI: percutaneous coronary intervention; ACS: acute coronary syndrome.

Demand ischemia during endurance exercise is not trivial and was identified to be the leading cause of cardiac arrest during exercise among aging marathon runners in the Race Associated Cardiac Arrest Registry (RACER).[3] It is also noteworthy that in this study, the highest proportion of these sudden cardiac deaths occurred in the final stretches of the marathon when runners typically engage in a "finish-line surge", suggesting that an intensity-dependent phenomenon may be precipitating malignant ventricular arrhythmia and subsequent cardiac arrest. Overall, these observations suggest that the risk of a "stable CAD" may not be the same in endurance athletes as in their less active counterparts. This may be most pronounced in triathlon participants, described to have a 2-to-3 fold increase in these events.[11] This elevated cardiovascular risk, when coupled with the general unwillingness of these competitors to take anti-ischemic medications, has the potential to alter the risk/benefit balance for intervention over medical therapy (or vice versa) for a given FFR or iFR "cut point."

Thus, with stakes this high and indecision regarding the precise role of invasive coronary physiological assessment in competitive athletes, clinicians should be cautious in their interpretation of borderline values. It is within this "grey zone" that measurement uncertainty increases dramatically,[12] and thus acting hastily on one indeterminate data point may be ill-advised.[12] For this reason, functional data from carefully conducted maximal effort, exercise stress test should be obtained before coronary angiography whenever possible and should be considered during the revascularization decision-making process. Among competitive athletes with documented evidence of ischemia during prior functional testing, revascularization of seemingly indeterminate lesions may be a preferred option over medical therapy as suggested by a recent European consensus statement (Class IIa).[13] At the present time, ACC/AHA task force guidelines do not provide a definitive recommendation regarding revascularization, but endorse restricting athletes with stable CAD and inducible ischemia to sports with low dynamic and low to moderate static demands (Class IIb). Thus, the decision boils down to restriction from all endurance sports or "elective" revascularization with a goal of eliminating demand ischemia.[14] Despite this difference between European and American recommendations, writing committees from both regions identify inducible ischemia as a high-risk feature among competitive endurance athletes.

Ultimately, more scientific investigation is needed to identify accurate FFR and iFR cut-points which reflect the true risk/benefit balance of percutaneous revascularization in competitive athletes with CAD. While we await further data, it is prudent to engage the athletic patient in a shared-decision making discussion about medical therapy versus revascularization prior to catheterization as both strategies have distinct pros and cons. This approach enables sports cardiologists and their patients to enter into a clinical decision-making partnership.[15,16] Such sharing of clinical decision making optimally positions the clinician to make revascularization decisions with the patient-athlete, by integrating clinical history, ancillary testing, and individualized goals of care.

Author contributions

Conception and design of the research: Issa OM, Baggish AL. Acquisition of data: Issa OM, Baggish AL. Writing of the manuscript: Issa OM, Guseh JS, Inglessis I, Baggish AL. Critical revision of the manuscript for intellectual content: Issa OM, Guseh JS, Inglessis I, Baggish AL.

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

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ORIGINAL ARTICLE

CLINIMEX Aerobic Fitness Questionnaire: Proposal and Validation

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Abstract

Background: Cardiorespiratory (aerobic) fitness is strongly and directly related to major health outcomes, including all-cause mortality. Maximum oxygen uptake (VO_2max), directly measured by maximal cardiopulmonary exercise test (CPET), represents the subject's aerobic fitness. However, as CPET is not always available, aerobic fitness estimation tools are necessary.

Objectives: a) to propose the CLINIMEX Aerobic Fitness Questionnaire (C-AFQ); b) to validate C-AFQ against measured VO_2max; and c) to analyze the influence of some potentially relevant variables on the error of estimate.

Methods: We prospectively studied 1,000 healthy and unhealthy subjects (68.6% men) aged from 14 to 96 years that underwent a CPET. The two-step C-AFQ describes physical activities with corresponding values in metabolic equivalents (METs) — ranging from 0.9 to 21 METs.

Results: Application of C-AFQ took less than two minutes. Linear regression analysis indicated a very strong association between estimated (C-AFQ) and measured (CPET) maximal METs - r2 = 0.83 (Sy.x = 1.63; $p < .001$) - with median difference of only 0.2 METs between both values and interquartile range (percentiles 25 and 75) of 2 METs. The difference between estimated and measured METs was not influenced by age, sex, body mass index, clinical condition, ß-blocker use or sitting-rising test scores.

Conclusion: C-AFQ is a simple and valid tool for estimating aerobic fitness when CPET is unavailable and it is also useful in planning individual ramp protocols. However, individual error of estimate is quite high, so C-AFQ should not be considered a perfect substitute for CPET's measured VO_2max. (Int J Cardiovasc Sci. 2019;32(4):331-342)

Keywords: Exercise; Breathing Exercises; Exercise Test; Exercise Therapy; Health Impact; Validation Studies; Surveys and Questionnaires.

Introduction

Several long-term cohort studies have clearly shown a strong and direct association between cardiorespiratory (aerobic) fitness and a better and longer survival in adult men and women from different countries.[1-3] Quantified in mL O_2.kg^{-1}.min^{-1} or simply as metabolic equivalents or METs (1 MET = 3.5 mL O_2.kg^{-1}.min^{-1}), aerobic fitness is also associated with lower chances of developing major clinically relevant diseases, such as coronary artery disease, arterial hypertension and several types of cancer.[4-6] Additionally, functional capacity, which is strongly related to aerobic fitness, has also been recently recognized as a clinical vital sign.[7]

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Perhaps, in a clinical context, there is no other variable that outweighs aerobic fitness in terms of relevance to major adverse outcomes such as cardiovascular, cancer and all-cause mortality,[8] and each 1 MET increase in aerobic fitness is associated with long-term risk reduction of 10 to 15% chance of dying.[9,10] Even more interesting, a recent analysis of important cohorts in United States and Finland has shown that middle-aged or older men that improve their aerobic fitness over time tend to substantially decrease their mortality rate.[11-13]

The gold standard for aerobic fitness determination is the measurement of maximum oxygen uptake (VO_2max) during maximal cardiopulmonary exercise test (CPET),[7,14,15] by progressively increasing exercise intensity in an ergometer, most often a treadmill or a leg cycle ergometer, until volitional exhaustion, while collecting and analyzing expired gases. However, despite the existence of several institutional guidelines,[14,16] for a number of reasons, the use of CPET for quantifying aerobic fitness remains quite limited around the world and in Brazil. In this context, non-exercise alternatives to estimate aerobic fitness could be worth exploring. Moreover, even when CPET is available, estimating aerobic fitness would help to plan a more precise ramp protocol, that is, initial and incremental rate per minute in watts or speed/slope for a maximal CPET that will last around 10 minutes.[17]

In a study with 63 subjects,[18] it was found that using measured VO_2max as the gold standard, well-educated adults were reasonably well capable of classifying themselves as having much lower, lower, similar, higher or much higher aerobic fitness of what should be expected for their sex- and age-matched peers. In a classical study, researchers[19] have proposed the Veterans Specific Activity Questionnaire (VSAQ) to estimate aerobic fitness, obtaining good association - r = 0.79 - between VSAQ and measured VO_2max. The VSAQ has been largely used[20-22] and it has been transculturally adapted to Brazil[23,24] with reasonable results. However, despite several merits, the VSAQ also has some important limitations: 1) it was primarily validated in a sample of middle-aged and old men; 2) the relatively long-time needed for the subject to read all the 21 lines in order to classify him(her)self; 3) the upper limited score - 13 METs - that excludes many healthy exercisers and athletes; and 4) the unique one-MET interval across all scales, potentially losing discrimination for those placed in the lower range of aerobic fitness.

Therefore, it seems an interesting proposal to develop a Brazilian questionnaire for estimating aerobic fitness that would be culturally adjusted to its population and that would circumvent the main limitations of VSAQ. The performance of CPET in a well-controlled setting, in men and women presenting a large age range and extremes of aerobic fitness, offered an outstanding and unique research opportunity to prospectively assess the validity of a new questionnaire, the CLINIMEX Aerobic Fitness Questionnaire (C-AFQ).

The objectives of this study were: a) to propose the C-AFQ; b) to validate C-AFQ against the gold standard measured VO_2max; c) to compare the physician's statistical error of estimating aerobic fitness by C-AFQ; and d) to analyze the influence of age, sex, clinical conditions, regular use of ß-blockers and two non-aerobic fitness test scores on the error of estimate of aerobic fitness by C-AFQ.

Methods

Study sample

Prospective data collection started in January 5th 2016 and was planned to continue until data from a total of 1,000 subjects was obtained. As previously defined in the research design, subjects younger than 14 or athletes[25] or those not completing a true maximal cardiopulmonary exercise test (CPET) were not included in the study.[26,27] In addition, those with any missing or incomplete relevant data were also excluded. The final sample of 1,000 subjects was completed in May 7th 2019. The vast majority of subjects (98%) were white and pertaining to a high socioeconomic class. All subjects voluntarily went to our Clinic for the evaluation protocol. Before the evaluation, all subjects read and signed a specific informed consent form previously approved by the institutional committee on ethics in research.

The final sample included 686 men (68.6%) aged 14 to 96 years (mean ± standard deviation: 55.2 ± 16.4 years). From the total of 1,000 subjects studied, 72.5% were evaluated for the first time in our Clinic, while the remaining 27.5% had been evaluated between two and 20 times. Regarding the subjects' clinical conditions, 22% were considered healthy (no cardiorespiratory or major diseases reported), 23.3% had a diagnosis of coronary artery disease, including 12.2% with previous myocardial infarction, 15.2% that had been submitted to coronary angioplasty and 5.9% to coronary artery bypass grafting. A total of 34.7% were being treated for arterial hypertension, 40.2% were classified as having dyslipidemia, and diabetes mellitus was diagnosed in 13.4% of the subjects studied. Regular use of ß-blockers was reported by 25.6% of the subjects.

Maximal cardiopulmonary exercise test (CPET)

Only four experienced and specialized physicians directly supervised all maximal CPETs performed in a proper temperature-humidity controlled room equipped for providing medical emergency support if needed. Digital electrocardiogram was continuously monitored and recorded before, during and for at least five minutes after the end of the CPET (Micromed Elite ErgoPC, Brazil).[27,28] The ergometer was chosen according to the subject's testing objective, whether for clinical diagnosis, exercise prescription or sport training advice. Maximal CPET was most often performed in leg cycling ergometer (85.2%) (Inbramed CG-04, Brazil) than in treadmill (14.8%) (Inbramed ATL Master, Brazil) using individual ramp protocols. For treadmill tests, a constant 0% slope was set and after one-minute walk at 5.5 km/h, the speed was quickly increased to 8.0 km/h and thereafter progressively increased until volitional exhaustion under strong verbal encouragement. For all CPETs, individualized rates of exercise intensity — speed or watts — increment was used. A combination of several physiological and perceptual criteria was utilized for characterizing CPET as maximal in both ergometers.[27,28] No major relevant clinical abnormalities occurred during all 1,000 CPETs performed.

During the CPET, subjects used a nose clip and breathed through a Prevent mouthpiece in order to collect expired gas. Calculation of air flow and O_2 and CO_2 expired fraction analysis were carried out in a VO2000 metabolic analyzer (Medical Graphics, United States) regularly calibrated using known syringe volumes and two different gas concentrations.

For comparison purposes, VO_2max related to body weight in cycling CPET was predicted according to age and sex by using the following equations proposed by Jones et al.[29]: men = 60 – 0.55 x age (years) and for women = 48–0.37 x age (years). For treadmill CPET, 11% was added to this predicted value. All data related to VO_2max - predicted, measured and estimated by C-AFQ - were reported as METs, where 1 MET = 3.5 mL $O_2.kg^{-1}.min^{-1}$.

CLINIMEX aerobic fitness questionnaire (C-AFQ)

C-AFQ data were obtained during consultation with the supervising physician either by objective questioning or by showing the list of activities and corresponding METs. C-AFQ was applied in a two-step sequence following standard instructions (please see footnote of Table 1 for more details). (see Portuguese C-AFQ version in supplemental materials). Almost all the corresponding MET values for each of the listed activities were obtained from the literature,[30] with few of them estimated from other sources or by the authors' scientific knowledge and clinical experience.

This two-step approach allowed refining the estimate of maximal exercise capacity and, consequently, maximal aerobic power in METs. By applying C-AFQ, it was possible to estimate aerobic fitness in one or two minutes, from < 1 to > 20 METs, with 0.5 intervals from 2 to 5 METs and thereafter, from one in one MET increments up to 20 or more METs.

Other study measurements

Our evaluation protocol was quite comprehensive and involved several other variables tests. In order to identify potential influential variables for this particular study, age, sex, height, weight, waist girth,[31] sitting-rising test[32,33] and maximal muscle power related to body weight in the upper row movement[34] were also tabulated and analyzed.

Statistical analysis

Descriptive statistics for continuous variables were presented as mean and standard deviations or as median and interquartile range, as well as several other potentially useful percentiles for data distribution and frequency distribution for nominal variables. Inferential statistics analyses were carried out by t-tests or ANOVA and Tukey's post-hoc comparisons, depending on the number of groups compared. Pearson product-moment correlation coefficients were calculated for assessing association and best-fit linear regression was used for data modeling. Statistical significance was set at 5% of probability and the Prism version 8.1.1 software package (GraphPad, United States) was used for statistical calculations and preparation of figures.

Results

Sex- and age-predicted VO_2max and measured (CPET) VO_2max were similar, being, respectively,

Table 1 - Application instructions

1	The C-AFQ (CLINIMEX Aerobic Fitness Questionnaire) should be applied in two steps, to make it faster and more efficient.
2	The objective of step 1 is to identify the range to which the individual belongs (0 to 10), by asking: - Do you think you can do this? If the answer is positive, move to the following sentence from the Zone immediately below, until a negative response is obtained. Otherwise, go back to the previous zone.
3	To speed up, the interviewer can already pre-select zones, as suggested below if the individual is less than 40 years old (male) - Zone Line 5 if he is between 51 and 60 years old - Zone Line 4 if he is over 60 - Zone Line 3
4	Once the correct zone is identified, proceed to step 2 In step 2, the various sub-band options are presented and the individuals should identify which of the sentences he/she believes it could do (it can be more than one or just one of the sentences).
5	The estimated aerobic fitness is characterized by the number of METs corresponding to the MET value that contains a sentence with any exercise or physical activity he/she believes that it will be able to perform.

Table 2 - CLINIMEX - Aerobic Fitness Questionnaire

AEROBIC FITNESS QUESTIONNAIRE [step 1]

Instruction to fill:
Identify the number corresponding to the most intense exercise / physical activity you are likely to do with your current aerobic fitness (disregarding recent orthopedic problems or other relevant motion limitations)

ZONE	Exercise or Physical Activity	METs
0	Lying in bed	0.9
1	Sitting: napping, reading, watching television or listening to the radio	1
2	Standing: working, talking, ironing, cooking or attending religious acts/shows/plays	2
3	Walking at least 1 km or 10 minutes (non-stop)	3.5
4	Running, slowly, one block or 100 meters	6
5	Running, slowly, at least 1 km or 10 minutes (no walking or stopping)	9
6	Running continuously, for up to 40 minutes	12
7	Completing a half-marathon in about 2 hours and a marathon in about 4 ½ hours	15
8	Completing a half-marathon in 1h30min–1h40min or a marathon in 3h15min–3h40min	18
9	Completing a half-marathon in 1h20min–1h30min or a marathon in 3h–3h15min	20
10	Running a half-marathon in less than 1h20min or a marathon for less than 3 hours	> 20

8.41 ± 0.08 METs [mean ± standard error of the mean] and 8.56 ± 0.12 METs ($p = 0.07$). However, for a given individual, measured VO_2max could range from 28.8% to 236% of sex- and age-predicted VO_2max, corresponding to differences ranging from -9.6 to 8.3 METs. The correlation coefficient between the sex- and age-predicted VO_2max and measured VO_2max was 0.69 ($p < 0.001$).

The minimum and maximum values obtained from the 1,000 subjects for C-AFQ and measured VO_2max were, respectively, 2 and 21 METs and 1.9 and 20.7 METs, with interquartile ranges [percentile 25–percentile 75] being 6.0–12.0 METs for estimated and 5.6–11.0 METs for measured aerobic fitness. When comparing the mean values, a small but statistically significant difference was found between estimated aerobic fitness - 8.92 ± 0.12

Table 3 - CLINIMEX - Aerobic Fitness Questionnaire

AEROBIC FITNESS QUESTIONNAIRE [step 2]

Instruction to fill:
Check the maximum or most intense exercise/physical activity that best represents what you would be able to perform with your current aerobic fitness (disregarding recent orthopedic problems or other relevant motion limitations)

METs	Exercise or Physical Activity	ZONE	METS
0,9	Lying in bed	0	< 1
1	Sitting: napping, reading, watching television or listening to the radio Meditating	1	1 to 1.9
1,5	Sitting: dressing or typing / playing on the cell phone or computer Sitting: eating or talking or attending Religious Services or watching games or sports competitions on site Sitting: playing cards or chess or bathing yourself		
2	Standing: working, talking, ironing, cooking or religious act/show/play Caring for the elderly / babies or sewing or bathing alone while standing Participate in Pilates, Hatha Yoga or water aerobics classes (very slow pace) Maintaining sexual intercourse (more passive and less intense participation)	2	2 to 3.4
2,5	Walking at a slow pace - 3.6 km/h (60 m/min) Playing musical instruments (sitting) or singing while standing Cleaning the house with non-motorized equipment or devices Driving cars with manual transmission in local transit Attending stretching or bodybuilding classes, alternating the exercises with rest breaks		
3	Walking at a normal pace - 4.8 km/h (80 m/min) Attending Pilates, Hatha Yoga or aqua fitness classes (at a moderate pace) Singing out loud or playing musical instruments while standing Maintaining sexual intercourse (more active and very intense participation)		
3,5	Walking at least 1 km or 10 minutes (non-stop) Car washing or heavy domestic housecleaning Working with equipment or instruments weighing between 1 and 5 kg	3	3.5 to 5.9
4	Brisk walking at 6 km/h (100 m/min) Playing (intense activities) with children or pets Attending Pilates classes, yoga, dance or aqua fitness classes (at a fast pace) Engaging in slow dancing activities		
4,5	Fast walking at a very fast pace at 6.5-7 km/h (108-118 m/min or 1 km in 8 to 9 minutes) Walking on a slope (up to 3%) * Playing ball or racquet sports on courts or on the sand for recreational purposes (low intensity)		
5	Walking on a slope (up to 5%) * Brisk walking at 6 km/h (100 m/min) carrying between 5 and 10 kg (child, shopping, equipment and similar) Engaging in fast dancing activities (ballroom dancing, rock, funk or similar)		
6	Running slowly one block or 100 meters Attending high-intensity workout classes Pedaling recreationally or pedaling to work/school for up to half an hour	4	6 to 8.9
7	Running at a slow pace for 1 to 3 minutes Walking on moderately inclined trails (5 to 10% on average) * Engaging in very fast dancing styles (salsa, samba, merengue, tango and alike)		
8	Running at a slow pace for 4 to 6 minutes Playing recreationally or attending a (single) tennis lesson or ball sports for over an hour Pedaling, outdoors or road, between 16 to 20 km/h or to go to work/school for up to one hour		

Continuation Table 3

9	Running slowly at least 1 km or 10 minutes (no walking or stopping) Attending spinning or step aerobics classes (low or moderate intensity) Engaging in martial arts for at least one hour with short breaks only	5	9 to 11.9
10	Running continuously for 10 to 15 minutes Running for at least one minute at 10 km/h (167 m/min) outdoors or 10.5 km/h on the treadmill Pedaling outdoors or on the road at 20 and 25 km/h for up to half an hour		
11	Running at least one minute at 11 km/h (184 m/min) outdoors or 11.6 km/h on the treadmill Attending fast-pedaling spinning or running classes		
12	Running continuously for up to 40 minutes Running for at least one minute at 12 km/h (200 m/min) outdoors or 12.7 km/h on the treadmill Playing ball sports at very intense pace and for at least 30 minutes without breaks	6	12 to 14.9
13	Running for at least one minute at 13 km/h (200 m/min) outdoors or 13.8 km/h on the treadmill Running 10 km in about 1 hour Pedaling outdoors or on the road at 20 and 25 km/h for more than one hour		
14	Running for at least one minute at 14 km/h (233 m/min) outdoors or 14.9 km/h on the treadmill Running 10 km in 53 to 57 minutes or completing a half-marathon in about 2h15min		
15	Running a half-marathon in about 2 hours or a marathon in about 4 ½ hours Running for at least one minute at 15 km/h (250 m/min) outdoors or 16 km/h on the treadmill	7	15 to 17.9
16	Running for at least one minute at 16 km/h (266 m/min) outdoors or 17.2 km/h on the treadmill Running a half-marathon in about 1h50min to 1h55min or a marathon in 4h to 4h15min		
17	Running for at least one minute at 17 km/h (283 m/min) outdoors or 18.4 km/h on the treadmill Running a half-marathon in about 1h40min or a marathon in 3h40min to 4h		
18	Running a half-marathon in 1h30min to 1h40min or a marathon in 3h15min to 3h40min Running for at least one minute at 18 km/h (300 m/min) outdoors or 19.6 km/h on the treadmill	8	18 to 19.9
20	Running a half-marathon in 1h20min to 1h30min or a marathon in 3h to 3h15min Running for at least one minute at 20 km/h (333 m/min) outdoors or 22 km/h on the treadmill	9	20
> 20	Running a half-marathon in less than 1h20min or a marathon in less than 3 hours	10	> 20

** slope: 1% means climbing 1 meter for every 100 meters walked on flat*

METs - and measured aerobic fitness - 8.56 ± 0.12 METs - ($p < 0.001$), with standard error of the mean differences of only 0.05 METs. The median of the difference between estimated and measured aerobic fitness was only 0.2 METs with interquartile range from -0.7 to 1.3 METs (see violin plot in Figure 1). Table 4 describes separately men and women's data for some of these results.

A very direct and strong association was found between estimated (C-AFQ) and measured (CPET) VO_2max values — $r = 0.91$ ($p < 0.001$). Linear regression analysis found a coefficient of determination or r^2 value of 0.833 ($p < 0.001$) and a standard error of estimate of 1.54 METs. The scatterplot of 1,000 subject's data, identity line and 2-MET individual difference lines are presented in Figure 2.

Considering that four different physicians have applied the C-AFQ for the 1,000 subjects, we analyzed estimated and measured aerobic fitness values and their respective differences for each one of them in order to search for any applicant C-AFQ bias. Median and interquartile measured METs were: physicians 1–8.7 [6.1–11.1], physician 2–6.8 [5.0–9.3], physician 3–7.9 [5.7–11.8] and physician 4–7.7 [4.9–13.7] ($p < 0.001$). Despite these quite distinct levels of aerobic fitness in the subjects evaluated by the four physicians, C-AFQ values were quite similar among them ($p = 0.055$) and multiple comparison analysis identified that the only the physician's pair 1–2 significantly differed (Figures 3 and 4) — exactly the two physicians that were in the extremes of median values for measured aerobic fitness.

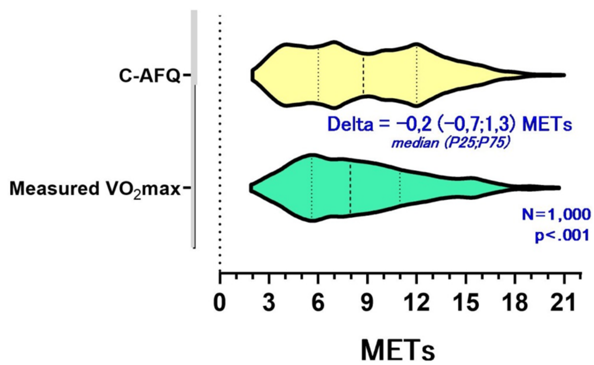

Figure 1 - Comparison of estimated (CLINIMEX-Aerobic Fitness Questionnaire) (METS) and measured (maximal cardiopulmonary exercise test) VO_2max (METS).

Table 4 - Descriptive statistics for men and women for main variables*

	Men	Women
N	687	313
Age (years)	56.2 ± 16.5 [34 - 78]	53.1 ± 16.2 [31 - 75]
Height (cm)	175.1 ± 7.5 [165.1 - 184.5]	161.9 ± 7.1 [153.4 - 171.9]
Weight (kg)	84.5 ± 14.9 [68.8 - 103.4]	67.0 ± 12.7 [52.8 - 84.8]
Body mass index (kg/m²)	27.5 ± 4.2 [23.0 - 32.5]	25.6 ± 4.9 [20.4 - 31.9]
Waist** (cm)	97.5 ± 12.6 [83.0 - 113.7]	85.5 ± 12.9 [70.8 - 103.5]
Measured VO_2 (METs)	9.02 ± 3.85 [4.5 - 14.9]	7.54 ± 3.35 [3.5 - 12.3]
C-AFQ (METs)	9.35 ± 4.02 [4.0 - 15.0]	7.98 ± 3.62 [3.5 - 13.0]
Predicted VO_2 (METs)	8.48 ± 2.77 [4.9 - 12.2]	8.26 ± 1.86 [5.8 - 11.0]

** data expressed as mean ± standard deviation and as [percentile 10 - percentile 90]; ** measured at umbilical level.*

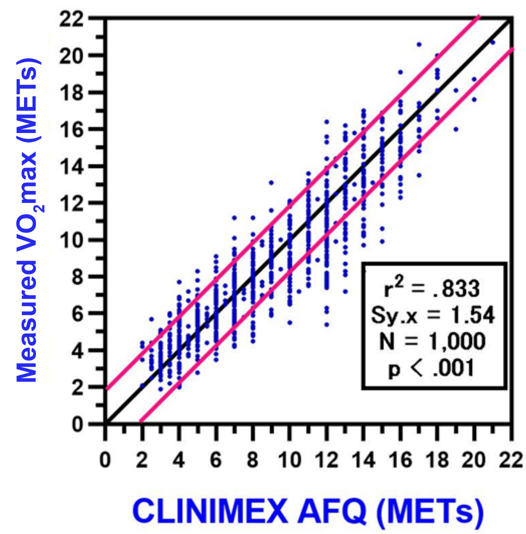

Figure 2 - Linear regression and scatterplot of measured VO_2max (METs) and estimated VO_2max (METS) by CLINIMEX Aerobic Fitness Questionnaire.

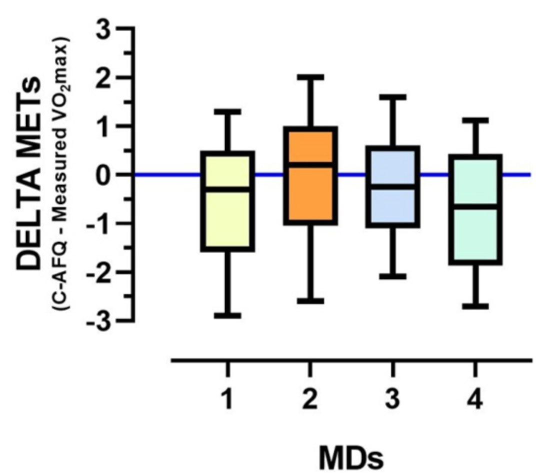

Figure 3 - Separate comparison of measured VO_2max (METs) and estimated VO_2max (METS) by CLINIMEX-Aerobic Fitness Questionnaire among the four physicians.
Footnote: Boxes represent percentiles 25–75 and whiskers limit percentiles 10 and 90; central boxes' line represent median value.

In order to analyze the potential influence of several other variables in the magnitude of the main result, we used two different approaches. First, we compared results for the delta METs, i.e., the difference between estimated (C-AFQ) and measured (CPET) VO_2max, dividing the total sample into two subgroups according to sex (men vs. women), clinical condition (healthy vs. unhealthy), regular use of ß-blockers (yes vs. no)

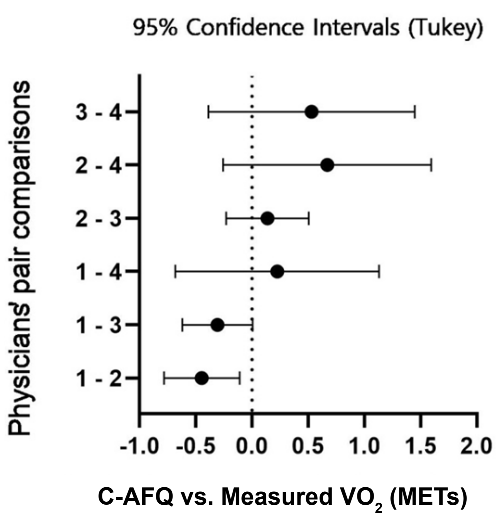

Figure 4 - Multiple comparisons for the delta METs among the four physicians.

and ergometer (treadmill vs. cycling). Unpaired t-tests showed that none of these variables were found to be relevant in influencing the magnitude of delta METs, with p-values of 0.31 for sex, 0.52 for clinical condition, 0.21 for ß-blocker regular use and 0.05 for ergometer.

In the second approach, a matrix correlation was calculated. Figure 5 presents the major association results in the format of a heatmap, in which white boxes indicate non-significant correlation coefficients and stronger coloration reflects more association and higher r2 values; additionally, blue and red color indicated, respectively, positive and negative correlation coefficients. As expected, measured VO_2max was inversely related to age — r = -0.63 (p > 0.001). Similar or slightly higher correlation coefficients were obtained for the associations between the scores of the two non-aerobic fitness tests and the measured VO_2max.

Regarding delta METs, i.e., the difference between estimated (C-AFQ) and measured (CPET) VO_2max, we

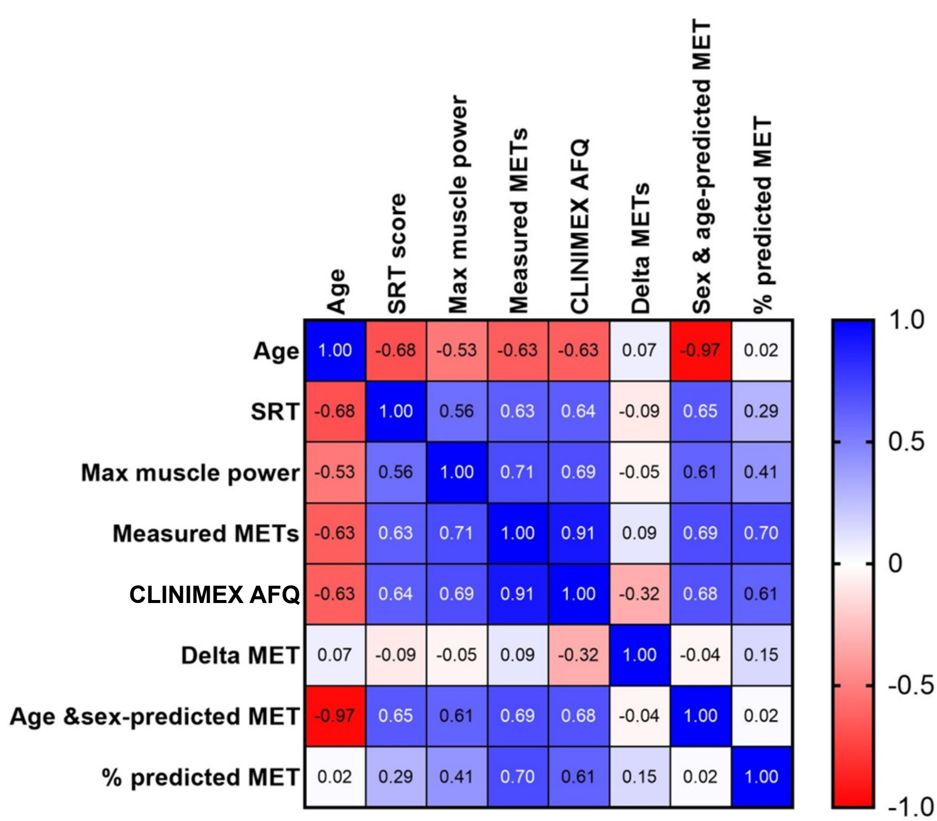

Figure 5 - Heatmap of the associations found for the main study variables.
Footnote: white boxes indicate non-significant correlation coefficients and stronger coloration reflects greater association and higher r-values; additionally, blue and red color indicate, respectively, positive and negative correlation coefficients.

found non-significant associations (r values > -0.1 and < 0.1; p > 0.05) with age and the anthropometric variables studied — height, weight, waist and body mass index (these last two not represented in figure 2). The r-values between delta METs with other non-aerobic components of physical fitness, as assessed by SRT scores and maximal muscle power were, respectively, -0.09 and -0.04, also suggesting no clinical relevance or implications.

The small but significant and positive associations found between delta METs and measured METs — r = 0.09 (p < 0.001) — and measured METs expressed as % sex- and age-predicted METs — r = 0.15 (p < 0.001), but not with sex- and age-predicted MET — r = -0.04 (p = 0.55), indicated that the delta METs slightly tends to increase for those subjects at an upper range of measured aerobic fitness. Median [percentiles 25–75] CPET duration was 11 [8–12] minutes with 75% of all 1,000 CPETs lasting between 8 and 15 minutes.

Discussion

This study proposed the C-AFQ, a new assessment tool for non-exercise estimation of aerobic fitness, and also validated it against the gold standard and criterion measurement of VO_2max obtained during a maximal CPET. In addition, it explored the potential influence of several other variables in the magnitude of the delta METs between estimated (C-AFQ) and measured (CPET) VO_2max.

The rationale for proposing the C-AFQ was primarily based on two major needs: a) to have a simple and valid tool for estimating VO_2max for the Brazilian population when CPET was not feasible or desirable to be carried out; and b) to obtain subsidies for a better and more precise planning of an individual CPET ramp protocol.

Regarding the main variable of the study, a small yet statistically significant difference was found between both means and medians of estimated and measured VO_2max, being, respectively, 0.38 and 0.2 METs. However, considering the minimal interval of 0.5 MET in the C-AFQ scale, these small differences were likely to be clinically irrelevant and acceptable. It should also be recognized that in some subjects that were more used to running than to cycling exercises, the clinical option (i.e., need for a more precise measurement of exercise blood pressure) of cycling rather than treadmill CPET might have produced some overestimation of estimated VO_2max when the C-AFQ was applied, and therefore, contributed to the modest yet significant difference found between the means and medians. Additionally, it should also be mentioned that in some cases, the use of C-AFQ was limited either by not contemplating some specific regular exercises, such as primarily swimming and rowing, or by not being able to offer adequate options and adjustments for those presenting major motion deficits or limitations, such as subjects that are wheelchair-dependent or that have severely limiting arthrosis.

The correlation coefficient of 0.91 observed between estimated (C-AFQ) and measured (CPET) VO_2max in our 1,000 subjects was quite impressive and higher than the one reported — r = 0.79 — in the 212 subjects in the VSAQ's original paper.[19] Using linear regression analysis, it was possible to show that C-AFQ explained 83% of the variation in the measured VO_2max. However, it should be pointed out that the standard error of the estimate was 1.54 METs and that, according to our data (Figure 2), the error of estimate was ±1 and ±2 METs for, respectively, 50% and 78% of the subjects. It is also relevant to emphasize that, since the C-AFQ values are based on the subjects' self-report, it was always likely that some of these individual differences could be explained either by self-misevaluation or due to purposeful misinformation — under or overestimation. So, while, in general, aerobic fitness assessed by C-AFQ was a quite good estimator of measured VO_2max, at an individual level, delta METs could be quite high in a relatively large portion of the subjects, with relevant clinical implications, especially when it is known that detraining and training interventions or conditions would rarely be able to produce more than 2 METs changes in measured VO_2max and, therefore, within this margin of error of estimate.

The application of C-AFQ and its use in planning the individual ramp protocol seemed to have been successful as shown by the profile of CPET duration in which a median value of 11 minutes was observed and the large majority of tests ended after 8 to 15 minutes. An interesting point to comment in our results was the fact that the mean values for sex- and age-predicted and measured (CPET) VO_2max were quite similar, which may reinforce the merit in using Jones' equation[29] to CLINIMEX's population. However, it is worth noting the huge inter-individual variability that ranged from -9.6 to 8.3 METs or from 28.8% to 236% of sex- and age-predicted VO_2max in the 1,000 subjects studied, which clearly indicates the limitation of using sex- and age-predicted VO_2max values for planning individual ramp protocols, much differently than what was observed with the estimated aerobic fitness obtained by C-AFQ.

The tool most often used in the literature to perform non-exercise estimate of aerobic fitness is the VSAQ.[19-21,23] Notwithstanding, as briefly mentioned in our introduction, it has several shortcomings or limitations and, as recently confirmed, its association with measured (CPET) VO_2max is only moderate.[22] For instance, there are several differences between C-AFQ and VASQ that may help to explain why our C-AFQ data presented better association between estimated and measured aerobic fitness than the original VSAQ data.

The first major difference is the range of exercise intensities covered in both questionnaires, with the 0.5 MET interval scale adopted in the lower range of the C-AFQ as compared to 1-MET interval across all VSAQ scales and the extension of scale to > 20 METs in C-AFQ as compared with the 13-MET maximal limit in the original VSAQ, allowing both severely unfit and fitter subjects to be better quantified and discriminated by the C-AFQ. The second major difference resides in the two-step approach used in C-AFQ versus the single-step approach in VSAQ. Interestingly, although apparently a two-step versus a single-step approach and the list of 63 activities in step 2 versus only 21 activities in the VSAQ would seem to be much more complicated, in practical terms, this was not true. Applying the step 1 of C-AFQ allowed a very simple and straightforward answer. Indeed, the vast majority of the subjects would be answering zones 3 to 6 and, according to sex, age and clinical conditions, an even more limited range could be initially asked by the interviewer. For example, in 50-year-old apparently healthy men, the interviewer could start C-AFQ by asking if they are able to "run, slowly, at least 1 km or 10 minutes without stopping or walking" (zone 5). If a negative response is given, the interviewed would downgrade to the question in zone 4 – are you able to "run, slowly, one block or 100 meters?," otherwise, in case of a positive response to the first question, the interviewer would upgrade to zone 6 and the question would be if they were able to "run, continuously, for up to 40 minutes" and the questioning would continue until the "best block or zone number" in step 1 is identified and then following to step 2. Having defined the proper block number in the step 2 of C-AFQ, five and twelve activities are listed according to exercise intensities estimated in METs. In this sense, C-AFQ is likely to be easier and faster to apply while still being more precise and more discriminative than VSAQ in identifying the subject's maximal tolerable exercise and in estimating aerobic fitness (please see a demonstration video in supplemental materials).*

Interestingly, the delta METs were quite similar among the four physicians that collaborated with C-AFQ data for this study. This suggests that adequately trained (after mastering the application C-AFQ instructions) health professionals would be able to successfully use C-AFQ in their practice to estimate aerobic fitness.

Finally, several other associations, at varying degrees, were found. For the major study variable — delta METs between estimated (C-AFQ) and measured (CPET) VO_2max — no clinically relevant influence was found regarding age, sex, height, weight, waist girth, body mass index, major clinical conditions, regular use of ß-blockers, type of CPET's ergometer, SRT scores and maximal muscle power related to body weight. A small association was found between delta METs and relative measured METs expressed as % sex- and age-predicted METs, indicating a small trend for higher absolute errors in those exercise practitioners at an upper range of aerobic fitness. Indeed, from a clinical perspective, a small error at > 12 METs is much less relevant than a similar magnitude of error at the lower range of aerobic fitness. Although it was not among the main objectives of the study, the presence of a significant yet moderate association — r values ranging from 0.63 to 0.71 — between measured (CPET) aerobic fitness and non-aerobic (SRT or maximal muscle power) fitness, with all these variables clearly and independently associated with all-cause mortality,[2,32,34] is a new finding that should be further explored in upcoming epidemiological studies using CLINIMEX's cohort.

This study has several positive points: 1) the prospective design; 2) the large and varied sample in terms of sex, clinical condition, ergometer and levels of aerobic fitness (as often seen in clinical practice); 3) all data collected under well-controlled conditions by only four specialized physicians; 4) the use of a gold standard for criterion validity and; 5) the possibility of assessing the influence of several other variables, including results of two assessment tools of non-aerobic physical fitness. On the other hand, the study also has some limitations: 1) the sample was primarily comprised of white subjects with high educational level and/or upper socioeconomical class; and 2) only four specialized physicians applied the C-AFQ. Both limitations could have influenced the external validity of our results and only future studies with other populations and a larger number of applicants will be able to show if the present results can be generalized or not.

Conclusions

In summary, we concluded that: a) C-AFQ was successfully applied in a large sample of subjects who voluntarily underwent CPET; 2b) C-AFQ was valid to estimate aerobic fitness by four specialized physicians and could be used as a non-exercise alternative when maximal CPET is unavailable or cannot be performed; c) C-AFQ can be very useful to support the planning of individualized CPET ramp protocols; d) C-AFQ's error of estimate of VO_2max was clinically too high in some of the subjects, with a small trend of larger errors in the upper extremes of aerobic fitness; e) C-AFQ's error of the estimate of VO_2max was largely independent of age, sex, major anthropometric measurements, clinical condition, regular use of ß-blockers, type of CPET ergometer and non-aerobic physical fitness levels.

Author contributions

Conception and design of the research: Araujo CG, Castro CL, Franca JF, de Souza e Silva CG. Acquisition of data: Araujo CG, Castro CL, Franca JF, de Souza e Silva CG. Analysis and interpretation of the data: Araujo CG, Castro CL, Franca JF, de Souza e Silva CG. Statistical analysis: Araujo CG, de Souza e Silva CG. Obtaining financing: Araujo CG. Writing of the manuscript: Araujo CG. Critical revision of the manuscript for intellectual content: Araujo CG, Castro CL, Franca JF, de Souza e Silva CG.

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 SUPREMA under the protocol number 218/2011. 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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*Supplemental Materials

For additional information, please click here.

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ORIGINAL ARTICLE

Classification System for Cardiorespiratory Fitness Based on a Sample of the Brazilian Population

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Abstract

Background: Peak oxygen consumption (VO_{2peak}) is an important prognostic marker and its classification helps the cardiologist in the therapeutic decision-making process. The most commonly used cardiorespiratory fitness (CRF) classification has not been validated for the Brazilian population.

Objective: To elaborate a CRF classification using a Brazilian sample and to compare it with the American Heart Association (AHA), Cooper and UNIFESP classifications.

Methods: A total of 6,568 healthy subjects were analyzed through cardiopulmonary exercise testing (CPET). They were distributed by sex and the following age groups (years): 7-12, 13-19, 20-79 (per decades) and > 80 years. After measurement of the VO_{2peak}, participants were distributed into quintiles of CRF in very poor, poor, moderate, high and very high (AEMA Table). The CRF classifications by AEMA, AHA, Cooper, and UNIFESP were compared using the Wilcoxon, Kappa and concordance percentages.

Results: VO_{2peak} presented an inverse and moderate correlation with age considering both sexes (R = -0.488, $p < 0.001$). All paired comparisons between CRF classification systems showed differences ($p < 0.001$) and disagreement percentage - AEMA versus AHA (k = 0.291, 56.7%), AEMA versus Cooper (k = 0.220, 62.4%) and AEMA versus UNIFESP (k = 0.201, 63.9 %).

Conclusion: The AEMA table showed important discrepancies in the classification of CRF when compared to other tables widely used in our setting. Because it was obtained from a large sample of the Brazilian population, the AEMA table should be preferred over other classification systems in our population. (Int J Cardiovasc Sci. 2019;32(4):343-354)

Keywords: Exercise Tests; Oxygen Consumption; Respiratory Function Tests; Exercise; Cardiorespiratory Fitness; Population Health.

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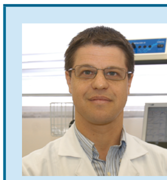

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Introduction

Cardiorespiratory fitness (CRF) is one of the main factors associated with general health, and a valuable predictor of cardiovascular morbidity and mortality and all-cause mortality.[1-4] Maximal oxygen uptake (VO_2 max) may be considered a "vital sign" in the CRF scenario.[2] A low CRF is associated with noncardiovascular clinical conditions such as depression, dementia,[5,6] breast cancer and digestive tract cancer.[7,8] Considering the importance of evaluating CRF, the American Heart Association (AHA) launched the principles for the construction of a national registry of the American population.[9]

The gold-standart method for CRF evaluation is the direct measurement of expired gases through the cardiopulmonary exercise testing (CPET), that evaluates the VO_2 max or peak VO_2 (VO_{2peak}). Since this instrument is not always available, VO_{2peak} may be estimated from the duration and/or maximal load reached during the treadmill or cycle-ergometer test and is expressed as metabolic equivalents (METs).[9-15] Classification of VO_2 max or VO_{2peak} is important in clinical practice, and may help health professionals to associate individuals' CRF with cardiovascular risk, and to encourage the practice of physical exercise/activity.

In Brazil, two classification system have been usually used in exercise test software, the Cooper[16] and the AHA systems.[17] The classification proposed by the Exercise and Sports Medicine Center (*Centro de Medicina de Atividade Física e Desporto*) of São Paulo Federal University (UNIFESP),[18] derived from a regional Brazilian sample, has been not widely used in our setting. Few years ago, Herdy and Caixeta[19] published a table from a population sample of physically active, healthy individuals from southern Brazil. In a retrospective study including 2,930 residents of Rio Grande do Sul State, Brazil, Belli et al.,[20] using a treadmill test for estimating VO_2max (Bruce protocol), observed discrepancies in the classification of CRF between Cooper, AHA and UNIFESP tables.

In this context, the aims of the present study were: (1) to evaluate to evaluate the concordance between AHA, Cooper and UNIFESP systems, taking VO_{2peak} measured by CPET as comparison reference value, and (2) to propose a classification table, by sex and age range, based on a Brazilian sample.

Methods

Population

A total of 11,350 individuals referred for diagnosis and assessment of functional capacity was prospectively evaluated. CPET was performed in a referral center in Joao Pessoa, Paraiba State, Brazil, between February 2007 and December 2017. Eighty percent of the patients were residents of Paraiba State, and 16% were from other states. Flow chart of patients' recruitment is depicted in Figure 1. A total of 4,448 subjects were excluded; 407 due to the absence of a total blood count and a echocardiogram. And the other 4,041 for the following criteria: hypertension and use of anti-hypertensive agents with cardiovascular action (36.5%), coronary artery disease (26.9%), vasculopathy (8.9%), valvular heart disease (7.1%), heart failure (8%), anemia (0.7%), chronic obstructive pulmonary disease (7.1%) and asthma (0.5%). Also, we excluded another 311 patients who did not meet the criteria of maximal CPET or due to disagreement regarding the VO_{2peak} value between the two observers, and 23 due to technical problems (electrical power failure). Thus, the final sample was composed of 6,568 asymptomatic individuals; none of them was using medication with cardiovascular action, and all of them had normal total blood count, resting 12-lead electrocardiogram, two-dimensional color flow doppler echocardiography, and pre-test spirometry, in addition to a CPET without any finding of pathological significance.

Physical activity level was determined according to the ACSM guidelines,[11] modified by the authors, as follows: a) physically inactive subjects were those who did not practice any physical exercise regularly, those who practiced exercise less than three times a week, and those who participated in household and occupational activities that generated energy expenditure lower than 3.2 METs; b) physically active were those individuals who practiced exercise regularly three-six times a week for at least three months, and those who participated in household and occupational activities that generated energy expenditure of 3.2-10.2 METs; c) athletes were those individuals who practiced sports at a competitive level, had daily training sessions, and energy expenditure greater than 10.3 METs. Participants were classified in one of these categories, based on their answers in the pre-CPET questionnaire on past practice of physical

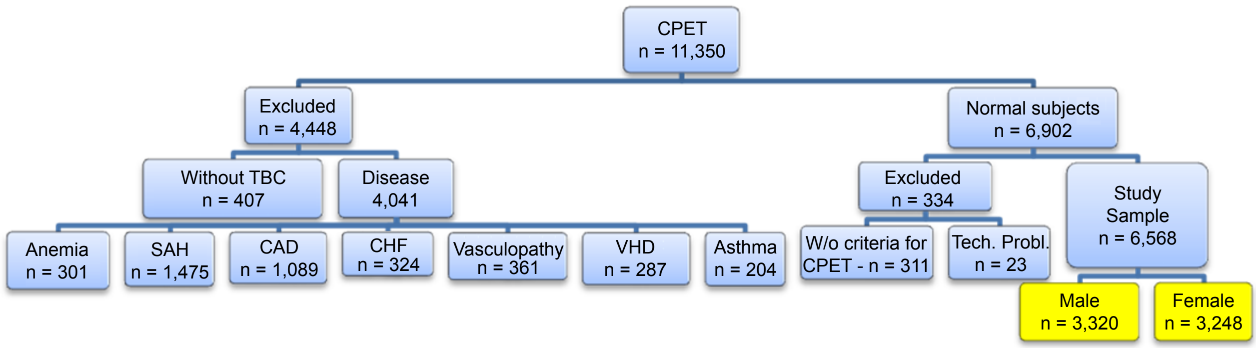

Figure 1 - Flow chart of patients' recruitment.
CPET: cardiopulmonary exercise testing; TBC: total blood count; SAH: systemic arterial hypertension (use of drugs with cardiovascular action); CAD: coronary artery disease; CHF: congestive heart failure; VHD: valvular heart disease; COPD: chronic obstructive pulmonary disease; W/o: without; Tech. probl.: technical problems.

exercise/activity (time, regularity, frequency, duration and intensity), past household and occupational activities focusing on energy expenditure.

All participants signed the informed consent form. The study was approved by the ethics committee of *Hospital de Clínicas de Porto Alegre*, approval number 13-0474).

Cardiopulmonary exercise testing

A CPET device (Metalyzer 3B; Cortex, Leipzig, Germany) combined with ErgoPC Elite (Micromed, Brasília, Brazil), was used with breath-by-breath measurements. All CPET procedures were performed in the same room, with environmental conditions monitored by an Oregon Scientific BAR 208 HGA advanced weather station - mean temperature of 24.47º C, relative humidity of 61.33 and atmospheric pressure of 1009.25 kPa (757 mmHg). Ventilation was regularly calibrated using a 3L-syringe, to apply the correction factor for respiratory volume. Measurements of the oxygen fraction in the expiratory gas (FEO_2) were made through highly accurate (0.1 Vol.%), fast-response electrochemical cells, and the expired fraction carbon dioxide ($FECO_2$) was measured using a highly-sensitive, ND infrared gas analyzer. Calibration of gas analyzers was made weekly (or according to the software recommendations), using a known gas mixture of O_2 (12%) and CO_2 (4.99%) balanced with nitrogen. Ventilatory variables were immediately recorded, and the means were subsequently calculated every 10 seconds with electrocardiographic monitoring. All tests were performed using a treadmill ergometer (Centurion-200 Micromed, Brasilia, Brazil), by the same cardiologist, specialized in exercise testing from the Brazilian Society of Cardiology. A ramp protocol was used, adapted to each participant according to the medical history, biomechanical analysis and physician's expertise, with a planned CPET duration of 8-12 minutes. The subjects were instructed about the test protocol and performed a symptom-limited exercise testing. A modified 10-point Borg scale and the respiratory quotient > 1.10 were used as criteria for maximal exercise.[21-24]

Oxygen uptake

Oxygen uptake was determined based on the agreement between the two specialists in CPET, both independent and blind to study. Test results were sent to the investigators, who identified the peak VO_2 point on the graph. Peak VO_2 was measured at the highest point reached during final stages of maximum effort, considering a sampling interval of two ten-second consecutive periods, and one-minute extrapolation for most participants. For this reason, the term VO_{2peak} was adopted throughout the article.[21,23,24] It is worth mentioning that most individuals reached the highest VO_2 value at the plateau of the curve, regardless of the increase in workload (VO_2 max).[22,24,25]

Study Classification

After analysis of CPET results, the 6,568 apparently healthy subjects were separated by sex and age ranges (7-12, 13-19, ten-year intervals from 20 to 70, and > 80 years). After the VO_{2peak} was measured, individuals were allocated into percentiles and classified into very poor, poor, moderate, good and excellent CRF and then compared. This classification was called the AEMA table.

Statistical analysis

All data were registered in a database by the same trained, independent investigator. Analysis of these data was performed using the IBM SPSS statistics 23 (IBM Company, USA). Continuous variables were described as mean ± standard deviation and categorical variables in percentage. The Student's t-test and the chi-square test were used for comparisons between the distributions of continuous and categorical variables, respectively. Correlations of VO_{2peak} with continuous and categorical variables were made using the Pearson's test and the Spearman's test, respectively. Percentage variation was calculated by VO_{2peak} values of all individuals by sex and age range. Subjects were compared for each table's (AEMA, AHA, Cooper and UNIFESP) criteria using the Wilcoxon test, Kappa (k) and percentage of agreement (%). An error probability (α) < 5% was set as statistically significant.

Results

The group of patients excluded from the study (n = 4,782) did not show any differences regarding sex, age, anthropometric data as compared with the study population. Demographic data (Table 1) showed a predominantly urban population, of pardo ethnicity for both sexes. Regarding educational attainment, most patients had some high school education, and the family income ranged from 250 to 750 American dollars. Table 2 shows a uniform sex distribution (50.5% of men), with mean age of 40 ± 14 years for men and 43 ± 15 years for women. Overweight was predominant in both sexes, and 53.9% of the individuals were physically inactive (44.9% of men and 63.1% of women). Table 3 describes total blood count, ejection fraction (by doppler color flow mapping with two-dimensional echocardiography), spirometry and CPET results, which guided the selection of this healthy sample population, and pointed out maximal CPET results (mean R of 1.23 and 1.21 in men and women, respectively).

In average, women (49.5% of the sample) showed lower VO_{2peak} than men (24.42 ± 6.7 vs. 33.70 ± 9.0 $mL.kg^{-1}.min^{-1}$, $p < 0.001$). There was an inverse, moderate correlation between VO_{2peak} and age in both sexes (R = -0.488, $p < 0.001$). Correlation of VO_{2peak} with family income, educational attainment and place of residence was R = 0.236; R = 0.293 and R = - 0.180, respectively. Table 4 shows mean VO_{2peak} in different age ranges and its percentage variation; a 16.2% increase and 4.0% increase in VO_{2peak} is observed for men and for women, respectively in the two first age ranges, with a descending trend as age increases in both sexes. Interestingly, such decrease is attenuated in the two last age ranges among women.

Table 5 shows the comparison between CRF tables, describing the number and percentage of individuals with lower, similar and higher CRF. As compared with the AEMA table, there was an overestimation of CRF by the AHA, Cooper and UNIFESP classification.

We found a significant difference, and low agreement between the CRF tables. Table 6 shows the proposed CRF classification (very poor, poor, moderate, high and very high) of the AEMA table, with VO_{2peak} intervals distributed by age and sex.

Discussion

This is an important population-based study reporting the functional capacity evaluated by CPET (VO_{2peak}) of Brazilian individuals and its relationship with demographic variables, and that proposes a genuinely national classification of CRF. The findings of the study revealed high discrepancies in CRF classification when AEMA table was compared with AHA, Cooper, and UNIFESP tables. According to these three classifications, individuals were classified as having higher CRF, with disagreement rates of 57%, 62% and 64% when AEMA was compared with the AHA, Cooper and UNIFESP tables, respectively. The AEMA table distinguishes from these three tables, as it includes the age ranges - 7-12, 70-79 and > 80.

Most CRF tables were composed with international sample data. For this reason, there may be ethnical and social differences that may affect the classification of the Brazilian population by these tables. We believe that external validity of data collected from foreign

Table 1 - Characteristics of the sample

Variables		Male n = 3,320	Female n = 3,248
Educational attainment	None	1.6%	2.1%
	Elementary school	11.4%	10.8%
	High school	42.4%	43.5%
	Higher education	41.8%	41.5%
	Postgraduate education	2.8%	2.0%
Family income	< 1 MW	2.1%	2.8%
	1 - 3 MW	32.5%	39.6%
	> 3 - 5 MW	29.5%	36.3%
	> 5 - 10 MW	27.3%	15.1%
	> 10 - 20 MW	4.7%	4.7%
	> 20 MW	4.0%	1.5%
Place of residence	City	95.0%	94.2%
	Rural area	5.0%	5.8%
Ethnicity	White	41.3%	43.0%
	Pardo	52.5%	50.1%
	Black	6.2%	6.9%

Minimun Wege: ~ 250 American dollars.

Table 2 - Characteristics of the sample

Characteristics		Male n = 3,320	Female n = 3,248	p value
		Mean ± SD or n (%)	Mean ± SD or n (%)	
Age (years)		40.30 ± 13.90	42.67 ± 14.55	0.001
Weight (kg)		81.44 ± 15.87	67.60 ± 13.41	0.001
Height (m)		1.71 ± 0.08	1.58 ± 0.07	0.001
BMI		27.74 ± 4.77	26.88 ± 5.07	0.001
Physical activity	Inactive	1,490 (44.9)	2,050 (63.1)	
	Active	1,620 (48.8)	1,140 (35.1)	0.001
	Athletes	210 (6.3)	56 (1.7)	

BMI: body mass index; SD: standard deviation; n: number of individuals.

Table 3 - Total blood count, doppler color flow mapping with two-dimensional echocardiogram, spirometry and cardiopulmonary exercise testing variables

Variables	Male (n = 3,320)				Female (n = 3,248)			
	Mean	±SD	Minimum	Maximum	Mean	±SD	Minimum	Maximum
Hemoglobin (g/dl)	13.8	0.98	12.00	16.90	13.60	0.96	12.00	16.90
Hematocrit (%)	42.7	3.31	37.00	53.10	42.27	3.40	37.10	51.80
Ejection fraction (%)	67.5	6.35	55.00	83.00	66.90	5.90	55.00	85.00
FVC (L)	4.33	1.01	1.76	8.00	3.17	0.85	1.65	6.42
VEF1 (L)	3.69	0.76	1.66	5.81	2.71	0.64	1.36	4.58
VEF1/FVC (%)	86.5	6.64	80.11	104.53	86.68	6.74	81.09	95.85
Speed (km/h)	8.43	1.72	3.60	17.20	7.11	1.83	2.5	16.90
Slope (%)	11.3	3.15	1.00	18.50	9.07	2.61	0.5	16.50
Stress duration (s)	572.3	124.6	313	1,139	530.63	111.2	312	1169
Max HR (bpm)	177.6	14.4	131	210	175.12	14.95	125	210
Max SBP (mmHg)	187.9	23.9	121	259	181.26	21.16	131	256
Max DBP (mmHg)	87.6	12.0	61	132	84.82	10.08	64	126
R	1.23	0.07	1.10	1.71	1.21	0.06	1.10	1.60
Max VE (L/min)	77.6	18.5	33.10	160.30	58.12	18.80	27.80	147.7
VO_{2peak} ($mL.kg^{-1}.min^{-1}$)	33.7	9.0	10.86	71.52	24.42	6.67	10.13	62.69

FVC: forced vital capacity; FEV1: forced expiratory volume in one second; Max HR: maximum heart rate; max SBP: maximum systolic blood pressure; max DBP: maximum diastolic blood pressure; R: respiratory quotient; Max VE: maximum ventilation; SD: standard deviation.

Table 4 - Distribution of peak oxygen consumption (mean and percentage variation) in 6,568 individuals by age and sex

Age range (years)	Men			Women		
	n	VO_{2peak} (Mean ± SD)	Variation (%)	n	VO_{2peak} (Média ± DP)	Variation (%)
07 - 12	32	36.92 ± 7.4	-	25	28.86 ± 5.8	-
13 - 19	151	42.90 ± 9.1	16.2	107	30.00 ± 7.1	4.0
20 - 29	543	37.54 ± 8.3	-12.5	471	28.24 ± 6.5	-5.9
30 - 39	969	35.78 ± 9.0	-4.7	874	26.70 ± 6.4	-5.5
40 - 49	853	33.03 ± 7.7	-7.7	759	24.00 ± 6.0	-10.1
50 - 59	440	30.10 ± 7.1	-8.9	551	21.84 ± 5.1	-9.0
60 - 69	229	26.10 ± 6.4	-13.3	322	19.30 ± 3.9	-11.6
70 - 79	77	22.06 ± 4.7	-15.5	123	17.41 ± 3.7	-9.8
> 80 years	26	19.20 ± 3.4	-13.0	16	16.56 ± 2.9	-4.9

VO_{2peak}: peak oxygen consumption; SD: standard deviation.

Table 5 - Comparison between cardiorespiratory fitness tables with the number of individuals classified as having higher, lower, or similar fitness

Comparison	Lower n (%)	Similar n (%)	Higher n (%)	Total n	Wilcoxon	Kappa
AEMA vs AHA	1,286 (21.41)	2,604 (43.29)	2,121 (35.30)	6,011	< 0.001	0.291
AEMA vs COOPER	458 (7.32)	2,354 (37.55)	3,457 (55.13)	6,269	< 0.001	0.220
AEMA vs UNIFESP	0 (0.00)	1,968 (36.04)	3492 (63.96)	5,460	< 0.001	0.201
AHA vs COOPER	782 (13.60)	2,426 (42.18)	2545 (44.23)	5,753	< 0.001	0.274
AHA vs UNIFESP	288 (5.84)	1,199 (24.26)	3457 (69.91)	4,944	< 0.001	0.112
COOPER vs UNIFESP	324 (6.23)	2,738 (52.62)	2,140 (41.14)	5,202	< 0.001	0.361

populations or from small samples should be tested in Brazilian people, since the mere extrapolation of data may lead to serious errors.[26] In addition, different methods used for VO_{2peak} estimation (mostly by mostly by treadmill test rather than CPET), the criteria used for CRF classification, and different ages of the populations may have contributed to the discordant results of our study. In Cooper's classification,[16] proposed with data from individuals aged older than 13 years, regardless of physical activity level, oxygen consumption was estimated by the maximal duration of the modified Balke protocol. This classification was based on small studies that reported a correlation between test duration and oxygen consumption of 0.92 for men[27] and 0.94 for women.[28] The UNIFESP classification[18] was based on physically inactive, apparently healthy individuals (311 men and 187 women) aged between 20 and 59 years, with adjustment of the curve VO_{2peak} vs. age and direct measurement of oxygen consumption by CPET.

It is of note that, despite its wide use, there is no original publication in the literature demonstrating that the AHA classification table was actually developed by the AHA. After an exhaustive search in the literature, and even making contact with members of the Association, we did not find any original article published in indexed journals or any document issued by the AHA. All we know is that the supposed AHA classification for CRF was developed with individuals of both sexes, aged between 20 and 69 years.

More recently, a nationwide classification system was published by Herdy and Caixeta.[19] The authors studied only individuals described as physically active, with no correlation with demographic data, which made it impossible to compare their data with ours. Also, generalization of results was limited due to the fact that the authors excluded physically active subjects as well as healthy obese individuals, since these characteristics (sedentary lifestyle and obesity) are present in a large proportion of the Brazilian population.

The AEMA table derived from a sample predominantly (84% of the sample) composed of residents of the northeast region of Brazil, with proportional representation of variables such as sex and physical activity level, comparable to the general population. Clear and strict criteria used in the methodology and the measurement of the VO_{2peak} by the CPET (individualized ramp protocol), make this classification system an attractive instrument, with high potential to be used in clinical practice. It is of note that not only the differences observed in the study group but also the method used in the study seem to explain the different results obtained in comparison with those of the other tables.[16-18]

The AEMA table include children aged between 7 and 12 years old; this age range is not included in the other tables, and hence a direct comparison in this age group was not possible. It is worth pointing out that in this age group, there was a high percentage of physically inactive (62.5%), overweight children, and with a family income of three minimum wages (67.5%). Rodrigues et al.,[29] evaluated 380 school children aged 10-14 years attending public schools. Mean VO_{2peak} in children aged between 10 and 12 years was 43 $mL.kg^{-1}.min^{-1}$ (boys) and 38 $mL.kg^{-1}.min^{-1}$ (girls); mean BMI was 17 for boys and 18 for girls. In our study, in children aged 10-12 years, mean VO_{2peak} was 37 and 29 $mL.kg^{-1}.min^{-1}$ for boys and girls, respectively. A possible explanation for such difference may be related

Table 6 - Classification of cardiorespiratory fitness - AEMA table

Men										
Classification	Percentile	7 - 12 years (n = 32)	13 - 19 years (n = 151)	20 - 29 years (n = 543)	30 - 39 years (n = 969)	40 - 49 years (n = 853)	50 - 59 years (n = 440)	60 - 69 years (n = 229)	70 - 79 years (n = 77)	≥ 80 years (n = 26)
Very poor	≤ 20	< 28.77	< 34.76	< 29.79	< 28.57	< 26.53	< 24.23	< 20.61	< 18.26	< 16.11
Poor	40	28.78 - 35.30	34.77 - 39.73	29.80 - 34.41	28.58 - 32.73	26.54 - 30.43	24.24 - 27.75	20.62 - 23.79	18.26 - 20.64	16.12 - 17.20
Moderate	60	35.31 - 38.21	39.74 - 44.60	34.42 - 38.51	32.74 - 37.08	30.44 - 34.30	27.76 - 31.29	23.80 - 27.08	20.65 - 22.22	17.21 - 19.04
High	80	38.22 - 44.64	44.61 - 50.10	38.52 - 42.76	37.09 - 42.58	34.31 - 39.07	31.30 - 35.56	27.09 - 31.00	22.23 - 25.64	19.05 - 22.76
Very high	100	> 44.65	> 50.10	> 42.76	> 42.58	> 39.07	> 35.56	> 31.00	> 2 5.64	> 22.76
Women										
Classification	Percentile	7 - 12 years (n = 25)	13 - 19 years (n = 107)	20 - 29 years (n = 471)	30 - 39 years (n = 874)	40 - 49 years (n = 759)	50 - 59 years (n = 551)	60 - 69 years (n = 322)	70 - 79 years (n = 123)	≥ 80 years (n = 16)
Very poor	≤ 20	< 23.00	< 24.90	< 23.15	< 21.61	< 19.22	< 17.63	< 15.95	< 14.18	< 13.97
Poor	40	23.01 - 26.20	24.91 - 27.80	23.16 - 26.05	21.62 - 24.42	19.23 - 21.92	17.64 - 20.16	15.96 - 18.13	14.19 - 15.95	13.98 - 15.87
Moderate	60	26.21 - 29.23	27.81 - 30.44	26.06 - 29.00	24.43 - 27.10	21.93 - 24.54	20.17 - 22.33	18.14 - 20.04	15.96 - 17.78	15.88 - 17.25
High	80	29.24 - 35.15	30.45 - 35.0	29.01 - 33.00	27.11 - 30.51	24.55 - 27.92	22.34 - 25.25	20.05 - 22.29	17.79 - 20.90	17.26 - 19.11
Very high	100	> 35.15	> 35.00	> 33.00	> 30.51	> 27.92	> 25.25	> 22.29	> 20.90	> 19.11

to higher rates of physically inactive subjects, and a higher BMI in our sample.

A Norwegian study[22] including 759 physically active individuals aged from 20 to 85 years reported higher VO_{2peak} values compared with our results. Again, this could be explained by the greater proportion of inactive and overweight/obese subjects in our population. However, in a Canadian study by Nelson et al.,[21] involving 816 active men, VO_{2peak} was similar to our study group classified as physically active.

When individuals in the age group of 7-12 years were compared with those in the age range immediately above, there was a mean VO_{2peak} increase (positive percentage variation - Table 4). This seems to be associated with the lower capacity of young individuals in performing work, due to structural limitations of cardiorespiratory system (lower height), and lower anerobic production of ATP.[28,29] Analysis of VO_{2peak} in ten-year periods showed an expressive decrease from 50 years old on among men. Such decrease occurred from 40 years on among women and attenuated at the age of 80. We also observed a regular, inverse correlation between age and VO_{2peak} in our study (r = -0.488), which are similar to the findings reported by Jae et al. (r = -0.501).[30] In an AHA document, Arena et al.,[31] reported that VO_{2peak} can decline approximately 10% per decade in nonathletic subjects, varying from 3% to 6% per decade in individuals aged between 20 and 30 years. In our study, we observed an average decrease of 10.8% in male and 8.1% in female subjects in individuals older than 20 years, with faster decline in men, as shown by Weiss et al.[32]

It is important to highlight that data of more than 18,000 CPETs have been recently published. In this large retrospective study, all tests were performed in a chain of a Brazilian laboratory in the state of São Paulo.[33] CPET had been performed for check-up examination and all individuals had normal resting and exercise electrocardiography tests. Despite a robust sample, Rossi Neto et al.,[33] studied a highly selected group of patients as reported by the authors themselves in their manuscript.[33] Thus, these data may not represent the actual CRF of the Brazilian population.

Considering the CRF classification per se, each classification system has its own particularities. Cooper classification system included individuals aged older than 13 years, regardless of the physical activity level.[15] The AHA table was composed of subjects aged between 20 and 69 years, physically active or not.[16] Finally, the UNIFESP table selected only physically inactive individuals aged between 20 and 59 years.[17] In the AEMA table, 6,011 individuals were allocated to different age ranges and compared with the AHA´s table. A discrepancy of 56.7% (higher or lower CRF) was found, in addition to a low agreement (Kappa 0.291). When the AEMA classification was compared with the Cooper classification, 6,269 subjects were allocated, with a disagreement of 62.4% and low agreement (kappa 0.220). Finally, in the UNIFESP classification, 5,460 individuals were allocated, with disagreement of 63.9% and kappa of 0.201. It is of note the high percentage of disagreement in the CRF level of the three tables compared with the AEMA classification (56.7 - 63.9%, $p < 0.001$). These findings seem to be explained by the difference between study populations and by the presence of genetic factors.[11,34-38] Regarding ethnicity, our sample was characterized by a mixed population, representing white, black and Indian ethnicities, comparably to IBGE (Brazilian Institute of Geography and Statistics) data.[39] No difference between the sexes was found regarding educational attainment, family income, place of residence, physical activity level. In addition, different methods to estimate VO_{2peak} were used between the CRF classification systems. While VO_{2peak} was estimated by exercise duration in Cooper and AHA tables, in our study, this parameter was measured during CPET, and was not estimated by formulas. Previous data published by our group showed that oxygen consumption equations, such as Wasserman's and Jones' equations, may overestimate the oxygen consumption by 11.3% and 31.4%, respectively. UNIFESP classification included physically inactive individuals aged between 20 and 59 years. Although this table was also composed using data from the Brazilian population, comparison between this table with the AEMA table revealed the greatest revealed the greatest discrepancy (63.9%). Discrepancy (63.9%). This may be explained by the fact that, in the age ranges of 40-49 and 50-59 years, the values of oxygen consumption were the same for the classification scale, affecting the agreement between the CRF levels.[40] Therefore, considering the distribution of our study population by CRF levels, there was disagreement in CRF classification by the AEMA table compared with the AHA, Cooper and UNIFESP classifications.

It is worth mentioning that the treadmill or cycle-ergometer test evaluates clinical, hemodynamic, autonomic, electrical and metabolic responses to exercise. Information about CRF guides the medical staff to inform patients and family members about aerobic fitness of the subjects, prescribe exercise and evaluate their prognosis.[10] Since the present study showed a great discrepancy in CRF classification between the AHA, Cooper and UNIFESP tables compared with the AEMA table, our findings may be relevant for clinical practice in different ergometric laboratories in Brazil. Our proposed table provides a more accurate classification of CRF compared with other tables derived from foreign populations, since it was developed with Brazilians' data, thereby eliminating possible biases of international tables.

Limitations

Since data collection was not performed in all federated states of Brazil, the possibility that our findings may not have external validity throughout the country cannot be ruled out. However, the sample was composed of individuals coming from all the country (84% from Paraiba State and 16% from other states), of different ethnicities and multiracial background, which we known as a mixed-race, national sample. It is worth pointing out that comparison of our data with data matched by IBGE age groups, we did not find any difference ($p = 0.401$), including a similar distribution by sex.[39] Our sample showed a higher prevalence of overweight subjects, which is in accordance with data reported by 2012 Vigitel[41] (i.e., 51% of the Brazilian population). Also, the prevalence of individuals that practice regular physical exercise or exercise on the way to work is 47.7%,[41] which is similar to our population.

The low number of individuals aged between 7 and 12 years may be explained by the low frequency of clinical indication of CPET at this age range. On the other hand, at the age of 80's, there were few people who were healthy and met all inclusion and exclusion criteria of the present study. Nevertheless, despite this limitation, we believe that it is important for the clinician to have initial reference values for this age group. Finally, all CPETs were performed using a treadmill, and the applicability of our findings to a cycle ergometer should be tested.

Conclusion

The AEMA table showed important discrepancies when compared with the AHA, Cooper and UNIFESP tables, which are widely used instruments for CRF classification in our setting. We propose the use of the AEMA table, which was constructed with data from a large sample (predominantly regional, though) of the Brazilian population in centers and laboratories where the treadmill exercise testing is test is performed throughout the country.

Author contributions

Conception and design of the research: Almeida AEM, Ribeiro JP, Stein R. Acquisition of data: Almeida AEM, Santander IRMF, Nascimento JA, Agnaldo do Nascimento J, Stein R. Analysis and interpretation of the data: Almeida AEM, Santander IRMF, Campos MIM, Nascimento JA, Agnaldo do Nascimento J, Stein R. Statistical analysis: Almeida AEM, Campos MIM, Nascimento JA, Agnaldo do Nascimento J, Stein R. Writing of the manuscript: Almeida AEM, Ritt LEF, Belli KC, Stein R. Critical revision of the manuscript for intellectual content: Almeida AEM, Ritt LEF, Belli KC, Stein R.

Potential Conflict of Interest

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

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Appendix I - General characteristics of the sample by age range

Variables	Age Range								
	07 - 12	13 - 19	20 - 29	30 - 39	40 - 49	50 - 59	60 - 69	70 - 79	≥ 80
Sex					**Male**				
N	32	151	543	969	853	440	229	77	26
Age	10.65 ± 1.4	16.66 ± 1.9	25.40 ± 2.9	34.52 ± 2.8	44.04 ± 2.8	53.74 ± 2.8	63.70 ± 2.8	73.58 ± 2.8	82.67 ± 2.5
Weight (kg)	51.87 ± 10.5	72.93 ± 18	81.90 ± 16	84.20 ± 16	83.47 ± 14	80.49 ± 12	76.75 ± 15	68.98 ± 10	66.9 ± 11
Height (cm)	151.0 ± 0.08	173.6 ± 0.7	174.5 ± 0.1	172.9 ± 0.1	171.1 ± 0.1	168.4 ± 0.1	165.5 ± 0.1	162.3 ± 0.1	161.8 ± 0.1
BMI	22.64 ± 3.21	24.10 ± 5.3	27.05 ± 5.1	28.22 ± 4.8	28.42 ± 4.3	28.45 ± 4.6	27.90 ± 4.6	26.27 ± 3.6	25.45 ± 3.6
Inactive (%)	52.20	28.70	37.10	45.00	43.80	47.40	43.20	54.90	54.20
Active (%)	47.80	57.40	54.50	44.90	50.20	48.30	54.70	43.70	45.80
Athlete (%)	-	13.90	8.40	10.10	6.00	4.30	2.10	1.40	-
VO_{2peak}	36.92 ± 7.4	42.90 ± 9.1	37.54 ± 8.3	35.78 ± 9.0	33.03 ± 7.7	30.10 ± 7.1	26.10 ± 6.4	22.06 ± 4.7	19.20 ± 3.4
Sex					**Female**				
N	25	107	471	874	759	551	322	123	16
Age	9.82 ± 1.7	16.73 ± 1.8	25.19 ± 2.9	34.53 ± 2.9	44.42 ± 2.8	54.23 ± 2.8	64.21 ± 2.8	73.44 ± 2.7	83.40 ± 2.9
Weight (kg)	51.69 ± 12.9	61.43 ± 18	65.62 ± 14	67.46 ± 13	69.25 ± 12	69.03 ± 12	64.82 ± 10	62.90 ± 10	57.13 ± 10
Height (cm)	147.7 ± 0.11	163.1 ± 0.8	162.8 ± 0.6	160.6 ± 0.1	158.5 ± 0.1	156.3 ± 0.1	152.8 ± 0.1	151.5 ± 0.1	152.1 ± 0.0
BMI	23.58 ± 4.5	23.01 ± 6.1	24.83 ± 5.1	26.14 ± 5.0	27.59 ± 5.0	28.23 ± 5.0	27.85 ± 4.6	27.39 ± 4.2	24.73 ± 4.0
Inactive (%)	76.50	68.80	61.00	61.00	62.50	61.00	62.90	71.60	46.70
Active (%)	23.50	27.50	36.00	35.80	34.60	37.50	37.10	28.40	53.30
Athlete (%)	-	3.80	2.90	3.20	2.90	1.50	-	-	-
VO_{2peak}	28.86 ± 5.8	30.00 ± 7.1	28.24 ± 6.5	26.70 ± 6.4	24.00 ± 6.0	21.84 ± 5.1	19.30 ± 3.9	17.41 ± 3.7	16.56 ± 2.9

BMI: body mass index; VO_{2peak}: peak oxygen consumption.

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ORIGINAL ARTICLE

The Physical Activity Level, Body Composition and Diabetes Mellitus Influence the Association Between Depression and Hypertension in Community-Dwelling Elders

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Abstract

Background: Depression and hypertension are highly prevalent among elderly people. Although the relationship between these conditions is well recognized, however, the factors that may influence such association are not clearly understood.

Objective: To analyze the association between depression and hypertension in community-dwelling elders.

Methods: Two-hundred and thirty-one community-dwelling elders provided information regarding the following variables: sex, age, ethnicity, smoking habit, physical activity level (PA), body mass index (BMI) and diabetes mellitus (DM). These variables can potentially influence depression and hypertension, as well as its relationship. Screening for depression was made using the Geriatric Depression Scale (GDS). The presence of hypertension was defined based on self-reported data and/or the use of antihypertensive drugs. The logistic regression technique was applied, using hypertension as the dependent variable and depressive state as a predictive variable. Logistic regression was applied with and without adjustment for the potential intervening variables.

Results: The prevalence of depressive state and hypertension in the studied population was 14% and 59%, respectively. The association between depression and hypertension without adjustments was not significant (odds ratio [OR] = 2.28, 95% confidence interval [95%CI] = 0.98 - 5.32; p = 0.06). However, after adjusting for PA, BMI and DM, the strength of association between depression and hypertension significantly increased (OR = 3.08, 95%CI = 1.12 - 8.46; p = 0.03).

Conclusion: The association between depression and hypertension in the elderly is directly influenced by PA, BMI and DM. This finding may guide strategies to increase the adherence to a healthier lifestyle. (Int J Cardiovasc Sci. 2019;32(4):355-361)

Keywords: Aging, Mood Disorders; Hypertension; Diabetes Mellitus; Depression; Obesity, Sedentarism; Exercise; Independent Living; Lifestyle.

Introduction

Senescence is a natural life process associated with increased risk of non-communicable diseases, as hypertension. In fact, there is a growing prevalence of hypertension with increasing age.[1] This is worrying, since it is expected that the world population over 60 years old will be approximately two billion in the next decades[2] and the prevalence of hypertension could reach up to 80% among elders.[3]

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Hypertension is recognized as a multifactorial clinical condition, with lifestyle- related factors, such as smoking, high sodium intake, sedentary lifestyle, among others, widely associated with this condition. However, recent studies have pointed to a close relationship between hypertension and depression,[4] which becomes even more worrying when considering the elderly people, due to the known association between depression and aging.[5]

Depressive disorder is common among the elderly; it is a multi-causal condition, whose etiology may vary from depressive disorders, observed in young adults, to those associated with chronic age-related processes (cardiovascular, inflammatory, endocrine, autoimmune processes), continuous use of some medications, psychological adversity, and cognitive deficits.[6] Approximately 10% of individuals over 60 years old require therapeutic intervention for depressive disorder, and the prevalence of depression may be greater than 40% among elders living in geriatric institutions.[7]

Changes in autonomic nervous system control, characterized by worse vagal control and increased heart rate, are observed in depressive subjects and are pointed out as factors that may explain the predisposition to hypertension.[8] In addition, it is known that, among elders, the association between depression and hypertension seems to be influenced by obesity.[9]

The study by Long et al.,[9] raises an important perspective in the understanding of the relationship between depression and hypertension among elders. In fact, Meng al.,[10] had already reported that variables such as gender, race, smoking, physical activity level, obesity / body mass index (BMI), DM and other psychological factors are potentially confounding variables in the relationship between depression and hypertension. In this context, the present study aimed to analyze the association between depression and hypertension in community-dwelling elders, as well as to analyze the influence of confounding variables that are potentially capable to influence this association.

Material and methods

Sample

All community-dwelling old adults (≥ 60 years old) from Aiquara, Bahia, Brazil were invited to take part in this survey study. Two hundred eighty-nine subjects were screened, all of them answered an extensive health questionnaire, and were submitted to clinical and physical examinations. Bedridden individuals and/or those with severe cognitive impairment (n=20) were excluded. Cognitive status was assessed using the translated and validated version of the Mini-Mental State Examination (MMSE).[11] The cutoff points for cognitive impairment was set as: 13 points for no schooling, 18 points for schooling from 1 to 11 years, and 26 points for more than 11 years of schooling.[11] Additionally, 38 elders had technical problems during data recording, which limited their inclusion in the analysis. Data were collected between January and July 2015.

Ethical aspects

The individuals included in this study were informed about all the procedures and provided written informed consent to participate. This study was approved by the ethics committee of the institution (CAAE: 10786212.3.0000.0055) and abides by the CONEP resolution 466/2012.

Definition of hypertension and depression

The stratification of hypertensive and normotensive elderly subjects was based on previous diagnosis reported by the elders, while the stratification of depressive and non-depressive elders was based on the Geriatric Depression Scale (GDS), which was validated to the Brazilian population.[12] The cut-off score for depression was set as 6 positive items.[13]

The most commonly used psychotropic medications among depressive elders were tricyclic and selective serotonin-reuptake-inhibitors, benzodiazepines and muscle-relaxation drugs.

Adjustment variables

The dichotomous variables sex (male or female), race (white or non-white), smoking habit (yes or not), physical activity level (sufficiently active or insufficiently active), and self-reported diagnostic of DM (yes or no), and the continuous variables age and body mass index (BMI, Kg/m^2) was used as adjustment variables.

Physical activity level was obtained using the International Physical Activity Questionnaire (IPAQ) and the results were dichotomized according to the proposed cut-point of ≥ 150 min/week of moderate and vigorous activity (i.e., ≥ 150 min/wk, sufficiently active; < 150 min/week, insufficiently active).[14]

Statistical analysis

The chi-square test was used to identify differences in proportions between hypertensive and normotensive groups, and between depressive and non-depressive groups. Distribution of dichotomous variables (sex, race, smoking habit, physical activity level, and previous DM) was tested; for continuous variables, normality of distribution was tested with Kolmogorov-Smirnov test. As the assumption of normality was rejected, the Mann-Whitney test was used for comparisons of age and BMI between hypertensive and normotensive groups, and between depressive and non-depressive groups.

Descriptive analyses were made using absolute and relative frequencies (dichotomous variables), and median and interquartile interval (continuous variables). The association between hypertension and depression was tested by a logistic regression method. Additionally, the variables that achieved a significance level of $p < 0.1$ in the chi-square test (categorical variables) or in the Mann-Whitney test (continuous variables) were included as adjustment variable in the logistic regression, as proposed by Conover.[15] Then, logistic regressions were conducted with and without adjustment for each eligible variable, and with adjustment including all eligible variables together. A significance level of $p < 0.05$ was used for analyses using the chi-square test, the Mann-Whitney test and logistic regressions, and all procedures were performed using tge IBM SPSS V.21.0 (SPSS, IBM Corporation, Armonk, New York, USA).

Results

In the study population, the prevalence of depressive state was 14% and of hypertension was 59%. Hypertensive elderly subjects had significantly higher BMI compared with normotensive subjects (27.20 ± 5.75 kg/m^2 vs, 23.80 ± 7.13 kg/m^2, $p < 0.05$. Age was not different between hypertensive and normotensive elders (72.00 ± 11.00 years old vs. 71.00 ± 13.00 years old, respectively, $p > 0.05$). Hypertension was significantly associated with DM ($p < 0.05$), while the variables sex, race, smoking habits, and physical activity level were not significantly associated ($p > 0.05$). Table 1 shows the association of categorical variables (sex, race, smoking habits, DM and physical activity level) with hypertension.

Depressive elders were significantly older than non-depressive elders (76.00 ± 11.50 vs. 71.00 ± 11.00 years old, $p < 0.05$). Regarding BMI, there was no significant difference between depressive and non-depressive elders (25.20 ± 6.95 kg/m^2 vs. 25.60 ± 7.33 kg/m^2, respectively, $p > 0.05$). Depression was significantly associated with physical activity level ($p < 0.05$), but not with the variables sex, race, smoking habit, and diabetes mellitus were not significantly associated ($p > 0.05$). Table 1 shows the association of categorical

Table 1 - Absolute and relative frequency of sex, race, diabetes mellitus, smoking habits and physical activity level of elderly individuals (n = 94) according to blood pressure status (hypertension vs normotensive), Aiquara, Bahia, Brazil (2015)

		Normotensive	Hypertensive	p value
Sex	Women	52 (55.3%)	86 (62.3%)	0.256
	Men	42 (44.7%)	51 (37.2%)	
Race	White	15 (16.3%)	17 (13.2%)	0.515
	Others (pardo and black)	77 (83.7%)	112 (86.8%)	
Smoker	No	79 (87.8%)	114 (91.2%)	0.414
	Yes	11 (12.2%)	11 (8.8%)	
Diabetes mellitus	No	84 (89.4%)	99 (72.3%)	0.002*
	Yes	10 (10.6%)	38 (27.7%)	
Physical activity level	Sufficiently active (≥ 150 min/week)	48 (53.9%)	53 (57.5%)	0.605
	Insufficiently active (< 150 min/week)	41 (46.1%)	54 (52.5%)	

(*) Statistically significant at $p \leq 0.05$.

Table 2 - Absolute and relative frequency of sex, race, diabetes mellitus, smoking habit and physical activity level of elderly individuals (n = 197) according to depressive status (non-depressive vs depressive), Aiquara, Bahia, Brazil (2015)

		Non-depressive	Depressive	p value
Sex	Women	117 (59.4%)	19 (59.4%)	0.999
	Men	80 (40.6%)	13 (40.6%)	
Race	White	30 (15.8%)	2 (6.7%)	0.188
	Others (pardo and black)	160 (84.2%)	28 (93.3%)	
Smoker	No	166 (90.2%)	26 (86.7%)	0.553
	Yes	18 (9.8%)	4 (13.3%)	
Diabetes mellitus	No	160 (81.2%)	22 (68.8%)	0.105
	Yes	37 (18.8%)	10 (31.3%)	
Physical activity level	Sufficiently active (≥ 150 min/week)	109 (58.9%)	11 (36.7%)	0.023*
	Insufficiently active (< 150 min/week)	76 (41.1%)	19 (63.3%)	

(*) Statistically significant at p ≤ 0.05.

variables (sex, race, smoking habits, diabetes mellitus and physical activity) with hypertension.

Since the variables DM, BMI, and physical activity level were associated with hypertension and depression, logistic regression analysis was performed, with and without adjustments for the cited variables. Table 3 shows the regression coefficient, and the odds ratio (OR) and its 95% confidence interval of the variables included in the adjusted and unadjusted logistic regression analysis. It is possible that the association between hypertension and depression was directly influenced by BMI, and physical activity level, while the analysis adjusted for all the variables (DM, BMI and physical activity level) together also confirmed the significant influence of these variables on the relationship between depression and hypertension in community-dwelling elders.

Discussion

The present study aimed to analyze the association between depression and hypertension in community-dwelling elders, and to analyze the influence of potential confounding variables. Our results showed that the association between depression and hypertension was significantly influenced by BMI, physical activity level and DM.

In fact, no significant association was found between depression and hypertension (OR [95%CI] = 2.28 [0.98 - 5.32]; p = 0.06) when analyzed without adjustment variables. However, after adjustment for the variables BMI (OR [CI95%] = 2.66 [1.04 - 6.79], p = 0.04) and physical activity level (OR [CI95%] = 3.41 [1.31 - 8.85], p = 0.01) a significant association was found between depression and hypertension in the study population. The analysis adjusted for BMI, physical activity level and DM together also influenced significantly the association between depression and hypertension (OR [95%CI] = 3.08 [1.12 - 8.46]; p = 0.03).

In our study, DM was significantly associated with hypertension, but not with depression, which may explain the lack of influence of the adjustment for DM on the association between hypertension and depression. Previous studies have shown that DM is common among depressed people;[16,17] in fact, in our study, 31.3% of depressed elderly people were diabetic, whereas this prevalence was only 18.8% among non-depressed elderly people. However, no significant difference was achieved. Despite this, the considerably higher prevalence of diabetic elderly among depressive and (statistically significant) hypertensive elders justifies the maintenance of this intervening variable (i.e., DM) in the regression model adjusted for DM, BMI and level of physical activity.

The close association of obesity with depression[18,19] and hypertension[20,21] explains the strong influence of this variable on the relationship between depression

Table 3 - Regression coefficient, odds ratio (OR) and its 95% confidence interval of the variables included in the adjusted and unadjusted logistic regression analysis

Variable	Regression coefficient (RC)	Standard error	Odds ratio (OR)	95% CI	p value
Unadjusted					
Depression	0.823	0.433	2.28	0.98 - 5.32	0.06
Constant	0.276	-	-	-	-
Adjusted for diabetes mellitus					
Depression	0.731	0.441	2.08	0.86 - 4.93	0.09
Constant	0.093	-	-	-	-
Adjusted for body mass index					
Depression	0.977	0.479	2.66	1.04 - 6.79	0.04*
Constant	-3.00	-	-	-	-
Adjusted for physical activity level					
Depression	1.23	0.486	3.41	1.31 - 8.85	0.01*
Constant	0.348	-	-	-	-
Adjusted for diabetes mellitus, BMI and physical activity level					
Depression	1.124	0.516	3.08	1.12 - 8.46	0.03*
Constant	-2.515	-	-	-	-

(*) Statistically significant at $p \leq 0.05$.

and hypertension. Follow-up studies have corroborated such relationship, since the presence of obesity increases by 1.55 times the odds to develop depression, just as depression increases 1.58 times the odds to develop obesity.[19-22] Therefore, a higher cardiovascular risk comes from the association of these conditions, i.e., obesity and depression.[18,23]

The adoption of a physically active lifestyle has been pointed out as an effective behavioral intervention to treat depression symptoms.[24,25] Josefsson et al.,[26] in a systematic review with meta-analysis on this issue, concluded that the use of exercise as an intervention generates positive results in mild-to-moderate depression. Blake et al.[27] stated that physical activity programs can achieve positive results in the treatment of depressive symptoms in the elderly.

The recent study of Holmquist et al.,[28] broadens the basis of these findings. In the cited study, the authors evaluated the association of depression with several lifestyle-related variables, previous illnesses and physical performance in the elderly. It was observed that depressed elders (GDS ≥ 5 points) were predominantly obese, diabetic, and physically less active (or had worse physical performance). In fact, these same variables may be associated with hypertension, and thus can influence the association between hypertension and depression. In this sense, two aspects are relevant: 1) the identification of depressive, obese, diabetic and insufficiently active elderly subjects can guide the screening of those prone to hypertension, since this set of factors among elders increases in 3.08 (1.12 - 8.46) times the odds of being hypertensive; 2) all the studied factors associated with hypertension and depression here are amenable to intervention; thus, as proposed by Blake et al.,[27] preventive strategies focused on physical activity could represent an excellent strategy from the point of view of cost-effectiveness to prevent hypertension in depressed elderly people, since the level of physical activity increases 3.41 (1.31 - 8.85) times the odds of a depressed elderly subject being hypertensive.

Conclusion

Our results showed that BMI, DM and physical activity level influence the association between hypertension and depression in community-dwelling elders. DM affects the association between depression and hypertension when combined to physical activity and BMI. In addition, the level of physical activity seems to be the main influencing factor of this relationship. This promotes positive perspectives regarding therapeutic interventions, since, unlike drug interventions, the adoption of a physically active lifestyle is an excellent, cost-effective intervention for both hypertension and depression.

Author contributions

Conception and design of the research: Cassoti CA, Ribeiro IJS and Pereira R. Acquisition of data: Araújo CGS, Freire IV and Ribeiro IJS. Analysis and interpretation of the data: Pereira R, Casotti CA, Montino YF. Statistical analysis: Pereira R, Ribeiro IJS. Obtaining financing: Casotti CA and Pereira R. Writing of the manuscript: Araújo CGC, Freire IV, Montino YF. Critical revision of the manuscript for intellectual content: Casotti CA, Pereira R and Ribeiro IJS.

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 Estadual do Sudoeste da Bahia* (UESB) under the protocol number 171464. 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

Comparative Analysis of Direct and Indirect Methods for the Determination of Maximal Oxygen Uptake in Sedentary Young Adults

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Abstract

Background: Maximal oxygen uptake is a powerful prognostic indicator and a reliable measure of physical conditioning. It can be measured directly by cardiopulmonary exercise testing (CPET) or indirectly by formulas derived from conventional protocols.

Objective: We compared the VO_2 max obtained by formula using exercise testing with Bruce protocol (BP) with the VO_2 max obtained by CPET on the treadmill.

Methods: We selected 41 healthy, non-obese, physically inactive young volunteers, aged between 21 and 50 years, residents of Florianópolis, Brazil.

Results: Twenty-one women (52%) with mean age of 35.62 ± 8.83 years, and 20 males, with mean age of 32.5 ± 7.18 years participated in the study. Statistically significant differences were found for VO_2 max between the two methods (BP - 42.31 ± 5.21 ml/kg.min vs. CPET - 30.46 ± 5.50 ml/kg.min., p < 0.0001). The Bruce formula overestimated the result by 34.1% (BP - 45.95 ± 3.94 ml/kg.min vs. CPX - 34.27 ± 4.20 ml/kg.min, p < 0.0001) for men, and by 44.8% (BP - 38.84 ± 3.72 ml/kg.min vs. CPX - 26.83 ± 3.90, p < 0.0001) for women. A moderate correlation was observed between the methods (r = 0.65). When classifying the results according to the table of aerobic capacity of the American Heart Association, the agreement was null (kappa = 0.0034; Pearson chi2 = 0.001).

Conclusion: VO_2 estimated by BP is not capable of demonstrating the true aerobic capacity in these individuals, while CPET is an important tool for early detection of diminished functional capacity in sedentary young men and women. (Int J Cardiovasc Sci. 2019;32(4):362-367)

Keywords: Cardiovascular Diseases; Exercise Test; Oxygen Consumption; Adolescent; Physical Fitness; Sedentarism.

Maximal oxygen uptake is a powerful prognostic indicator and a reliable measure of physical conditioning. It can be measured directly by cardiopulmonary exercise testing (CPET) or indirectly by formulas derived from conventional protocols. We compared the VO_2 max obtained by formula using exercise testing with Bruce protocol (BP) with the VO_2 max obtained by CPET on the treadmill. We selected 41 healthy, non-obese, physically inactive young volunteers, aged between 21 and 50 years, residents of Florianópolis, Brazil. Twenty-one women (52%) with mean age of 35.62 ± 8.83 years, and 20 males, with mean age of 32.5 ± 7.18 years participated in the

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Introduction

Maximal oxygen uptake (VO_2 max) is the product of the arteriovenous oxygen difference and cardiac output.[1,2] It is the most important physiological measurement in defining functional capacity of an individual (aerobic power).[3] VO_2 max varies with body weight, age, physical activity level and presence of cardiorespiratory disease.[1,4,5] The parameter is used to prescribe exercise, evaluate the effects of training and therapeutic interventions, and as a risk stratification tool for the occurrence of cardiovascular disease.[3,6] VO_2 max can be directly measured by analysis of breathing gases during cardiopulmonary exercise testing (CPET) or estimated by the stress test using prediction equations.[2]

Physical fitness has been shown in several studies to be an important predictor of all-cause and cardiovascular mortality.[7-12] On the other hand, a sedentary lifestyle is an important cardiovascular risk factor, with increasing prevalence in the world population.[13] The Bruce protocol (BP) is the main non-invasive method for cardiovascular assessment performed in asymptomatic individuals.[14] However, functional capacity estimated by formulas during the test may be inaccurate for physically inactive young individuals, leading to a wrong assessment of fitness and minimizing the real cardiovascular risk posed by a low physical fitness, commonly seen in these individuals.

Aiming at evaluating the difference in functional capacity between the direct and indirect method in inactive young individuals, VO_2 max was measured by the CPET and the BP formulas.

Methods

Fifty healthy, non-obese and physically active individuals were invited to participate in the study. All were residents of Florianópolis city, Brazil. Nine individuals declined to participate, and 41 were then included. Participants were randomly assigned to CPET on a treadmill (Inbramed® 1999, Brazil), with ramp protocol (ErgoPC Elite version 3.3.6.2, 1999, Micromed®, Brazil) and gas analyzer (Metalyzer®, 2004, Germany) or to the BP (ErgoPC13 version 2.4.8.5, 1998, Micromed®, Brazil), with a 48 interval between the tests. The formula used to estimate VO_2 by the BP was the one available in the most popular ergometry software in Brazil: physically inactive men - VO_2 = (TIME (min) x 2.9) + 8.33. Women - VO_2 = (TIME (min) x 2.74) + 8.03.[1] The estimated predicted VO_2 for each individual was estimate by the formulas (mL/Kg.min):[3,5]

- Men: VO_2 = 60 – 0.55 x age (years);
- Women: VO_2 = 48 – 0.37 x age (years).

All tests were performed by an experienced cardiologist, qualified to perform ergometric test and CPET. Treadmill tests were carried out following the Brazilian Society of Cardiology guidelines on ergometric and cardiopulmonary tests.[3] VO_2 max was considered as the highest VO_2 reached during stress (VO_2 peak). After direct or indirect measurement of VO_2, participants were classified by cardiorespiratory fitness using the American Heart Association table and grouped into four groups – low, moderate, high and very high.[5] All participants signed the informed consent form and the study protocol was approved by the ethics committee of the institution.

Statistical analysis was performed using the Stata SE 9 and the Microsoft Excel software. The Student's t-test was used to compare means between matched samples. Correlation was analyzed by Pearson correlation. Agreements were analyzed using weighted kappa statistic. A $p \leq 0.05$ was set as statistically significant.

Results

Twenty-one (52%) of the 41 individuals included were women. Mean age was 34.1 ± 8.12, varying from 21 to 50 years. Mean body mass index (BMI) was 24.5 Kg/m² ± 3.34, and mean weight and height was 72.8 ± 15.7 kg and 1.73 ± 0.11 m, respectively. Mean VO_2 max was 42.31 ± 5.21 mL/Kg.min for the BP and 30.46 ± 5.50 mL/Kg.min for the CPET with ramp protocol, p < 0.0001. Analysis by sex (Figure 1) revealed significant difference between

VO_2 max estimated by the BP and the CPET (38.85 ± 3.72 mL/Kg.min versus 26.83 ± 3.90 mL/Kg.min, respectively, $p < 0.0001$) for women, and for men (45.94 ± 3.94 mL/Kg.min versus BP 34.26 ± 4.21 mL/Kg.min, respectively, $p < 0.0001$) The BP overestimated VO_2 max by 44.8% for women and by 34.1% for men compared with the CPET.

No difference was found in maximal effort, measured by maximal heart rate (HRmax) between the tests. During the BP and CPET, HR max was 184.8 ± 9.47 vs 183.1 ± 10.03, respectively, for men, and 179.8 ± 11.68 versus 180.8 ± 12.63, respectively, for women, p = NS).

There was a moderate correlation between the two methods (r = 0.65), and the agreement between the tests regarding cardiorespiratory fitness was null (Figure 2) (Kappa = 0.0034 and chi-square = 0.001). Most participants showed high or very high cardiorespiratory fitness by the BP and moderate or low cardiorespiratory fitness according to the CPET.

Discussion

Cardiorespiratory fitness has been shown to be an important prognostic marker of morbidity and mortality in young, older, healthy individuals with heart diseases.[8,15,16] Most studies have classified individuals according to their performance in ergometric tests. In Brazil and in the USA, the ergometric test on the treadmill has been widely used, and the BP is the main test performed.[14]

Although individual risk to stress tests may be stratified by test duration, functional capacity may be overestimated in young adults, even in physically inactive ones. In this regard, when age range is used for risk stratification, conventional stress test is not an accurate test to evaluate functional capacity. Sedentary habits have long-term, cumulative effects, and several studies have shown that it is never too late to decrease the risk by improving physical fitness.

In most computer programs for exercise stress testing in Brazil, VO_2 is estimated using the BP formula, and used to classify subjects according to cardiorespiratory fitness. Our study showed an important overestimation of the indirect assessment of VO_2 by the BP.

In 1973, Bruce et al.,[1] studied 295 physically active or inactive adults by exercise testing on the treadmill, and direct analysis of gases, from which derived the formulas currently used. Ong et al.,[4] measured VO_2 max by CPET and compared it with that obtained by cycle ergometer test (prediction equations). The formulas overestimated the results by 13.74% for men and 10.55% form women.[4] Fairbarn et al.,[17] evaluated 231 non-athletes aged from

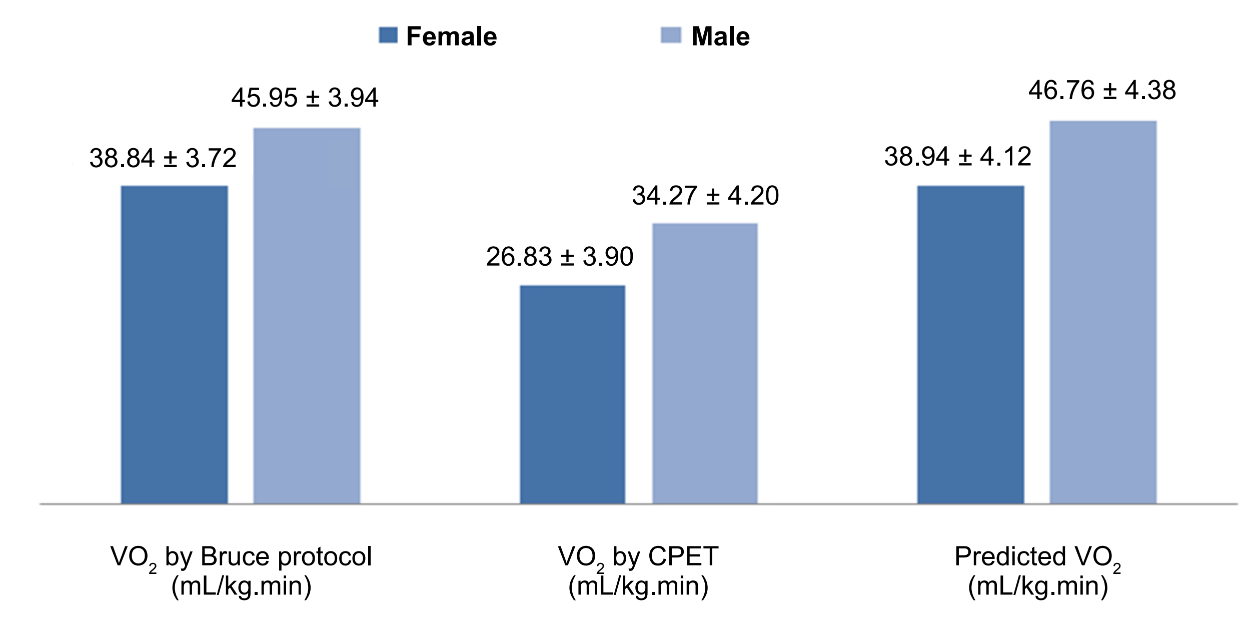
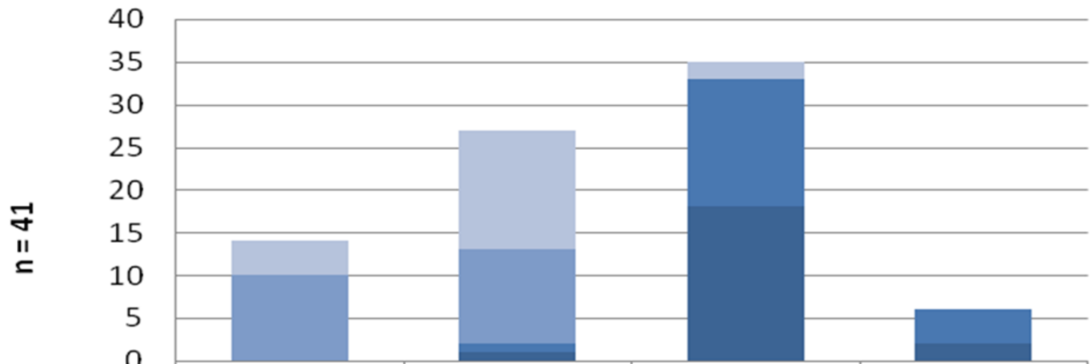


Figure 1 - Comparison of VO_2 max in Young, physically inactive individuals by sex (men; n = 20 and women; n = 21), $p < 0.0001$ (mean ± SD); VO_2: oxygen uptake; CPET: cardiopulmonary exercise testing.



	Low	Moderate	High	Very high
CPET Men	4	14	2	0
CPET Women	10	11	0	0
BP Men	0	1	15	4
BP Women	0	1	18	2

Figure 2 - Null hypothesis of agreement between the methods (Kappa = 0.0034; chi² = 0.001; p = 0.3713) based on the American Heart Association classification of the aerobic capacity; CPET: cardiopulmonary exercise testing; BP: Bruce protocol.

20 to 80 years by cycle ergometer test and found a difference in VO_2 max measured by the equations of 36.17% and 26.47% for men and women, respectively, with higher values obtained by the equations.[17] Neder et al.,[18] conducted a study with 120 physically inactive volunteers and observed an increment in VO_2 by 14.71% among men and 22.29% among women. Most studies have used the cycle ergometer test for this comparison, and reported VO_2 values 5-11% lower than those obtained from treadmill tests. However, in the American continent, the treadmill exercise test is the most commonly performed, mainly the BP.[19] In our study sample, results obtained from the treadmill test were even higher, maybe because we have used a treadmill ergometer. Similar to our study, Fairbam et al.,[17] also reported the biggest differences in VO_2 max among men, although they used an ergometer cycle to assess aerobic capacity. In a nation-wide Brazilian study published in 2011, Peserico et al.,[20] assessed aerobic capacity in trained female runners, by measuring VO_2 max both by direct method and indirectly by Foster's formula (1996) using a treadmill ergometer. The authors found that VO_2 was significantly underestimated when estimated by the prediction formula as compared with direct analysis of gases, indicating substantial limitations of the approach in determining functional capacity in these individuals.[20] Most of previous studies reported contrasting results, showing an overestimation of the VO_2 max indirectly estimated by regression and conventional ergometer test, regardless of the protocol and type of ergometer used.[21,22] Also, according to Santos[21] and Rondon et al.,[22] the results of VO_2 max obtained by indirect measurement are influenced by cardiorespiratory fitness of the study subjects. In these studies, greater VO_2 max values, estimated by the ACSM formula, were higher in individuals with poor cardiorespiratory fitness than in those with moderate fitness. These findings suggest that both the type of exercise test protocol and the type of prediction formulas may affect VO_2 estimation, by either overestimating or underestimating the true values. Our study was the first to perform treadmill ergometer exercise test in a group composed of both men and women, young and older subjects, physically active and inactive individuals for a comparative analysis of VO_2 max directly measured by CPET with that estimated by formulas.

VO_2 prediction equations derive from studies conducted in North America and Europe. Thus, the results may not be extended to other populations, as pointed by Ong et al.,[15] The formula used in the BP[1] was developed in a North American population in the 70's. When applied to the Brazilian population, the formula was found to overestimate VO_2 max values. According to Neder et al.,[18] this difference is common in studies using prediction equations for VO_2 max. We have recently published reference values for CPET in our population,[23] and a direct and unequivocal measurement of VO_2 gives us the chance to evaluate actual cardiorespiratory fitness of each individual by sex and age range.

The fact that the tests were performed on different days, using different protocols (Bruce versus ramp) may have been a limitation of this study. However, the hemodynamic parameters obtained from the tests were not significantly different, allowing us to infer that there was a similar cardiorespiratory and physical performance by the subjects in both tests. In the present study, we found a significant discrepancy in the classification of cardiorespiratory fitness by the AHA and by the VO_2 prediction formulas. The BP is more widely used for VO_2 calculation in clinical practice in Brazil than spiroergometric tests. Therefore, a possible overestimation of VO_2 values by the BP results in an erroneous evaluation of the cardiorespiratory fitness of the individuals. This, in turn, may represent a lack of opportunity to advise young individuals about the negative effects of a sedentary lifestyle and a low cardiorespiratory capacity.

Conclusion

The assessment of aerobic capacity is an important risk stratification tool in young, physically inactive subjects. Prediction formulas of VO_2 max, derived from cycle or treadmill exercise tests using the BP, are not able to reproduce the true cardiorespiratory capacity in this population, overestimating it. The present study draws attention to the need for an accurate measurement of fitness in this group by CPET, aiming at enabling early warning of these individuals about the risks of a sedentary lifestyle.

Author contributions

Conception and design of the research: Rocha Neto AM, Herdy AH. Acquisition of data: Rocha Neto AM, Herdy AH, Souza P. Analysis and interpretation of the data: Rocha Neto AM, Herdy AH, Souza P. Statistical analysis: Rocha Neto AM, Herdy AH, Souza P. Obtaining financing: Rocha Neto AM. Writing of the manuscript: Rocha Neto AM, Souza P. Critical revision of the manuscript for intellectual content: Rocha Neto AM, Souza P.

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

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ORIGINAL ARTICLE

Cardiopulmonary Exercise Testing in Patients with Implantable Cardioverter-Defibrillator: A Retrospective Study

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Abstract

Background: Cardiopulmonary exercise testing is widely used in the evaluation of patients with left ventricular dysfunction, and some of these patients have an implantable cardioverter-defibrillator (ICD). However, this test presents specific challenges because of the susceptibility to ventricular arrhythmias during maximal levels of exercise.

Objective: To evaluate the safety of cardiopulmonary exercise testing in patients with ICD.

Methods: The study included patients with ICD who underwent cardiopulmonary exercise testing between 2007 and 2015. The tests were completed once the electronic devices were programmed. The maximum allowed heart rate reached during exercise was 10 beats below the first therapy zone programmed.

Results: The study included 69 patients with mean age 53.7 ± 10.8 years, including 68% men. Exercise time was 8.7±2.3 minutes, with peak oxygen consumption of 13.3 ± 4.3 $ml.kg^{-1}.min^{-1}$. Peak heart rate was 62.9 ± 13.4% of the maximum rate predicted, with all patients taking specific medication. Ventricular arrhythmia was observed in 29% of the patients, and paired ventricular extrasystoles, ventricular bigeminism or non-sustained ventricular tachycardia were observed in only 14.5% of the patients. There was no sustained ventricular arrhythmia resulting in ICD therapy or other complications, such as inappropriate therapies. The frequency of severe events was 0%, 95% CI (0 – 5.2%).

Conclusion: In the sample of patients evaluated, the cardiopulmonary exercise testing was shown to be safe during its performance in a hospital setting, following the safety standards. (Int J Cardiovasc Sci. 2019;32(4):368-373)

Keywords: Cardiovascular Diseases; Sudden Cardiac Death; Left Ventricular Dysfunction; Breathing Exercise; Defibrillators, Implantable; Arrhythmias, Cardiac.

Introduction

Sudden cardiac death (SCD) is a major problem in patients with cardiovascular disease and it is mostly caused by ventricular arrhythmia.[1] The pathophysiology of SCD involves an electrical instability event with induction of ventricular tachycardia (VT), which leads to ventricular fibrillation (VF) in 80 to 85% of the cases. Since the first report of implantable cardioverter-defibrillator (ICD) implantation in 1980, treatment of ventricular tachyarrhythmia underwent major changes. Initially used in patients surviving SCD, ICD was also recommended as a preventive therapy in patients at high risk for arrhythmic events.[1-5]

Cardiopulmonary exercise testing (CPET) adds information on ventilatory dynamics and gas exchange during exercise, allowing greater precision in the evaluation of the aerobic functional capacity of individuals

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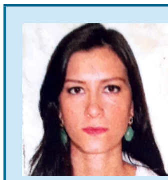

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Original Article

with ICD. It is equally important in patients with left ventricular dysfunction, for prognostic evaluation, therapeutic control, prescription of physical activity and indication of cardiac transplantation.[6]

In patients with ICD, CPET should be preferably performed in a hospital setting. It is essential to be aware of basic parameters and implantable device programming. The physician should be aware of the heart rate zones where ICD therapies are programmed, in order to avoid inappropriate therapies. This type of therapy is harmful to the patient, due to its psychological and clinical implications.[7,8]

Literature data demonstrate that symptom-limited exercise testing causes ventricular extrasystole in more than half of patients with coronary artery disease.[9-11] However, 20% of exercise-induced arrhythmias are manifested as paired ventricular extrasystoles or nonsustained VT.[9] Young et. al.,[12] reported complications, such as VT, VF and bradycardia, requiring immediate medical treatment in 24 out of 263 patients (9.1%) at high risk for ventricular arrhythmias during maximal exercise testing. In another study in which 107 exercise tests were evaluated in individuals with ICD, ventricular arrhythmias requiring therapy or death[13] were not observed.

Few data are available on the responses and complications associated with CPET in patients with ICD. This study aimed at evaluating the incidence of complications during this test in this population. To do this, the occurrence of ventricular arrhythmias (isolated extrasystoles, paired extrasystoles, ventricular bigeminism and ventricular tachycardia), appropriate therapies, inappropriate therapies, cardiorespiratory arrest during or immediately after exercise, hemodynamic instability, need for hospital admission due to cardiovascular complications and death were observed. Besides, other variables such as metabolic, ventilatory and cardiovascular response, symptoms, duration of exercise achieved and maximal oxygen consumption (VO_2) were also reported.

Methodology

This is a retrospective unicentric observational study conducted between 2007 and 2015, including which male and female patients with ICD for more than three months, for primary or secondary prevention of SCD, who underwent cardiopulmonary exercise testing as recommended by the attending physician.

CPET was performed using a calibrated breath by breath gas analyzer, Ultima, Medical Graphic Corporation (MGC), performed according to traditional guidelines. Continuous 12-lead electrocardiographic monitoring and recording system modified by Mason and Likar, *Tecnologia Eletrônica Brasileira* (TEB), model APEX 2000, was used throughout the test. Measurement of arterial saturation was performed by pulse oximetry (CMS50D) and blood pressure measurement by aneroid sphygmomanometer (Welch Allyn). In addition, latex insulating gloves were used by the medical and technical team throughout the test in order to avoid potential electrical therapies. A magnet was available in the test room in case of inappropriate ICD therapies.

The patients were submitted to ICD programming analysis by means of telemetry prior to the CPET. Telemetry was performed using specific equipment related to the manufacturer of the device, in order to obtain detailed programming information, such as VT and VF zones, and the relevant therapies. No therapy was changed or disabled before the test.

For each patient, a heart rate cutoff value was determined, based on individual device programming. The maximum heart rate established for the protocols applied during exercise was 10 beats below the first VT zone (VT1) programmed in the ICD. In the VT1 zone, established during ICD programming, usually only the monitoring of electrocardiographic events occurs. In the second VT or VT2 zone, there are three usual extra-stimulus series and in case of non-reversal, analyzed by the device algorithm, sequential joule discharges are automatically applied. In the VF zone, series of joule discharges are triggered, aiming at arrhythmia interruption.

The tests were performed with ramp protocols individually applied according to the estimated functional capacity of each patient, physician's experience and predicted VO_2 calculated using the Wasserman algorithm.[14]

Traditionally, the criteria used are exhaustion, dyspnea, angina or dizziness, pathological abnormalities in blood pressure, sustained ventricular arrhythmia, orthopedic complaints and, in patients with interpretable rest electrocardiogram, ST segment depression greater than 3.0 mm or ST segment elevation greater than 1.0 mm. All tests would be discontinued if the heart rate reached 10 beats below the programmed VT1 zone as a safety measure intended to avoid inappropriate therapies.

Data analysis was performed by IBM SPSS software version 19 and Microsoft Office Excel 365 was used for data tabulation. The quantitative variables were presented by mean and standard deviation and qualitative variables by absolute frequency and percentage, then descriptive analysis of the data was performed. A 95% confidence interval (95% CI) was calculated using the binomial test. To test whether the frequency of serious events was smaller than 10%, exact binomial test was used.

Results

In this study, 69 patients with ICD were included. Table 1 shows the characteristics of the study population.

Exercise time was 8.7 ± 2.3 minutes, with peak VO_2 of 13.3 ± 4.3 $ml.kg^{-1}.min^{-1}$. The heart rate reached at the peak of exercise was 105.9 ± 22.9 beats per minute (bpm), corresponding to 62.9 ± 13.4% of the upper limit for the predicted age. All tests were discontinued due to patient exhaustion. Mean final speed was 3.9 ± 0.9 km/h, while mean final inclination was 11.2 ± 3.1% in this protocol. The other CPET variables are presented in Table 2.

The heart rate programmed for the VT1 zone in the ICD was 150 ± 9.1 bpm on average. During exercise, the patients achieved 71.8% of the heart rate programmed in the VT1 zone, 61.7% in the VT2 zone and 53.4% in the VF zone.

Chart 1 shows the arrhythmias found in the study. The following were considered as complex arrhythmias: paired ventricular extrasystoles, ventricular bigeminism, ventricular tachycardia. There were no sustained ventricular arrhythmia resulting in ICD therapy or inappropriate therapies. Also, there was no cardiorespiratory arrest, hemodynamic instability during or immediately after exercise or hospital admissions due to cardiovascular complications or death. The frequency of severe events was 0%, 95% CI (0 – 5.2%). Thus, we have that the frequency of serious events will be less than 10%.

Table 1 - Baseline characteristics of the study population

Variable	Value
Age (years)	55 ± 10
Gender (%)	
Male	68.1
Female	31.9
BMI (kg/m^2)	25.5 ± 4.8
Diagnosis (%)	
Ischemic cardiomyopathy	40.6
Dilated cardiomyopathy	56.5
Hypertrophic cardiomyopathy	2.9
Resting ECG (%)	
Pacemaker rhythm	40.6
Sinus rhythm	15.9
Left bundle branch block	15.9
Right bundle branch block	7.2
Electrically inactive zone	7.2
Atrial fibrillation	2.9
Medication (%)	
Beta-blockers	94.2
Calcium channel blockers	5.8
ACEI or ARB	87.0
Diuretics	89.9

BMI: body mass index; ECG: electrocardiogram; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Discussion

CPET is a fundamental test recommended by consensus for the evaluation of patients with left ventricular dysfunction, both for prognostic characterization and for therapeutic control and assistance in the indication for cardiac transplantation.[15,16] However, there is little information regarding the safety of this test in individuals with ICD. As we know, CDI therapy has become a standard indication in this population, both for primary and secondary prevention.[1,3,4] Therefore, the importance of this study was to check the safety of CPET in this type of population.

The major concern in performing CPET in patients with ICD is the risk of complications such as ventricular arrhythmias during exercise, resulting in therapies by the device.[7,17] Another risk inherent in the procedure is that it triggers inappropriate therapies by the implantable electronic device. It is known that unnecessary shocks should be avoided, while rapid appropriate therapy for ventricular tachyarrhythmia should be affordable. Inappropriate ICD therapy is not only traumatic for

Table 2 - Variables analyzed during the CPET

Variable	Value
SBP at rest (mmHg)	117.3 ± 22.7
SBP (mmHg)	134.1 ± 31.0
HR (bpm)	68.3 ± 10.8
Peak HR (bpm)	105.9 ± 23.0
Peak VO_2 ($ml.min^{-1}$)	973 ± 361
Peak VO_2 ($mL.kg^{-1}.min^{-1}$)	13.3 ± 4.3
Predicted VO_2 (%)	49 ± 16.7
Peak LV ($L.min^{-1}$)	53.8 ± 50
Peak VE/VO_2	51 ± 17.5
Peak VE/VCO_2	45 ± 14.4
Slope VE/VCO_2	42.4 ± 18.1
Peak RER	1.12 ± 0.14
Peak pulse O_2 ($ml.beat^{-1}$)	10.3 ± 3.5
T1/2 (seconds)	150 ± 46.9
OUES	800 ± 479

SBP: systolic blood pressure; HR: heart rate; VO_2: oxygen consumption; RER: respiratory exchange ratio; OUES: oxygen uptake efficiency slope; VE/VCO_2: ventilatory equivalent for CO_2; VE/VO_2: ventilatory equivalent for oxygen.

patients but it is also associated with an increased risk of death.[18]

The ICDs present algorithms for the detection of ventricular tachyarrhythmia and discriminatory algorithms for supraventricular tachycardia. However, these may fail and result in inappropriate therapies, such as supraventricular tachycardia therapy. To avoid this risk, during CPET, it was established that the heart rate during exercise should have the zone of the first programmed therapy as a limit of attention. Hence the importance of prior knowledge of device programming by telemetry.

Although exercise may predispose to ventricular arrhythmia, which is common in heart failure, the overall frequency of arrhythmia during exercise testing is low. In this study, we demonstrated that CPET is safe because no severe arrhythmia has been identified. This is consistent with an earlier study by Chinnaiyan et al.,[13] who evaluated 84 patients (mean age 67 ± 12 years; 76% men). Participants underwent 107 stress tests, including 44 exercises and 63 pharmacological evaluations (22 dobutamine, 41 dipyridamole). No ICDs were inactivated before the test. Four patients presented nonsustained self-limited VT at the peak of stress. None of them had sustained VT requiring therapy. There were no deaths or hospital readmissions due to ventricular arrhythmias.

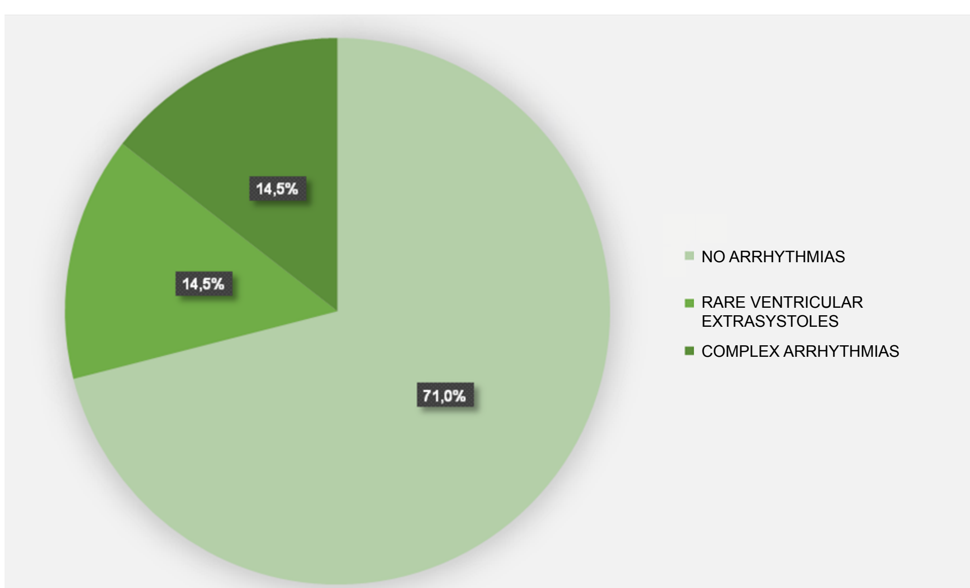

Chart 1 - Incidence of ventricular arrhythmias in the study population.

Voss et al.,[19] also demonstrated the safety of exercise testing in 400 patients with ICD. Of these, 200 patients performed a ramp protocol with an initial load of 0 W increased by 15 W every minute. Another 200 patients with ICD had a slightly modified ramp protocol with an initial workload of 0 W, but with capacity increased by 15 W every 2 minutes. The study population consisted mainly of patients with ischemic heart disease (63%). Atrial fibrillation was present in 16% of the individuals. Left ventricular ejection fraction was 28%±8. In this cohort of patients, no sustained ventricular arrhythmia and no death occurred during or after the exercise testing. No inappropriate shock was observed.

In this study, during CPET, the heart rate of patients did not reach the device therapy zones, most likely because they were on negative chronotropic medications. Although safe heart rate limits were set for each patient, most tests were discontinued due to exhaustion before the heart rate limit was reached. Although the tests were discontinued at a heart rate below the ICD programming, it is observed that the mean RER was greater than 1.1, demonstrating maximum exercise.[6]

In the current study, ventricular arrhythmias were observed in 29% of the individuals, including paired ventricular extrasystoles, ventricular bigeminism or nonsustained VT in 14.5%. However, there were no sustained ventricular arrhythmias that resulted in ICD therapy or inappropriate therapies. There was no cardiorespiratory arrest, hemodynamic instability during or immediately after exercise, or hospital admission due to cardiovascular complications. As an implication for clinical practice, CPET performed in patients with ICD was safe when performed in a hospital setting, with prior knowledge of device programming and respecting the heart rate of the therapy zones.

The limitations of this study refer to the small number of patients included which, to some extent, is justified by the fear of referring patients with implantable devices to perform CPET, and because it is a retrospective study. As implications for future research, further prospective studies with larger samples should be conducted in order to obtain more robust results.

Conclusion

CPET in patients with ICD is a safe procedure in terms of severe acute complications, with low incidence of ventricular arrhythmia. Physicians performing CPET in these specific patients must be aware of ICD settings to limit heart rate below the first programmed therapy zone. There is no need for changes in device programming, such as deactivation of therapies, prior to this test.

Author contributions

Conception and design of the research: Mizzaci CC, Meneghelo RS, Mastrocola LE. Acquisition of data: Mizzaci CC, Fagundes TTS, Malafaia FL, Felicioni SP, Buglia S, Hossri CAC, Ferraz AS, Buchler RDD. Analysis and interpretation of the data: Mizzaci CC, Fagundes TTS, Malafaia FL, Felicioni SP, Buglia S, Hossri CAC, Ferraz AS, Buchler RDD, Meneghelo RS, Mastrocola LE. Statistical analysis: Mizzaci CC, Malafaia FL, Felicioni SP, Buglia S, Hossri CAC, Ferraz AS, Buchler RDD. Writing of the manuscript: Mizzaci CC, Fagundes TTS, Malafaia FL, Felicioni SP, Buglia S, Hossri CAC, Ferraz AS, Buchler RDD, Meneghelo RS, Mastrocola LE. Critical revision of the manuscript for intellectual content: Mizzaci CC, Fagundes TTS, Meneghelo RS, Mastrocola LE.

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

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ORIGINAL ARTICLE

Speed and Grade Increment During Cardiopulmonary Treadmill Testing: Impact on Exercise Prescription

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Abstract

Background: Maximal oxygen uptake (VO_2max) and both first (VT_1) and second (VT_2) thresholds have been used as reference points for exercise prescription in different populations.

Objective: We aimed to test the hypothesis that exercise prescription, based on VTs determined by treadmill cardiopulmonary exercise testing (CPET), is influenced by the rate of increase in treadmill workload.

Methods: Nine healthy individuals underwent two CPETs, followed by two sessions of submaximal exercise, both in randomized order. For the "speed" protocol, there was an increment of 0.1 to 0.3 $km.h^{-1}$ every 15s. The "grade" incremental protocol increased 1% every 30s and 0.1 $km.h^{-1}$ every 45s. This was followed by submaximal exercise sessions lasting 40min at an intensity corresponding to heart rate (HR) between the VT_1 and VT_2.

Results: The "speed" protocol resulted in higher VT_1 ($p = 0.01$) and VT_2 ($p = 0.02$) when compared to the "grade" incremental protocol, but there was no effect on VO_2max. The target HR for the submaximal exercise sessions was higher in the "speed" protocol compared to the "grade" incremental protocol ($p < 0.01$) and remained stable during the two steady-state exercise sessions. Blood lactate remained stable during the submaximal exercise sessions, with higher values observed during the "speed" protocol than those "grade" incremental protocol ($p < 0.01$).

Conclusions: Compared to a grade-based protocol, a speed-based protocol resulted in higher VT_1 and VT_2, which significantly affected cardiorespiratory and metabolic responses to prescribed exercise intensity in healthy young adults. (Int J Cardiovasc Sci. 2019;32(4):374-383)

Keywords: Cardiovascular Diseases; Exercise Test; Exercise Tolerance; Oxygen Consunption.

Introduction

Cardiopulmonary exercise testing (CPET) provides valuable diagnostic and prognostic information for healthy subjects and patients with cardiovascular disease[1,2] and has long been used in the assessment of athletic performance, as well as for various research applications.[3] CPET responses have also been extensively used for the prescription of exercise intensity during aerobic training.[4] In this context, maximal oxygen uptake (VO_2max) and, both first (VT_1) and second (VT_2) thresholds, have been used as reference points for

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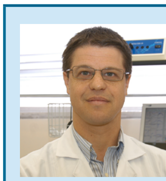

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exercise prescription among both athletes and patients with cardiovascular disease.[4-7]

Tests based on ramp protocols are recommended for CPET because they generally provide a linear increase in VO_2 relative to workload, particularly when performed on the cycle ergometer.[8-11] The VT_1 and the VT_2 occur at similar VO_2, independent of the rate of increase in exercise intensity on the cycle ergometer[12,13] and the same is true for the determination of the VT_1 on the treadmill.[14] Regardless of differences between cardiorespiratory fitness measured on a cycle ergometer and a treadmill, the choice of the ergometer may influence VT_1 determination.[14,15]

In the Americas, the treadmill is the exercise mode of choice in clinical settings.[1,2,16] When using the treadmill, it can be difficult to achieve a linear response in metabolic rate because of the walk-run transition,[17] the rate of increase in speed and grade,[18-20] or handrail support and its effect on economy.[14] Moreover, there is little information available on the effects of different treadmill ramp protocol increments on the detection of the VT_1 and VT_2.[14,15]

Changes in speed and/or grade may be used to develop an appropriate treadmill ramp protocol in efforts to make the work rate increments as linear as possible.[20] In this regard, work rate increments can have notable effects on the response to exercise due to the disproportionate interaction between muscle activation,[21-23] kinematic variables related to gait, and oxygen uptake (VO_2) kinetics;[24] and each of these factors can significantly influence VO_2 during exercise. Moreover, the impact of the type of increment during CPET performed on a treadmill with regard to exercise prescription has not been previously studied. Therefore, this study was conducted to compare the effects of two treadmill ramp protocols on the detection of VT_1 and VT_2. We applied one protocol mainly using speed increments and another using mainly grade increments. In addition, we evaluated the steady-state response to exercise prescription based on the measured ventilatory thresholds from the two protocols.

Material and methods

Participants

Four male and five female subjects, aged 29 ± 6 years [95% CI = 25; 33], height 170 ± 8 cm [95% CI = 165; 175], and weight 65 ± 8 kg [95% CI = 60; 71], participated in the study. All subjects were active and otherwise healthy as determined by medical history, physical examination, and resting and exercise electrocardiograms. None were taking medications. The subjects did not vary their activity levels during the testing period. All rights and privileges were honored in accordance with an established human subject's protocol, and informed consent was obtained. The ethics committee of the institution approved the protocol.

Protocol

The protocol included two maximal incremental CPETs and two submaximal exercise sessions, performed on different days; the type of increment was chosen in random order. All tests were performed in a comfortable laboratory environment, with a minimum of 48 hours between tests. The CPET system underwent gas and volume calibration before each exercise test. No handrail support was allowed during the tests.[3] The randomization of protocols was performed by an independent researcher using the software Rx 64 version 13. The protocol randomized for the first incremental CPET was the same for the first submaximal exercise session.

Incremental cardiopulmonary exercise tests

Two incremental protocols were used for determination of VT_1, VT_2, and VO_2max. The subjects were positioned on the treadmill (Inbramed, TK10200, Porto Alegre, Brazil) and initially walked 2.0 $km.h^{-1}$ and 1% grade for 2 min. The speed protocol then increased to 5.5 $km.h^{-1}$ and 1% of grade and increments of 0.1 to 0.3 $km.h^{-1}$ were added every 15s (Figure 1A), with a constant grade (Figure 1C). If the maximal speed of the treadmill (16 km/h) was attained, exercise intensity was further increased by grade increments of 0.5% per 30s. The grade protocol started at 5.5 $km.h^{-1}$ and 1% of grade, with increments of 0.1 $km.h^{-1}$ every 45s (Figure 1B) and 1% increases in grade every 30s (Figure 1D). Subjects exercised until volitional fatigue. During recovery from the incremental tests, subjects walked on the treadmill at 2 $km.h^{-1}$ for 7 min. Fingertip blood samples were collected at 1, 3, 5, and 7 min for the determination of maximal blood lactate during recovery.

Cardiorespiratory variables

Heart Rate (HR) was determinate based on the R-R intervals from a twelve-lead electrocardiogram

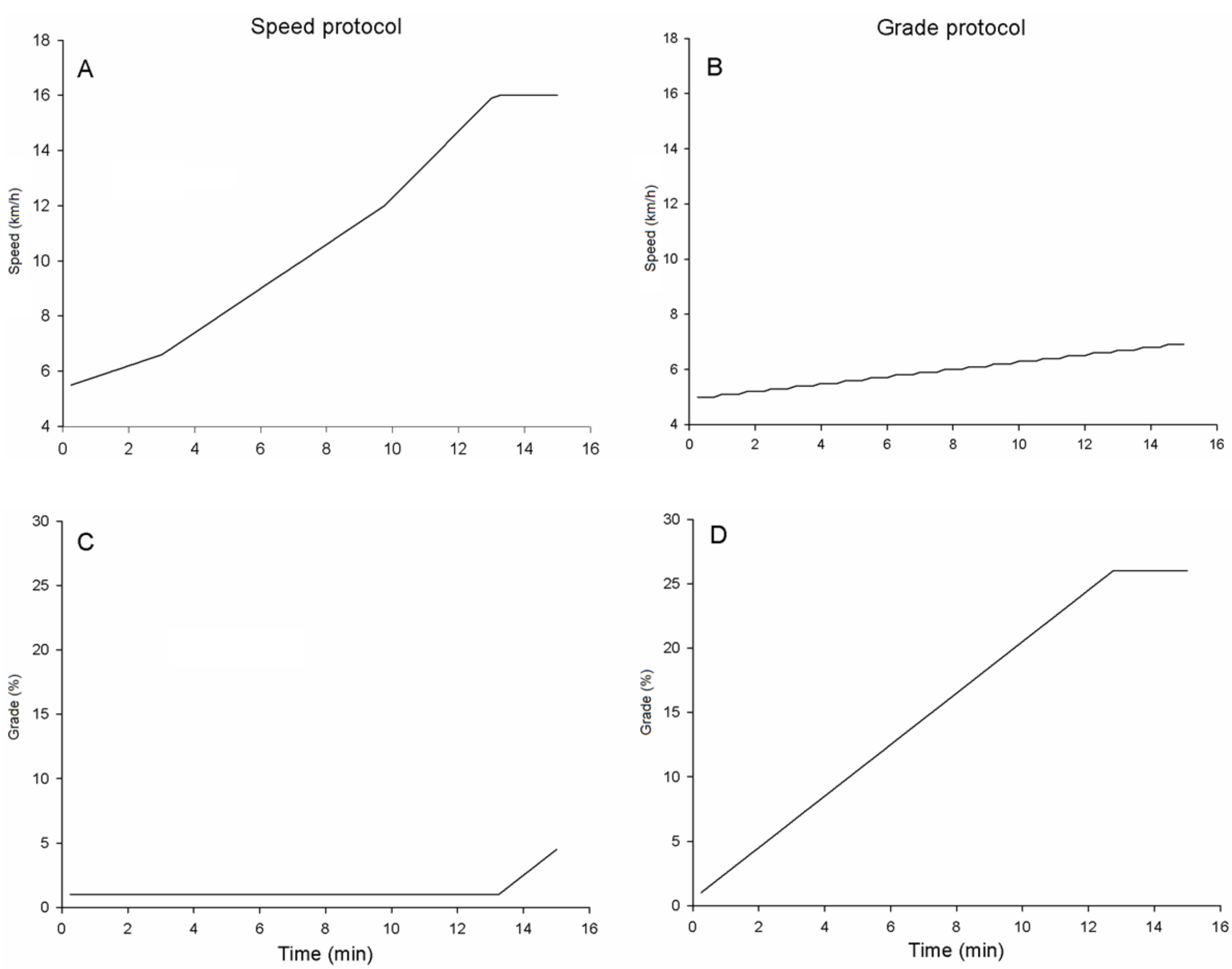

Figure 1 - Increments in speed and grade during the speed and grade protocols.

(Micromed-Biotecnologia, Brasília, Brazil). Perceived exertion using the 0 to 10 Borg scale[25] was obtained every 2 min. Gas exchange variables were measured breath-by-breath by a validated system (Metalyzer 3B, CPET System, Cortex, Leipzig, Germany) and expressed in 20s intervals.[26] VO_2max was defined as the highest value measured for a period of 20s during the CPET. VT_1 and VT_2 were determined by visual inspection. VT_1 was identified as the VO_2 or HR immediately before a systematic increase in the ventilatory equivalent for oxygen (minute ventilation [VE] / VO_2), without an increase in the ventilatory equivalent for carbon dioxide (VE / carbon dioxide output [$\dot{V}CO_2$]).[3,27] The V-slope method was also used to confirm the VT_1. VT_2 was identified as the point immediately before a systematic increase in VE/$VECO_2$, usually at the same time that the end-tidal CO_2 decreased systematically.[3] All ventilatory thresholds and VO_2max evaluations were determined by the same experienced researcher, who was blinded to the protocols.

Exercise prescription

The exercise intensity during the submaximal exercise sessions was based on the HR corresponding to the mean point between VT_1 and VT_2, obtained from the speed and grade protocols. During submaximal exercise sessions, the subjects underwent 10 min of walking-running in order to reach the target HR, followed by 30 min running at target HR. The treadmill was maintained at a constant level during the submaximal exercise sessions and speed was adjusted to maintain a stable HR. Rather than applying a constant workload, we chose to maintain a stable HR because the individuals exercised at intensities above the VT1, where the steady state is not established with a constant work rate.[13,28] Moreover, the target HR is frequently used to monitor aerobic training exercise sessions in practice.[4] During the submaximal exercise sessions, HR and gas exchange responses were continuously monitored as described above. Perceived exertion and blood lactate samples were obtained at rest and every 10 min.

Blood lactate analysis

Twenty-five μL fingertip blood samples were mixed with 50μL of 1% sodium fluoride. This solution was then frozen for later analysis of blood lactate concentration using a dedicated analyzer (YSI 1500-L Sport, Yellow Springs, Ohio, USA).

Statistical analysis

Based on a previous study,[29] a minimum sample size was estimated to be 7 subjects, using a power of 90% and an alpha of 0.05 to detect a 10% difference (16 bpm) in the prescribed HR between protocols. Two subjects were added to the sample to account for dropouts. We used the Kolmogorov-Smirnov test to assess the normality of variables. Descriptive data are presented as mean (M) and standard deviations (SD) and 95% confidence interval (95% CI). To evaluate intra-observer reproducibility in the detection of VT_1, VT_2, and VO_2max, gas exchange curves of all tests were reviewed by the same blinded investigator twice within a one-week interval. Paired t tests, Pearson's correlation coefficients, and Bland-Altman analyses[30] were used to assess intra-observer reproducibility. The responses to incremental and submaximal exercise tests were compared using paired t tests for two means and by generalized estimating equations for three or more means. When appropriate, multiple comparisons were evaluated using Bonferroni correction. The calculations for sample size, planning for randomization and Bland-Altman analyses were performed using R 3.0 (Free Software Foundation's GNU Project), and all other analyses were performed using SPSS 21.0 software (IBM, New York, USA).

Results

All subjects completed the incremental exercise tests and the exercise sessions without complications. For the intra-observer reproducibility analysis, there were no significant differences in VO_2 ($ml.kg^{-1}.min^{-1}$) between the two evaluations in terms of detection of VT_1 ("speed": 27.5 ± 7.4 [95% CI = 21.8; 33.2] vs 26.4 ± 7.2 [95% CI = 20.9; 31.9], p = 0.11; "grade": 24.9 ± 6.1 [95% CI = 20.2; 29.6] vs 25.9 ± 6.2 [95% CI = 21.1; 30.7], p = 0.16); VT_2 ("speed": 32.4 ± 9.2 [95% CI = 25.3; 39.5] vs 32.5 ± 9.2 [95% CI = 25.4; 39.6], p = 0.85; "grade": 29.7 ± 6.5 [95% CI = 24.6; 34.7] vs 30.9 ± 6.9 [95% CI = 25.6; 36.2], p = 0.08), and VO_2max ("speed': 35.8 ± 10.8 [95% CI = 27.5; 44.2] vs 35.8 ± 10.8 [95% CI = 27.2; 44.2], p = 0.99; "grade": 34.7 ± 9.7 [95% CI = 27.2; 42.1] vs 34.7 ± 9.8 [95% CI = 27.2; 42.1], p = 0.99). Intra-observer agreement results are presented in Figure 2. The two protocols exhibited strong correlation coefficients between the first and second evaluations, varying from 0.95 to 1.00 (1st and 3rd columns of Figure 2). Likewise, Bland-Altman plots demonstrated values within the acceptable limits of agreement between the first and second evaluations (2nd and 4th columns of Figure 2).

Table 1 shows the incremental exercise test results performed according to the speed and grade protocol. Resting HR and blood lactate were similar between the protocols. At peak exercise, HR was higher with the speed protocol, while no differences were observed between VO_2max, VCO_2max, and VEmax. Peak respiratory exchange ratio was lower with the speed protocol, as well as perceived leg exertion. Maximal blood lactate concentrations and time to maximal blood lactate concentration during recovery were similar with the two protocols.

Figure 3 shows VO_2 and HR responses to incremental exercise according to VT_1, VT_2, the mean point between VT_1 and VT_2, and VO_2max. VO_2 at these 4 intensities was higher with the speed protocol (Figure 3A). When expressed as a percentage of VO_2max, these differences were also statistically significant (Intensity: $P < 0.01$; Protocol: $P = 0.01$; Interaction: $P = 0.18$). The "speed" protocol resulted in higher HR (bpm) for the VT1 (153 ± 14 [95% CI = 146; 168] vs 144 ± 8 [95% CI = 137; 150], $p < 0.01$), the VT_2 (176 ± 7 [95% CI = 171; 182] vs 165 ± 8 [95% CI = 159; 171], $p < 0.01$), the mean point between VT_1 and VT_2 (169 ± 9 [95% CI = 162; 176] vs 156 ± 8 [95% CI = 150; 162], $p < 0.01$), and peak exercise (189 ± 8 [95% CI =

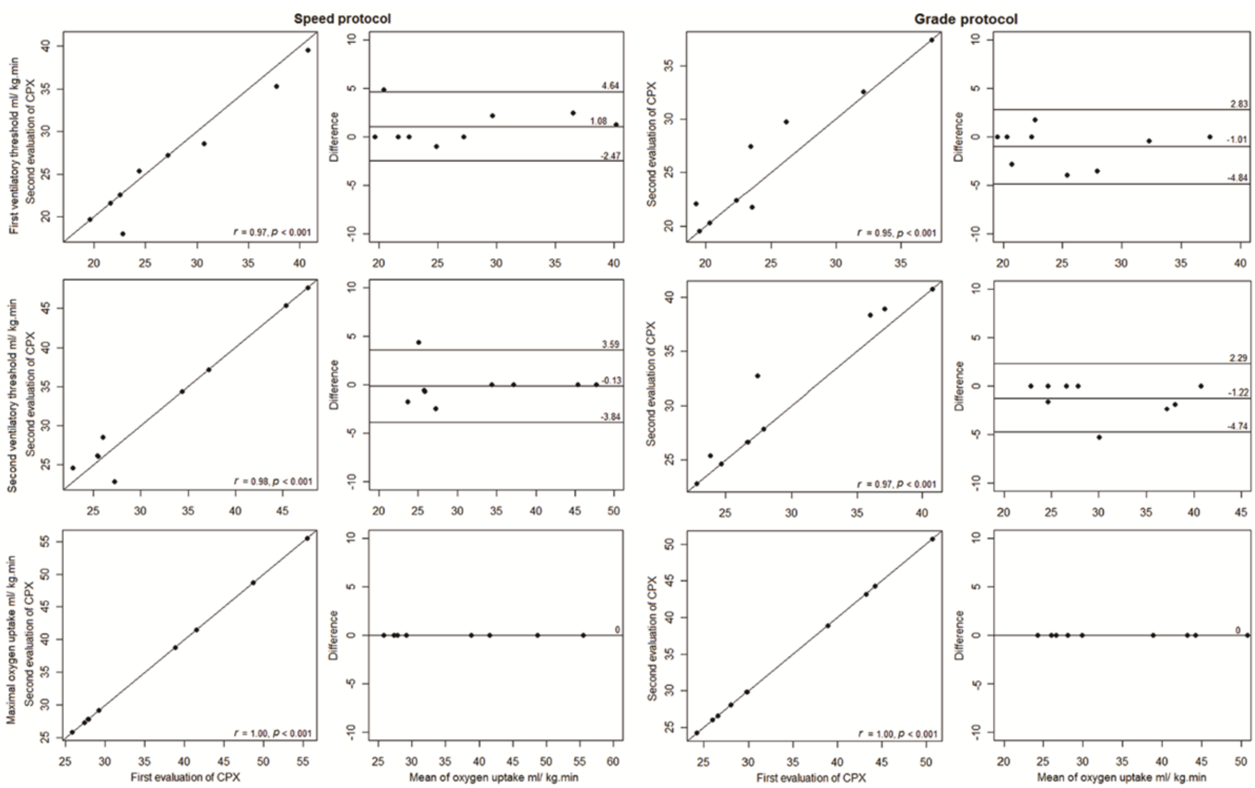

Figure 2 - Validity testing of the first and second evaluations of ventilatory thresholds and maximal oxygen uptake. The first and third columns of the graphs show scatter plots and correlation coefficients. The diagonal lines represent the identity lines. Graphs on the second and fourth columns are Bland-Altman plots. The horizontal lines represent upper limit, bias and lower limit for difference between the two evaluations. CPET: cardiopulmonary exercise test.

183; 195] vs 183 ± 7 [95% CI = 178; 188], $p < 0.01$) (Figure 3B). The responses were also significantly different when HR was analyzed as a percentage of the peak (Intensity: $p < 0.01$; Protocol: $p < 0.01$; Interaction: $p = 0.01$).

The submaximal exercise sessions were analyzed from 10 to 40 min, corresponding to the steady-state phase of exercise (Figure 4). Similarly to the comparison of protocols, subjects exhibited stable HR responses (Figure 4A), with higher levels observed during the session based on the speed protocol. Blood lactate concentrations (Figure 4B) were stable after 20 min, with higher concentrations observed during the speed protocol. To maintain a stable HR, speed was progressively reduced (Figure 4C), resulting in a reduction of VO_2 (Figure 4D). VE/VO_2 increased progressively (Figure 4E), but there were no significant differences between protocols. The respiratory exchange ratio decreased progressively (Figure 4F), with significant differences between the protocols. Perceived rates of respiratory (Figure 4G) and leg (Figure 4H) exertion were significantly higher during the sessions based on the speed protocol.

Discussion

The major finding of the present study was that a treadmill protocol based mainly on speed increments resulted in higher VO_2 and HR corresponding to the VT_1 and VT_2 when compared to a treadmill protocol based mainly on grade increments. Moreover, the choice of the protocol had a significant impact on exercise prescription based on ventilatory thresholds. To our knowledge, this is the first report describing the impact of the type of increment during CPET performed on the treadmill on aerobic exercise prescriptions.

Previous studies have shown that, when the cycle ergometer is used for the detection of ventilatory

Table 1 - Ergometric data, cardiorespiratory, and metabolic results at rest and incremental exercise test with the speed and grade protocol

	Speed (n = 9) M ± SD (95% CI)	Grade (n = 9) M ± SD (95% CI)
Rest		
Heart rate (beats.min^{-1})	72 ± 12 (65; 79)	73 ± 12 (66; 81)
Blood lactate (mmol.L^{-1})	1.79 ± 0.62 (1.41; 2.17)	1.69 ± 0.59 (1.33; 2.06)
Peak exercise		
Time (s)	694 ± 206 (574; 821)	568 ± 151 (483; 662)*
Speed (km.h^{-1})	13.5 ± 2.5 (12.0; 14.9)	6.2 ± 0.3 (6.0; 6.4)*
Grade (%)	2.6 ± 2.6 (1.2; 4.3)	19.7 ± 4.9 (16.8; 22.7)*
Heart rate (beats.min^{-1})	189 ± 6 (184; 193)	183 ± 7 (179; 187)*
Oxygen uptake (ml.kg^{-1}.min^{-1})	35.8 ± 10.8 (29.7; 43.2)	34.7 ± 9.7 (28.9; 41.0)
Carbon dioxide output (L.min^{-1})	2.69 ± 1.0 (2.05; 3.28)	2.88 ± 1.16 (2.16; 3.54)
Minute ventilation (L.min^{-1})	102 ± 33 (81; 122)	106 ± 34 (84; 127)
Respiratory exchange ratio	1.14 ± 0.11 (1.06; 1.20)	1.25 ± 0.11 (1.17; 1.31)
Perceived exertion		
Respiratory	9 ± 2 (8; 10)	9 ± 1 (8-; 10)
Legs	8 ± 2 (7; 10)	9 ± 1 (9; 10)*
Maximal blood lactate during recovery		
Blood lactate (mmol.L^{-1})	9.07 ± 2.29 (7.30; 10.83)	9.95 ± 2.25 (8.21; 11.68)
Time to maximal (min)	2 ± 2 (0.5; 3)	3 ± 2 (1; 5)

*M: mean; SD: standard deviation; 95%CI: 95% confidence interval. * $p < 0.01$.*

thresholds, the results are independent of the rate of increment in power output.[9,31,32] The detection of VT_1 is also not affected by the rate of increment in exercise intensity on the treadmill.[14] Despite the fact that the treadmill is the ergometer of choice in many clinical settings, no study has previously evaluated the impact of changing grade versus speed on the detection of ventilatory thresholds using the treadmill. Kinderman et al.,[15] evaluated the influence of different incremental treadmill protocols on the detection of the 4 mmol.L^{-1} lactate threshold. In agreement with what had been shown for the cycle ergometer,[9] when fixed, absolute blood lactate concentrations are used to detect thresholds, and the results were dependent on the protocol used. In the present study, VO_2 values at the ventilatory thresholds were ~7% higher on the speed-based protocol when compared to the grade-based protocol. Likewise, HR at the ventilatory thresholds was ~8% higher on the speed-based protocol when compared to the grade-based protocol. The mechanisms by which a speed-based protocol results in higher ventilatory thresholds when compared to a grade-based protocol are not readily apparent from our data. Based on the findings of Kelsey & Duffin,[19] in which greater ventilatory responses to speed than grade increments were observed on the treadmill for the same VO_2, one would expect lower ventilatory thresholds with the speed protocol, assuming that greater limb movement frequency would be responsible for our findings. An additional potential explanation for the lower ventilatory thresholds for the grade-based protocol is activation of a larger muscle mass with increments in grade.[23] During uphill (+10%) running, the volume of activated limb muscles increases from 67% to 73%,

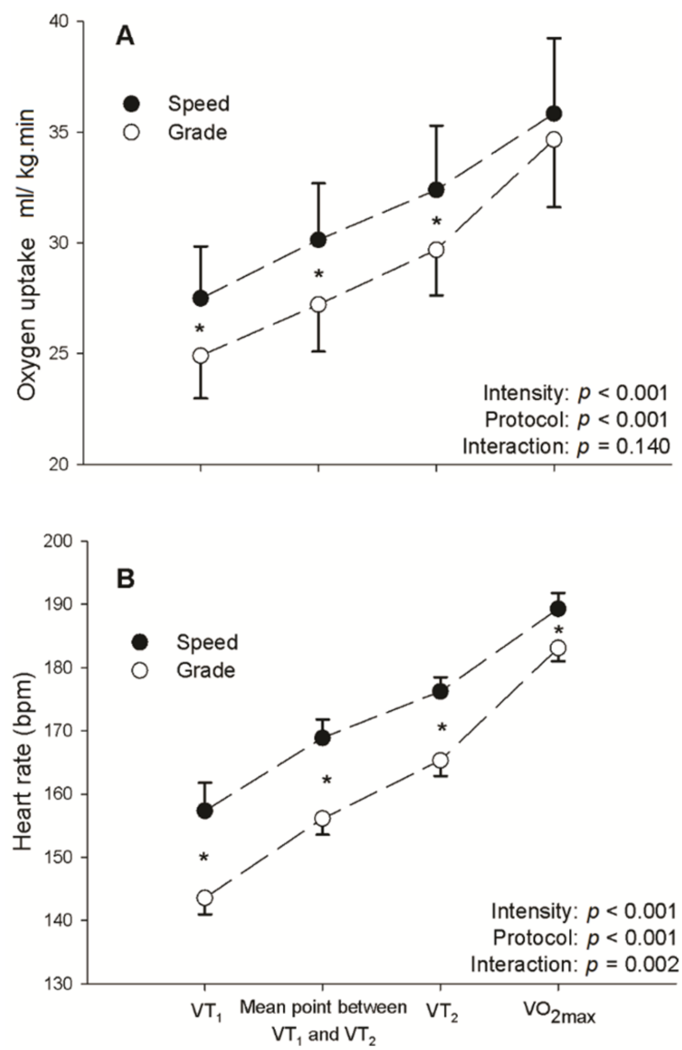

Figure 3 - Oxygen consumption and heart rate responses at four points during the maximal exercise tests with the speed and grade protocols. Data are expressed as mean +/- SE. VT_1: first ventilatory threshold; VT_2: second ventilatory threshold. * $p < 0.01$ between protocols.

and this is associated with greater oxygen deficit.[21] Moreover, uphill running is associated with greater glycogen depletion in the lower extremities.[33] Therefore, the grade-based protocol used in the present study probably resulted in the activation of a larger muscle mass, greater glycogen utilization, and earlier blood lactate accumulation, resulting in a lower VO_2 at the ventilatory thresholds.

Some investigators have suggested that the prescription of exercise intensities for aerobic training using ventilatory (or blood lactate) thresholds as the reference is more physiologically sound than using a percentage of VO_2max or a percentage of maximal HR.[4,6,34] Despite the fact that there are few data from controlled studies to support this strategy,[35] the concept that individuals with different ventilatory thresholds may exhibit different metabolic and cardiorespiratory responses to exercise at a given percentage of VO_2max is well established.[4,6,13,34] Therefore, we compared metabolic and cardiorespiratory responses during exercise sessions with the intensities determined on CPET based on either speed or grade increments. As is commonly done in practice, exercise intensity was

Int J Cardiovasc Sci. 2019;32(4):374-383
Original Article

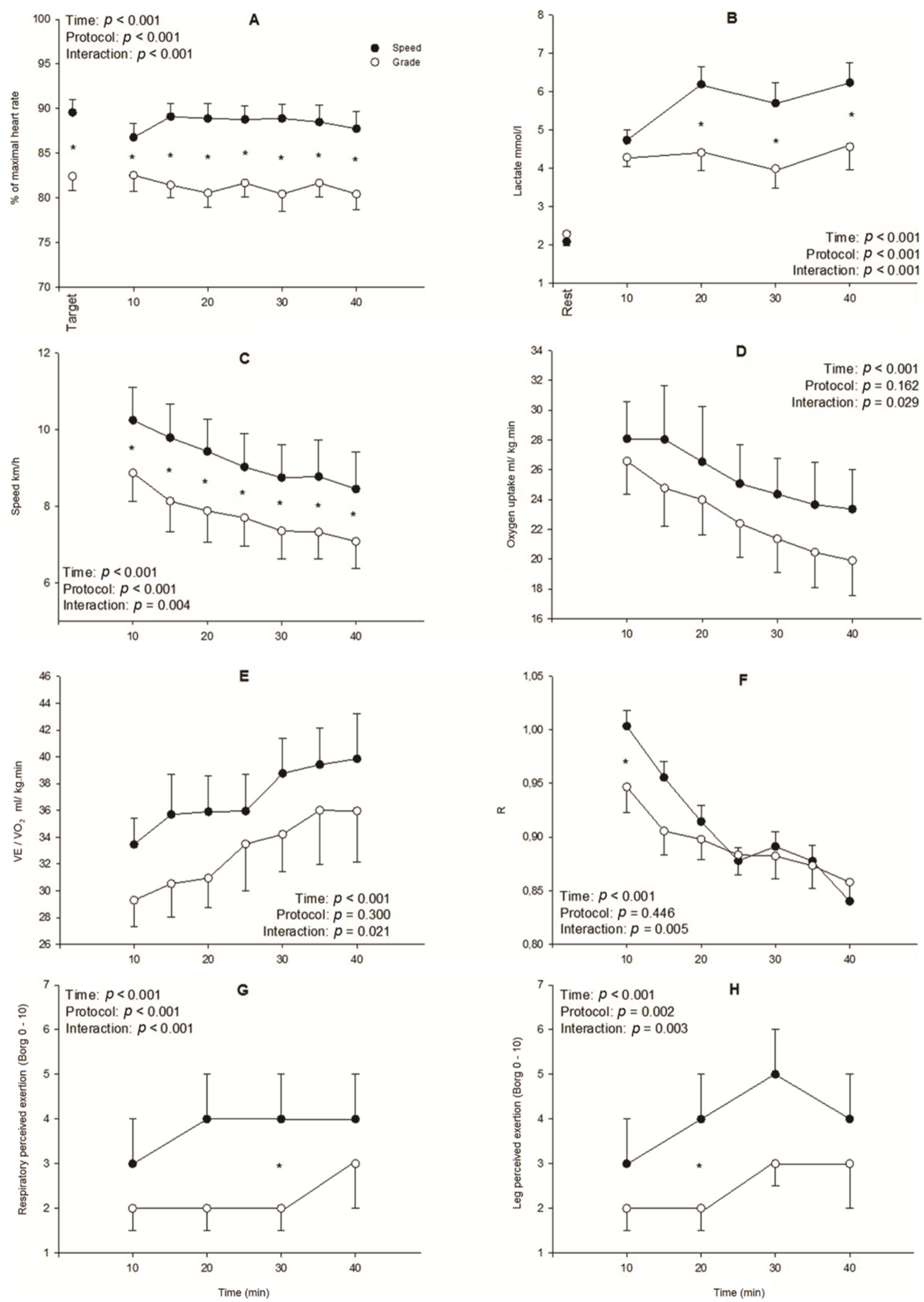

Figure 4 - Ventilatory and metabolic results from the prescribed submaximal exercise tests according to the speed and grade protocols. Darkened circles: exercise prescription based on the speed protocol; open circles: exercise prescription based on the grade protocol. All p values were obtained from generalized estimating equations. VE/VO_2: ventilatory equivalent for oxygen. * p < 0.05 between protocols.

adjusted according to the HR corresponding to the mean point between VT_1 and VT_2. Our data show that the choice of protocol has a significant impact on the exercise intensity prescribed for aerobic training based on the determination of ventilatory thresholds. The speed-based protocol resulted in a higher HR, blood lactate, speed, and perceived exertion during the exercise sessions. The size of this difference (~8% for HR and ~2 $mmol.L^{-1}$ for blood lactate) is substantial. If, for instance, the exercise prescription were to be set at the HR corresponding to VT_2, the steady state blood lactate concentration would be reached using a grade-based protocol, but blood lactate would likely accumulate if a speed-based protocol was used.[13]

Our study has several limitations. Ventilatory thresholds were visually determined by one experienced investigator (JPR) blinded to the identity of the subjects and the utilized protocol. Despite the fact that we did not evaluate the inter-observer agreement for the detection of thresholds, the intra-observer agreement was appropriate,[11,27] as demonstrated by similar mean values, high correlation coefficients, and Bland-Altman analyses within acceptable limits. Moreover, the standard criteria used in clinical practice, including ventilatory equivalents, V-slope, and the end-tidal CO_2, were applied.[3,36] With this approach, the reproducibility for the detection of the ventilatory threshold was in agreement with previous studies.[31,36-38] Furthermore, to avoid the walking-running transition, which affects the linearity of VO_2 response, both protocols began at 5.5 km/h, a speed at which all subjects were jogging. Perhaps, other faster transition speeds might produce different results, which in fact may be the subject of a future experiment. Therefore, our findings cannot be extrapolated to protocols in which individuals do not run. Finally, our findings are limited to healthy young adults, and therefore may not be applicable to elderly individuals, children or those with pathological conditions.

Conclusion

A speed-based protocol results in higher ventilatory thresholds when compared to a grade-based protocol during CPET performed on a treadmill. These findings have a significant impact on cardiorespiratory and metabolic responses to prescribed exercise intensity in healthy subjects. Due to fact that exercise prescription based on CPET often requires a high degree of confidence and safety, it is necessary to keep in mind that the same protocol must be utilized when the subject is re-tested during clinical practice. Finally, the speed-based protocol was more convenient because it was more applicable for exercise prescription.

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Author contributions

Conception and design of the research: Belli KC. Acquisition of data: Belli KC, Silva PF. Analysis and interpretation of the data: Belli KC, Silva PF, Franzoni LT, Myers J, Stein R. Statistical analysis: Belli KC, Franzoni LT. Writing of the manuscript: Belli KC, Myers J, Stein R. Critical revision of the manuscript for intellectual content: Belli KC, Franzoni LT, Myers J, Stein R.

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

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International Journal of Cardiovascular Sciences. 2019;32(4):384-390

ORIGINAL ARTICLE

Physical Activity and Incidence of Atrial Fibrillation - Systematic Review and Meta-Analysis

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Abstract

Background: The relationship between exercise and atrial fibrillation (AF) is controversial.

Objectives: To analyze the effects of physical activity on the incidence of atrial fibrillation using systematic review and meta-analysis.

Methods: Systematic review and meta-analysis of studies that relate physical exercise and atrial fibrillation. The following databases were searched: PubMed, BVS Saúde and Cochrane. The following descriptors were used: "atrial fibrillation", "exercise", "physical activity" and "exercise therapy". All prospective, retrospective, cross-sectional and cohort studies were investigated. All statistical analyzes were provided using Review Manager 5.3 to provide the mean difference (MD) and relative risk (RR) ratio with 95% confidence intervals (95% CI). The statistical method of heterogeneity index was used to assess heterogeneity. Level of significance was 5%.

Results: Combined analysis of 11 studies totaling 276,323 participants aged between 12 and 90 years did not suggest a significant increase in AF in individuals submitted to physical exercise (RR = 0.914, 95% CI = 0.833-1.003, heterogeneity: $p < 0.001$).

Conclusions: Physical exercise, *lato sensu*, without stratification by intensity, sex or age does not seem to be associated with an increase of atrial fibrillation. (Int J Cardiovasc Sci. 2019;32(4):384-390)

Keywords: Exercise; Atrial Fibrillation; Asthma; Exercise Therapy; Cardiorespiratory Fitness; Review; Meta-Analysis as Topic.

Introduction

Atrial fibrillation (AF) is the most frequent arrhythmia occurring in 0.1% – 4.0% of the population and the prevalence increased to 7.2% in patients aged ≥ 65, with an annual increase of 1.6% in patients aged ≥ 75. Characterized by loss of atrial contraction capacity (loss of atrial systole), AF is responsible for almost one-third of hospitalizations for heart rhythm disturbances. It may present high morbidity and mortality due to hemodynamic involvement, cardiomyopathy due to tachycardia and thromboembolic phenomena.

Risk factors for the development of AF include cardiac and non-cardiac factors such as age, structural heart disease, hypertension, diabetes mellitus and hyperthyroidism.[1] The change in cardiac function is associated with increased mortality and risk of infarction, decreased quality of life, decreased exercise capacity and impaired left ventricular function.[2]

It is known that physical activity is an effective adjunct in the treatment of various types of cardiovascular diseases. However, patients with AF present decreased tolerance to exercise, dyspnea and palpitations.[3] Some

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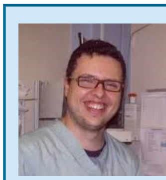

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studies report a J or U curve between the correlation of intensity of physical activity and AF.[4-10] On the other hand, some studies show a linear correlation between the amount of physical activity and the development of AF.[11-14]

Considering the regular practice of physical activity as a cardiovascular benefit and literature inconsistency about its potential arrhythmogenic effect, the objective of this study was to analyze the effects of physical activity on the incidence of AF.

Methods

Data source and search

In order to ensure a review of studies on the effects of physical exercise on the development of atrial fibrillation, we searched the following databases: PubMed, BVS Health and Cochrane. The following descriptors were used: "atrial fibrillation", "exercise", "physical activity" and "exercise therapy". The search was limited to articles published in English whose full texts were reviewed. We used prospective, retrospective, cross-sectional and cohort studies. Data collection took place between September and October 2017 and data analysis was performed between October and December 2017. References in all articles included were examined for other relevant publications.

Participants were patients without AF who underwent physical exercise and were followed up. Figure 1 shows the flowchart of the meta-analysis selection process according to the Jadad quality scale.

Criteria for data inclusion and extraction

The inclusion criteria were as follows: (1) study design: all cohort studies, prospective, cross-sectional, observational and randomized clinical trials with patients who performed physical exercises and the development of AF. The studies were excluded from the analysis if: (1) they included patients with previous atrial fibrillation, (2) they included athletes and/or patients submitted to vigorous physical exercise (3) they could not extract concrete data from published results, such as comments, letters, cases, abstracts, reviews, experimental studies and animal studies, (4) the results were not clearly reported. Screening, selection, data extraction and risk of bias evaluation were performed independently and duplicated by two researchers and, ultimately, the potential of disagreement and disagreement was resolved by the corresponding author.

Quality assessment

The quality assessments were evaluated by the composite scale of Jadad, a numerical score of zero meaning the weakest to seven meaning the strongest. The scale contains the following points: (1) generation of random sequence (0-2), (2) concealment of allocation (0-2), (3) blinding double (0-2), (4) description of withdrawals and drop-outs (0-1). The total score of 4-7 indicates high quality.

Methods of data synthesis and risk of bias in individual studies

All statistical analyses were provided using Review Manager 5.3 to provide the mean difference (MD) and the relative risk (RR) ratio with 95% confidence intervals (95% CI). The statistical method of heterogeneity index was used to assess heterogeneity. The level of significance was 5%.

Results

Search on the chosen databases resulted in 731 articles. After reviewing the titles, abstracts and articles repeated, a total of 11 studies were included in this systematic review.

Study and characteristics of patients

In the 11 studies included in the meta-analysis, there were 276,323 participants and, in the studies, the number of participants ranged from 2,014 to 81,317, with ages varying between 12 and 90 years. The characteristics of the studies and the patients are presented in Table 1.

Four studies were prospective (Bapat et al.,[6] Grundvold et al.,[7] Mokhayeri et al.,[8] Morseth et al.,[9] and Mozaffarian et al.,[10]) with mean follow-up periods of 7.7, 35, 11, 20 and 12 years, respectively; a cohort study (Williams et al.,[14]) with mean follow-up period of 6.2 years; a Post-Hoc analysis of a prospective study (Everett et al.,[13]), a cross-sectional study (Myrstad et al.,[11]) and an observational study (Qureshi et al.,[12]). In addition to these, one was a Post-Hoc analysis of a Randomized Clinical Trial (Aizer et al.,[4]) with follow-up period of 12 years, and a prospective observational study (Azarbal et al.,[5]) with follow-up period of 11.5 years. From the analyzed studies, no data were identified regarding patient hospitalization.

Study of the effect of exercise on the population analyzed

Figure 2 shows the results of the meta-analysis considering the selected studies.

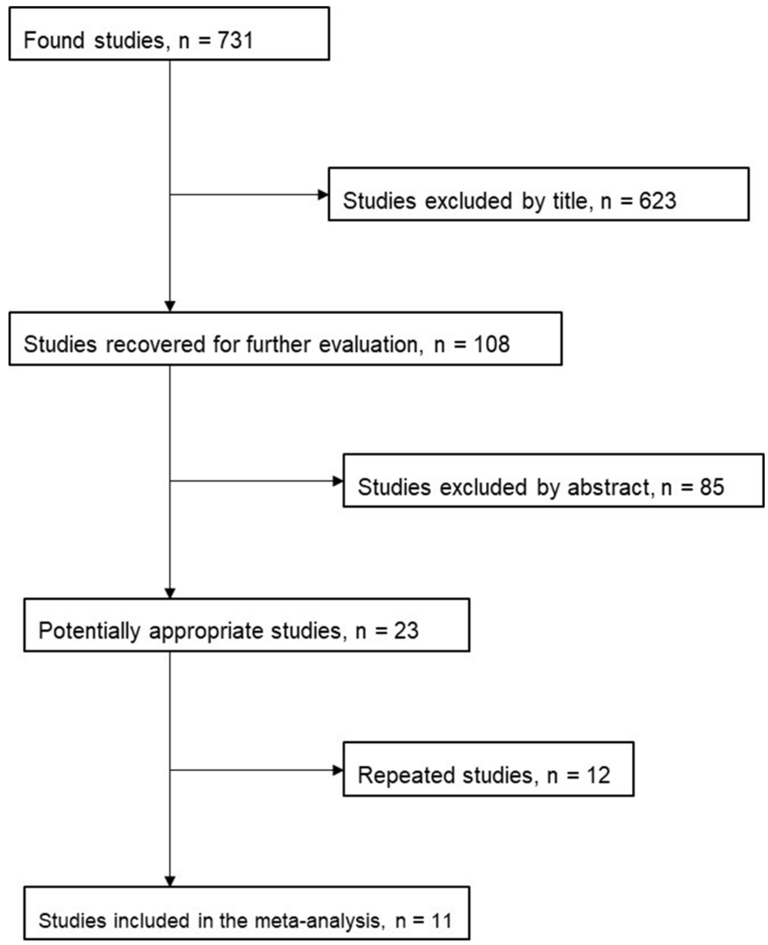

Figure 1 - Selection process of studies.

The combined analysis of the studies did not suggest a significant increase in AF in subjects submitted to exercise (RR = 0.914, 95% CI = 0.833 – 1.003, heterogeneity: $p < 0.001$).

Discussion

Although the benefits of physical exercise on cardiovascular diseases are well described, the same does not occur in relation to AF. In this sense, the results of this meta-analysis, based on the studies analyzed, indicate that individuals who exercise are less likely to have AF.

Mozaffarian et al.,[10] suggest that mild and moderate activities, especially leisure activities such as walking, are associated with a significantly lower incidence of AF. On the other hand, Drca et al.,[15] observed an increased risk of the development of AF in men under 30 years of age submitted to high levels of exercise, and this does not occur at older ages. In this sense, Larsson et al.,[16] suggest that maintaining a body mass index (BMI) of less than 25 kg/m^2, doing more than 20 minutes of exercise daily, not consuming or consuming alcohol in a mild to moderate manner (≤ 2 drinks/day for men and ≤ 1 drink/day for women) and not smoking reduce the risk of developing AF by half.

Bapat et al.,[6] from the Multiethnic Atherosclerosis Study (MESA), associated physical activity and AF in a diverse population without clinically recognized cardiovascular disease. The results showed that neither vigorous physical activity nor total intentional exercise were independently related to AF, when adjusted for some covariates. It has even been shown that the greater the relationship of the individual with vigorous activities,

Int J Cardiovasc Sci. 2019;32(4):384-390
Original Article

Table 1 - Characteristics of the studies included in the meta-analysis

Study	Design	Date	Sample size	Average age	p value adopted	Inclusion of participants
Aizer et al.[4]	Post-Hoc Analysis of a Randomized Clinical Trial	Randomization in 1982 with follow-up until 2001	22.071	40 to 84 years	0.01	Participants from the Physicians' Health Study aged 40-82 years in 1982 and randomized to aspirin and/ or beta-carotene
Azarbal et al.[5]	Prospective Observational	Data from medical centers collected between 1994 and 1998	81.317	50 to 79 years	0.01	Participants from the Multi-Ethnic Study of Atherosclerosis
Bapat et al.[6]	Prospective Cohort	The database is from 2000 to 2002	5.793	45 to 84 years	0.05	Participants from the MESA database
Grundvold et al.[7]	Prospective Cohort	The database is from 1972 to 1975	2.014	40 to 59 years	0.05	Five government institutions in Oslo
Mokhayeri et al.[8]	Prospective Cohort	Patients followed from the years 2000 to 2011	6.487	45 to 84 years	0.05	Participants from the Multi-Ethnic Study of Atherosclerosis
Morseth et al.[9]	Prospective Cohort	The database is from 1986/7	4.791	12 to 67 years	0.05	Tromsø Study participants
Mozaffarian et al.[10]	Prospective Cohort	The database is from 1999 to 2001	5.446	≥ 65 years	0,05	Participants from the Cardiovascular Health Study
Myrstad et al.[11]	Transversal	The database is for 2009	2.277	65 to 90 years	0.001	Elderly men undergoing long-term sports
Qureshi et al.[12]	Observational	The database is from 1991 to 2009	64.561	Extracts of ages (< 40, 40-49, 50-59, ≥ 60)	0.05	Participants from the Henry Ford Exercise Testing (FIT) Project
Everett et al.[13]	Post-Hoc analysis of a prospective study	Beginning in 1993 and randomization in 2004	34.759	≥ 45 years	0.05	Women participating in the Women's Health Study
Williams et al.[14]	Cohort	Partial reevaluation of 2006 from the National Health Study of Corridors II and the National Walkers' Health Study	46.807	33 to 72 years	0.05	Participants from the national study of runners and walkers for health

the lower the risk of AF. Also, Ofman et al.,[17] after meta-analysis involving 95,526 individuals, did not identify a statistically significant association between regular physical activity and increased incidence of AF. In this sense, the guidelines recommend performing at least 150 minutes of moderate physical activity or 75 minutes of intense physical activity per week.[18]

Patients with AF report symptoms such as decreased exercise tolerance, dyspnea, palpitations and fatigue, which directly affect the quality of life. However, physical exercise and training decrease these symptoms, and may have antiarrhythmic effects in individuals with paroxysmal AF, as well as protect against the development of AF.[19] In this sense, in order to verify

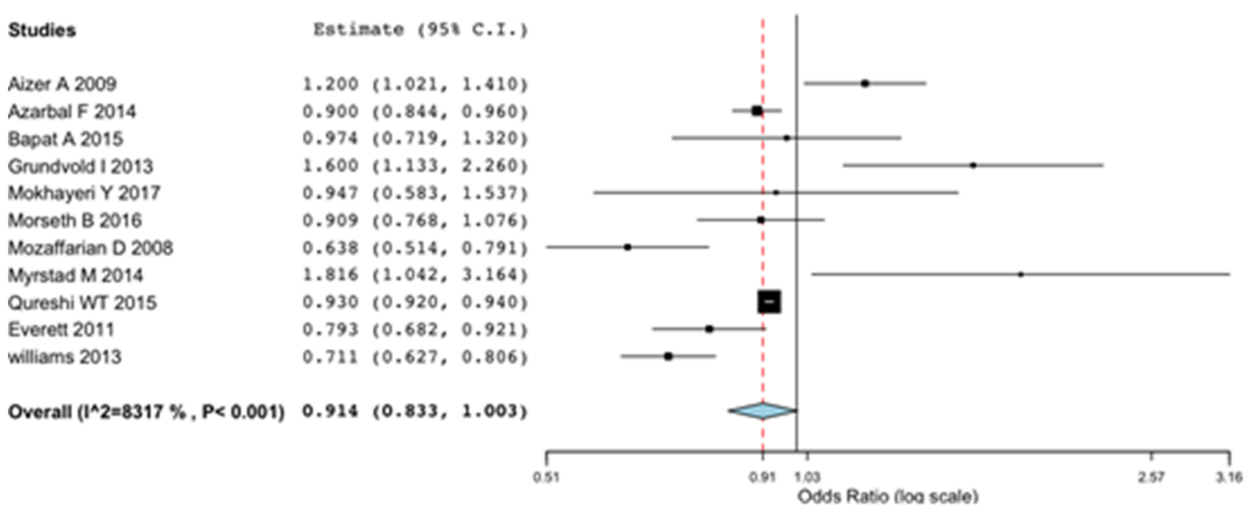

Figure 2 - Risk of incidence of atrial fibrillation in individuals submitted to physical exercises.

the effects of training on the functional capacity of individuals with AF, Luo et al.,[20] submitted patients with AF and patients after myocardial infarction with reduced ejection fraction to supervised training with aerobic exercises, three times a week for 36 sessions, then moving on to a home program for another two years. The training was efficient, resulting in increased cardiorespiratory capacity and peak VO_2 in both groups, but no significant differences were identified between the groups.

The international guidelines recommend the practice of physical activity in patients with AF in order to reduce their comorbidities.[21] When Malmo et al.,[22] submitted 26 AF patients to interval aerobic training, demonstrated that 12 weeks were enough to decrease arrhythmic load, besides causing a decrease in the symptoms related to AF. In addition, improvement in maximum work capacity, atrial and left ventricular function, lipid levels and quality of life were identified. For Osbak et al.,[3] patients with heart disease lose muscle mass and strength due to inactivity and local hemodynamic changes. This way, developing strategies that allow the increase of muscle strength in these patients becomes important in order to increase mobility, posture and balance.

In an observational study of 20,000 adults, Proietti et al.[23] observed lower all-cause mortality in AF patients who reported being involved with regular physical activity. Still, Hegbom et al.,[24] and Plisiene et al.,[25] demonstrated improvements promoted by physical exercise in quality of life, in addition to the reduction of symptoms in patients with AF.

According to Anderson and Taylor,[26] physical capacity is the main clinical outcome of cardiac rehabilitation, regardless of diagnosis. For each increase of 1 Metabolic Equivalent (MET) in physical capacity, mortality rate decreases by 17% in men and 14% in women. Thus, physical exercise seems safe for patients with AF besides triggering several benefits.[27]

Another important factor is the strong relationship between obesity and AF. According to Pathak et al.,[28] electrical factors and structural remodeling caused by obesity lead to the genesis and perpetuation of AF. In this sense, physical exercise, in addition to assisting in weight loss and consequent reduction in AF recurrence,[5,29] may protect against AF even in the presence of obesity.[30]

The study by Pathack et al.,[31] showed that an increase in cardiorespiratory fitness around 2 METs was associated with reduced density of AF. According to Abed et al.,[32] decrease in AF density due to exercise can be explained by increased cardiorespiratory capacity and weight loss. Increase in each metabolic equivalent (MET) results in a 20% decrease in the risk of recurrence of AF.[32] Skielboe et al.,[33] in order to verify if high-intensity exercises were more effective in decreasing AF density than low-intensity exercises, did not identify differences. However, it has been shown that high-intensity exercises do not increase risk and that patients tolerate exercises of this type.

Regular practice of physical activity has been reported to increase vagal tonus due to physiological adaptations resulting from increased cardiac work,[34] inducing electrical stability of the heart and maintenance of homeostasis. In this sense, low resting HR tends to represent a good health picture.[35] Thus, well-trained or physically conditioned individuals have lower resting HR, which suggests greater parasympathetic activity[36] or less sympathetic activity.[37] Still, Uusitalo et al.,[38] and Bonaduce et al.,[39] doing studies with longitudinal characteristics, observed a reduction in resting HR, although significant abnormalities in the autonomic indicators were not identified. Thus, Catai et al.,[40] suggest that exercise-induced bradycardia may result from intrinsic sinus node adaptations.

Like any systematic review, this study also presents limitations, since the results demonstrated here are limited by the quality of the studies available. This way, trying to make a complete literature review, all studies available, on the proposed theme, were included, and were evaluated, however, with a robust quality meta-analysis technique. In addition, the data analyzed were not stratified by type of exertion, gender or age.

Conclusion

It is concluded, therefore, that physical exercise, lato sensu, without stratification by intensity, sex or age, does not seem to be associated with an increase in the occurrence of atrial fibrillation.

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Author contributions

Conception and design of the research: Garlipp DC, Leiria TLL. Acquisition of data: Garlipp DC, Guimarães RB, Savaris SL, Froemming Junior C, Dutra O. Analysis and interpretation of the data: Garlipp DC, Guimarães RB, Savaris SL, Froemming Junior C, Dutra O, Leiria TLL. Statistical analysis: Froemming Junior C, Leiria TLL. Writing of the manuscript: Garlipp DC, Guimarães RB, Savaris SL, Froemming Junior C, Dutra O, Leiria TLL. Critical revision of the manuscript for intellectual content: Leiria TLL.

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the IC/FUC under the protocol number 1797.204. 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

Update on Sports Participation for Athletes with Implantable Cardioverter Defibrillators

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Abstract

Prior statements have recommended restriction from competitive sports participation for all athletes with ICDs. Recent data, however, suggests that many athletes can participate in sports without adverse events. In the ICD Sports Registry, 440 athletes, aged 8-60 years, 77 of which were high-level interscholastic athletes, who had continued to practice sports, were prospectively followed for 4 years, with no deaths or failures to defibrillate during practice, and no injuries related to arrhythmia or shock during sports. Shocks did occur, for ventricular and supraventricular arrhythmias. While more athletes received shocks during physical activity than at rest, there were no differences between competition or practice, versus other physical activity. Programming with higher rate cut-offs and longer durations was associated with fewer inappropriate shocks, with no increase in syncope. Based on this study, current recommendations now state that returning to competition may be considered for an athlete with an ICD. In considering this decision, the underlying disease and type of sport should be discussed, and shared decision-making between doctor, patient, and often family, is critical.

Introduction

The number of athletes diagnosed with cardiovascular disease placing them at risk for sudden death, whether through presentation with symptoms such as syncope or cardiac arrest, or through screening efforts, will likely continue to increase. In Europe, ECG screening of athletes is recommended by professional societies[1] and while consensus statements in the US continue to support pre-participation evaluation (PPE) with just history and physical examination,[2] these too may diagnose life-threatening cardiac conditions, and many universities in the US have added ECG to the PPE.[3] Furthermore, family cascade screening increases the rate of diagnosis of asymptomatic family members after presentation of a symptomatic proband.[4,5] Many of these symptomatic and asymptomatic athletes will receive defibrillators, raising the question of the safety of returning to practice.

Historical perspective

Until recently, consensus statements from the American College of Cardiology and European Society for Cardiology[6-8] advised that patients with ICDs should not participate in sports more vigorous than the "IA" class, low-dynamic/low-static activities such as bowling or golf. The basis for these recommendations were postulated risks, based on the consensus of experts, of failure to defibrillate, injury caused by loss of control due to arrhythmia-related syncope and/or shock, or damage to the ICD system. However, restriction from sports also has downsides, as the psychological as well as physiological benefits of exercise and sports are well-

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known. Restriction from sports, for any reason, has been shown to decrease both physical and emotional quality of life for athletes.[9] For many adolescents with ICDs, restriction from sports was the biggest factor impacting their quality of life.[10]

Further, a 2006 retrospective survey of Heart Rhythm Society physician-members,[11] suggested that many ICD patients were participating in sports, despite the consensus recommendations, and and the survey respondents did not describe adverse events. While survey results are limited by selection and recall bias, these results suggested that a prospective registry of athletes with ICDs was feasible, ethical, and necessary. Feasible, as many ICD patients were participating in sports. Ethical, as study participants were already practicing sports and were not asked to perform activities of which safety was unknown. Necessary, as if the risks were as high as hypothesized, those participating needed to know, while if the risks were not so high, others might choose to participate. Based on the preliminary results provided by this survey, the ICD Sports Safety Registry, a multinational, prospective, observational registry, was established to identify and quantify risks associated with sports participation for ICD patients.

The ICD sports registry

In this study, of which two-year results were published in 2013 and four-year results in 2017,[12,13] 440 athletes with ICDs, aged 10-60 years, 2/3 males, 46% with a history of ventricular arrhythmia (secondary prevention) who had chosen to continue competing in sports higher than Class "IA" regarding static/dynamic intensity, were prospectively followed. Participants were contacted regularly during the follow-up, and ICD records obtained, and rhythms adjudicated for shocks received at any time. The most common cardiac diagnoses were LQTS, HCM, and CAD, and the most common sports, running, soccer, and basketball. Among the twenty athletes participating at the university interscholastic level, diagnoses were similar, and the sports included soccer, basketball, lacrosse, and others.[14]

Over a median follow-up of 44 months, there were no occurrences of the primary endpoints—no failures of the ICD to defibrillate or externally resuscitated arrests, and no injuries due to syncopal arrhythmia or loss of control following shock. The 95% confidence interval for the occurrence of adverse events based on 376 participants followed for at least 2 years was 0% to 0.9% and based on 167 participants followed for at least 4 years, it was 0% to 2.2%. Many participants received shocks, with forty-six (10%) receiving appropriate shocks (for VT/VF) during competition or practice, a rate of 3 per 100 person-years. While more athletes received shocks during some form of physical activity than during rest, there was no difference between competition/practice and other physical activities.[13] In this population, older athletes were more likely to receive shocks during sports than those under 18 years old.

While the ICD Registry demonstrated that it is safe for many athletes with ICDs to continue competing, whether ventricular arrhythmias requiring shock for termination are more common in competitive athletes is yet to be determined. A subanalysis of the ICD Registry which compared the primary population with a subpopulation of intensive recreational athletes enrolled in Europe[15] (and not described in the papers focused on competitive athletes) suggested that arrhythmias with physical activity were more common in those competing. However, there were differences between the European and US athletes. In the general population, the "paradox of exercise" is well-described.[16] While overall, sudden death is less common in those who exercise vigorously, the risk of an event is higher during exercise. While often considered a "paradox", this is likely explained by the role of the autonomic nervous system in arrhythmogenesis. Catecholamines are known to promote arrhythmias.[17] For well-conditioned individuals, catecholamines will be at the highest levels when they are vigorously exercising. Whether a similar "paradox of exercise" exists in the most common genetic cardiovascular diseases in the athlete-ICD population, is unknown. An ongoing observational study, the "Exercise in Genetic Cardiovascular Disease" (NIH # R01 HL125918-01) is currently enrolling individuals with HCM and LQTS (in two parallel studies, Lifestyle and Exercise in HCM (LIVE-HCM) and Lifestyle and Exercise in LQTS (LIVE-LQTS) at all levels of exercise, both with and without ICDs, to determine whether arrhythmic endpoints are more or less frequent in patients who exercise when compared to those who do not (http://www.livehcm.org/ and http://livelqts.org/).

The impact of shocks on quality of life was not measured in the ICD Sports Registry. ICD shocks decrease quality of life, as shown in many studies.[18] However, while about one-third of those athletes who received shocks during sports stopped playing one or all sports for a period of time, most returned to sports later on, suggesting that the beneficial impacts of sports participation on quality of life outweighed the negative impact of shocks for most athletes.

Programming the ICD in the athlete

A recent subanalysis[19] has focused on the appropriate programming to minimize the likelihood of inappropriate shocks in this population. In the ICD Sports Study, those athletes whose ICDs were programmed with higher rate-cut-offs for the first therapy zone (greater than 200bpm), and those programmed with detection-duration greater than the nominal settings, were less likely to receive inappropriate shocks, and those with both these settings, the least likely.[19] Programming was not prescribed in this study, but findings were similar to large randomized controlled studies in the general ICD population.[20] There was no increase in syncope prior to shock in those athletes with higher rate-cut-off/longer duration. While two athletes had ventricular tachycardia below the rate cut-off and thus not treated, the arrhythmias were minimally symptomatic, presenting as palpitations. There was no difference in shock-rates based on dual-versus-single chamber device, or number of therapy zones.

Based on data from the ICD Sports Registry, in the updated "Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Task Force 9: Arrhythmias and Conduction Defects: A Scientific Statement From the American Heart Association and American College of Cardiology",[21] competitive sports participation for patients with an ICD no longer carries a blanket restriction, but rather, a "IIB" recommendation, i.e., "may be considered".

Factors in the decision-making process around return to play: importance of the underlying disease

What factors need to be considered in the decision-making process around return to play for an athlete with an ICD? The most important one is the underlying disease. The ICD Sports Registry has not evaluated if or to what degree vigorous exercise may exacerbate the progression of cardiomyopathies. While in that study the ICD was always successful at converting ventricular arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC,) these were the patients most likely to experience both single and storms of ventricular arrhythmias during sports. Furthermore, there are increasing data in both animals[22,23] and human patients[24,25] that high-level exercise may accelerate cardiomyopathy progression in this disorder. For patients with ARVC, the disease process, rather than the ICD itself, should guide the risk-evaluation of sports participation.

How exercise may impact the myopathic process in HCM is yet to be clarified. In a murine model of HCM, exercise was actually beneficial. In animals who had not yet developed the HCM phenotype, exercise prevented fibrosis and myocyte disarray, and in animals who had already developed HCM, exercise led to disarray regression and to improvements in the apoptotic signaling pathway components.[26] In a recent study of controlled increases in moderate exercise in sedentary HCM patients,[27] physical conditioning improved, there were no arrhythmias, and no changes in echo parameters, although this was a short intervention, and did not include maximal vigorous exercise.

Catecholaminergic polymorphic VT (CPVT) is unique in that an ICD is not nearly as successful at converting an arrhythmia as it is in other arrhythmogenic conditions.[28] ICD shocks increase catecholamines, even in a sedated patient[17] and this can create a vicious cycle of arrhythmia recurrence for a patient with CPVT. One small series has described appropriately-treated CPVT patients, mostly without ICDs, participating in sports.[29] In one series of 15 CPVT patients with ICDs, 6 were treated for ventricular arrhythmias. Two died of VT refractory to ICD treatment, including one whose VT was triggered by an inappropriate shock for AF.[28] In the ICD Sports Registry, another subset of patients with ventricular arrhythmias requiring multiple shocks for termination were those with "idiopathic VF". As CPVT is electrically silent at rest, it is highly possible that some "idiopathic VF" may represent undiagnosed CPVT. Treadmill testing is imperative to evaluate CPVT, and genetic testing should be considered.

Factors in decision-making: sports

The type of sports should also be taken into consideration. In the ICD Sports Registry, there were few athletes engaged in high-level contact sports. Basketball and soccer, which are considered "contact sports" by the American Academy of Pediatrics,[30] comprised a significant proportion of the sports practiced by the athletes, but there were very few engaged in sports in which violent contact was an intrinsic and purposeful part of the practice, such as American football or hockey. In the ICD Sports Registry, lead malfunction rates were similar to those reported in unselected populations,[31] but whether the risk of damage to the ICD system is higher during the practice of the more violent contact sports remains undetermined.

Importance of shared decision-making

Finally, the most important consideration is the athlete's values and preferences, and often his or her family's, and a shared decision-making approach is imperative.[32] Shared decision-making, termed the "pinnacle of patient-centered care",[33] requires the physician to explain the risks and benefits of options and to help patients understand how to reconcile these options with their personal preferences and values. This means full discussion with the patients, and often with their families--What are the risks? What data do we have, and how does this patient compare to the patients in the studies? For instance, for a hockey player, it is important to explain that system damage may be greater. What data are lacking? For instance, as mentioned above, while we know that shocks occur during sports, whether shocks would be less likely with the discontinuation of sports is still unknown. Furthermore, while there has been no adverse events described in the 440 patients in the ICD Sports Registry over four years, this study is not large enough to declare that the risk is zero. What do the professional society guidelines recommend? What does this patient and family think about risk in general? For instance, some families allow their children to climb Mount Everest, while others would not allow them to play American football. This shared decision-making approach requires a combination of knowledge of the data, and willingness to engage the patients (and often their families) as partners in the decision-making process. Most importantly, we need to stress that we do not have all the answers, while providing a framework for decision-making.

Author contributions

Acquisition of data: Lampert R. Analysis and interpretation of the data: Lampert R. Obtaining financing: Lampert R. Writing of the manuscript: Lampert R. Critical revision of the manuscript for intellectual content: Lampert R.

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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 Yale Human Investigation Committee under the protocol number 0608001736. 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

Measuring Heart Rate During Exercise: From Artery Palpation to Monitors and Apps

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Abstract

The use of technology has increased tremendously, by means of more reliable, smaller, more accessible and specially more user-friendly devices, which provide a wider range of features, and promote significant benefits for the population and health professionals. It is in this context that monitors and apps for heart rate (HR) measurement have emerged. HR is a clinical vital sign of diagnostic and prognostic importance. In response to body movement, HR tends to increase, in a direct relationship with the intensity of exercise. HR was primarily measured by the count of arterial pulse, and recently, HR can be precisely measured by monitors, bracelets and smartphone apps capable to perform real-time measurements and storage of data. This paper aimed to make a brief and updated review on the theme, providing a broader view of advantages and limitations of these resources for HR measurement in exercise. HR monitors and apps use basically two types of technology, optical sensor (photoplethysmography) and electrical signal from the heart. In general, these devices have shown good accuracy in measuring HR and HR variability at rest, but there are differences between brands and models considering the type, mode and intensity of exercise. HR measurements by monitors and smartphone apps are simple, accessible and may help cardiologists in the monitoring of the intensity of aerobic exercise, focusing on health promotion and on primary and secondary prevention of cardiovascular diseases.

Keywords

Exercise; Heart Rate, Palpation; Exercise Therapy; Fitness Trackers; Monitoring, Physiologic.

Introduction

The use of technology in health has exponentially increased, fostering the use of monitors and mobile apps for heart rate (HR) measurement. Recent equipment and resources for HR monitoring are better, more accurate, more compact, cheaper and more user-friendly, and provide a wider range of features and greater recording and storage capacity. Therefore, be it in-person or via telemedicine, these technologies have the potential to generate benefits to the population and to facilitate and be a complement to medical services.[1]

HR is the most important vital sign; it is one of the most remote indicator of health since early civilizations.[2] The assessment of HR can be clinically used in case of suspected pulmonary embolism and acute infections.[3] HR is expressed as beats per minute (bpm), and is modulated by autonomic nervous system.[4] From a clinical and epidemiological point of view, life expectancy seems to be inversely correlated with HR at rest and positively correlated with maximum heart rate during exercise, magnitude of HR decrease after exercise, and the combination of these three variables, as assessed by HR gradient during exercise, proposed by Brazilian authors.[5]

In response to body movement, HR tends to rise, causing an increase in cardiac output, and transport of oxygen and substrates to the tissues, and removal of CO_2 and wastes from them.[2] In maximal incremental exercise, HR tends to gradually increase until its maximum

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value. Maximum HR, measured by laboratory and field tests, or estimated by predictive equations, tend to be linearly attenuated with ageing,[6] especially after the age of 35 years.[7] There are many predictive equations for maximum HR in aging. The equation: maximum HR = 208 – 0.7 x age (years) was validated in a Brazilian population.[8] However, the margin of error is quite large, and easily exceeds at any given age and in 5% or more of the individuals.

Therefore, when using HR as a tool for the assessment and prescription of exercise, it should be directly measured from an individual rather than predicted by equations.[8] Measured maximum HR can then be used to define, in a better and more precise way, the range of intensity of an exercise training program.[9]

However, despite its importance in clinical practice and in exercise prescription and monitoring, there are no standardized guidelines to measure HR.[10] On the other hand, recent technological advances have made HR measurement more accessible and popular due to high availability of monitors, armbands, and even smartphone apps.[2,3] Since 2012, more than 30 new products for HR measurement have been launched,[11] and this number tends to increase. In this regard, this paper presents a brief and updated overview about the use of devices and monitors for HR measurement in exercise and in clinical cardiology.

HR in exercise and sports: a brief contextualization

Resting condition

Resting HR is often used as an indicator of cardiorespiratory or aerobic fitness. Cross sectional studies have shown that cardiorespiratory fitness is inversely related to resting HR in adolescents,[12] adults,[13] and elderly.[14] In untrained women, aerobic training reduced resting HR regardless of age (< 41 or 41-60 years) of participants or duration of intervention they were exposed to (< 3, 4-6 or > 6 months).[15] Although this association may be attributed, at least in part, to increased resting cardiac vagal activity,[16] electrophysiologic changes intrinsic to the sinus node may also occur in many physically trained individuals.[17]

Cardiovascular drift

The balance between cardiac output and oxygen requirement during exercise may require a cardiovascular adjustment known as cardiovascular drift, which negatively influences performance.[18] In practical terms, it is important to identify this phenomenon, since HR tends to increase with prolonged effort performed at the same level, particularly if sustained for 30 minutes or longer or under unfavorable thermal conditions.[19] Two hypotheses have been suggested for this phenomenon, which involves an increase in HR associated with a reduction in systolic volume. First, dehydration has been proposed as the mechanism responsible for blood volume reduction, leading to impaired venous return and reduced end-diastolic volume and, consequently reduced systolic volume (Figure 1). In this process, cardiac output would depend on increased HR.[20] More recently, Coyle and Gonzáles-Alonso[21] proposed a inverse pathway, in which HR acceleration would limit the time for determination of the end-diastolic volume, resulting in lower systolic volume. In fact, during prolonged exercise, it is possible that HR increases regardless of variations in exercise intensity. Monitoring of HR during exercise facilitates the control of exercise intensity and maintenance of performance.

Maximal exercise

During incremental maximal exercise, HR increases in response to gradual decrease in cardiac vagal activity until its complete suppression at peak effort, at the same time that adrenergic stimulation becomes the protagonist of autonomic control of HR.[23] Maximal HR is limited by hypoxia, regardless of age and sex, but this reduction is more evident in individuals with lower cardiorespiratory fitness.[24] Nevertheless, a limitation to physiological increase in HR in response to increased activity is known as chronotropic incompetence.[25] This may also result from a late response of HR acceleration, instability or lowered response to exercise intensity.[26]

Considering that the increment in HR is the main responsible for the increase in cardiac output and thus for the possibility of performing an aerobic exercise,[25] the chronotropic incompetence turns out to be a restrictive factor to exercise performance, as in some patients with heart failure,[27] and is associated with increased mortality risk.[28]

Post-exercise recovery

Post-exercise HR recovery, or decrement, is the difference between HR at the end of exercise (maximal or submaximal) and HR at 1 minute or 2-5 minutes after exercise, and is similar in men and women.[29]

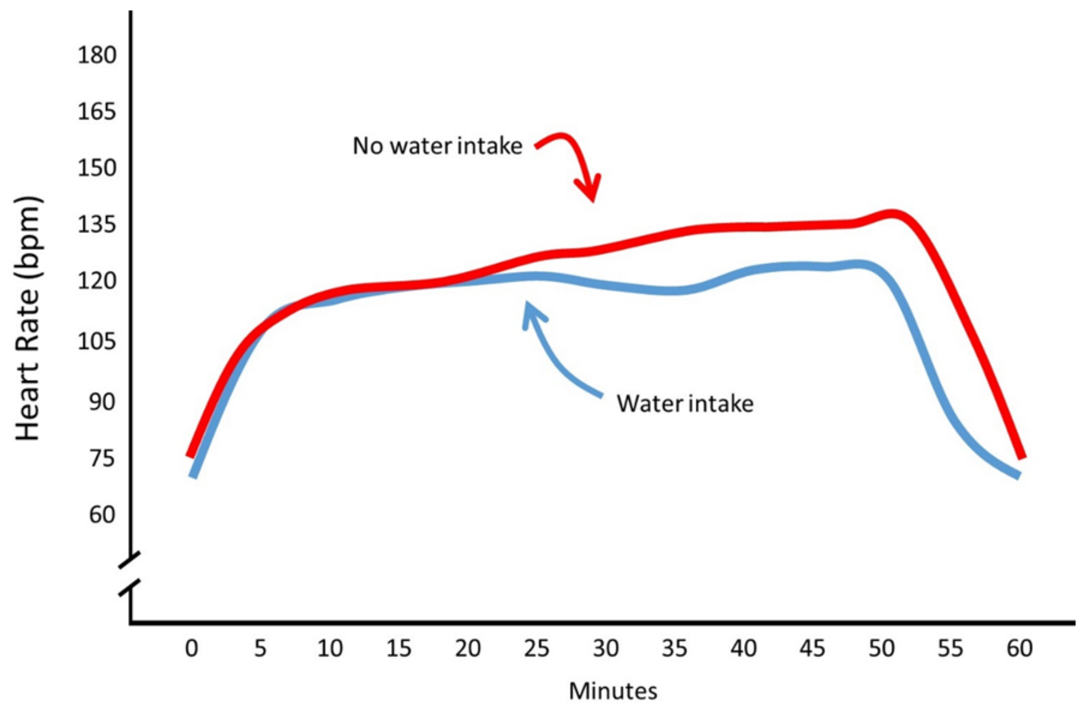

Figure 1 - Hypothetical example of heart rate variation in response to prolonged, constant-load aerobic exercise and dehydration. Even at constant exercise intensity, heart rate varies throughout the first two minutes of exercise, and the steady state is affected by dehydration, with an increase in heart rate. Adapted from Chagas et al.[22] and Araújo.[19]

Epidemiological data have shown that a slight decrease in HR after exercise represents an increased risk of mortality.[30,31] However, although HR recovery tends to be faster in men and women with higher maximal VO_2, there is a weak association between these two physiological variables, where regression model explains no more that 11% of HR variation.[32] The association between initial and final transient periods of HR recovery is not strong either.[33] On the other hand, analysis of post-exercise HR recovery may contribute to the identification of athletes of different sports with favorable autonomous nervous system adaptive changes.[34]

History of HR measurement in exercise

Palpating arteries or auscultating the heart

The simplest and most original way to measure HR is to palpate the arteries, and the most commonly used for this purpose are the radial, the common carotid and the superficial temporal arteries. The time of palpation may vary from 6 to 60 seconds, but it is important to highlight that the shorter the time, the greater the error, since the number of heartbeats is multiplied by a factor to obtain the number of heartbeats in one minute. For example, if the time of palpation was 6 seconds, the number of heartbeats is multiplied by 10 and the multiplier represents the margin of error.[35] On the other hand, a longer measurement time, or closer to 60 seconds, has lower margin of error but is more susceptible to autonomic modulation and other disturbances or artifacts, especially during or after exercise (Figure 2).[4]

Monitors

Obviously, it would be necessary something more efficient operationally, without stopping the run or other exercise to obtain a real-time measurement of HR, without mathematical calculations. The first devices had old technology optical sensors; the first versions were composed of wires connected to the panel of treadmills or similar devices, with sensors fixed under pressure on the digital pulp surface or the ear lobe, which were extremely sensitive to body motion during exercise. Thus, HR measures obtained by this method had low

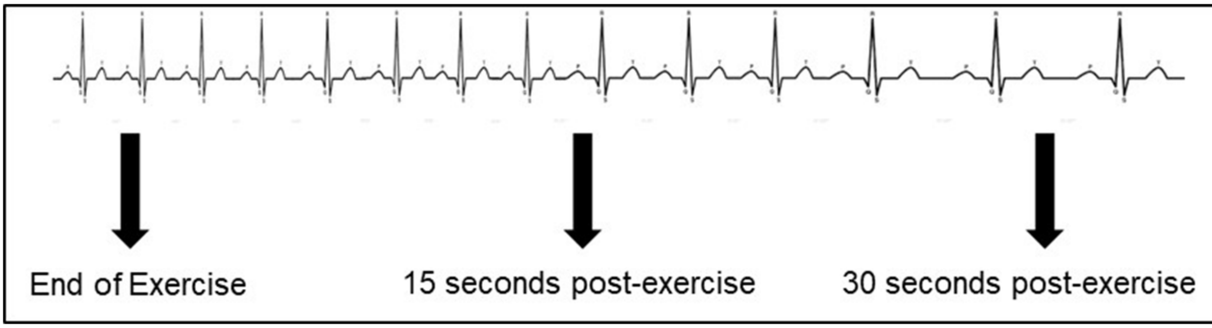

Figure 2 - Theoretical model of heart rate response after exercise, modulated by cardiac vagal reactivation during 30 seconds of digital palpation. We can see the widening of the time between the systoles (RR intervals at electrocardiography) at the end, and at 15 seconds and 30 seconds after exercise.

accuracy and reliability. Also, not rarely, the sensor was removed from the ear lobe during exercise because of a wider movement of the arms for example, affecting HR monitoring.

In the early 1970's, an exercise physiologist and future swimming coach, Dr. Robert Treffene, developed a handheld monitor with wires and electrodes that could be used by the coach outside the pool to check the HR of swimmers as soon as they stopped at the pool wall.[35]

At the end of the same decade, Professor Seppo Säynäjäkangas invented a HR monitor for Finland's national cross-country ski team to use while training. In 1977, he founded the Polar Electro Oy®, a pioneer company in this field, based in Kempele, Finland. Only six years later, the first HR monitor became commercially available, the Polar Sport Tester PE 2000,[35] that could be used by athletes and practitioners who wanted to obtain a more accurate HR measurement to adjust their training load.[36] Due to modern technology, there are several brands and models of HR monitors available nowadays, with more sophisticated features, including higher memory capacity, stopwatches, time and pace alarms, estimator of energy expenditure, GPS, among others.

Mobile apps

In the study by Lee et al.,[37] the authors reported that HR monitors could be expensive and, therefore, not accessible to patients. In addition, HR monitors worn with elastic bands could cause discomfort and limit a wider use of these devices.

Therefore, considering the increasing use of smartphones in Brazil and in the world, mobile apps for HR measurement seem to be very interesting. The technology required to detect cardiac chronotropy encompasses from photoplethysmography (PPG) via smartphone cameras[38] to accessories, including smartphone cases containing ECG sensors.[39] Therefore, mobile apps (and often associated watches and monitors) are capable not only to measure the HR but also to identify arrhythmias, such as atrial fibrillation.[40] However, Coppetti et al.[41] pointed out possible differences between HR measured by contact and non-contact PPG. The authors showed that non-contact PPG-based apps can show relatively high margin of errors (7 to 8 bpm), compared with errors varying from 2 to 4 of contact PPG-based apps.

Heart rate monitors

What is a HR monitor?

HR monitor is a device that allows the measurement and display of real-time HR data and, depending on the model, storage of data for posterior analysis. HR monitors have been widely used not only to evaluate aerobic performance but also to monitor the intensity of predominantly aerobic exercises. The monitors contain an elastic band with contact sensors (electrodes) that detect cardiac electrical activity (systoles) and send it to a receptor via radio waves,[42] or optical sensors (PPG). Today, there are many models and brands of HR monitors available in the market, providing different features, from those with time of exercise and HR measurement on the display, until more sophisticated ones, that include GPS and performance indexes, such as pace, average pace throughout the route, cadence, among others. GPS devices obtain components that give external training loads greater importance, as well as wider diversity of measurements. Altimeters, gyroscopes, magnetometers, accelerometers, and inclinometers provide real-time information regarding direction, amount of G-force, and vectors of force, allowing a precise control of variables that help to make better decisions.

Detection of HR by HR monitors occurs primarily by two types of technology, optical sensor (PPG) and ECG. While ECG-based HR monitors work with a chest strap (Figure 3), PPG-based monitors are wrist devices, although optical sensors have been adapted to products worn in other parts of the body, such as headphones, arm straps and even headbands.[43]

Precision and accuracy of heart rate measurements using HR monitors and apps

Cadmus-Bertram et al.[44] highlighted the need of health professionals and general population to know the accuracy of HR monitors and apps for correct use of the devices. The authors recognized the difficulties inherent to the validation of these tools. In addition, with the rapid development of technology, there are many recent publications on HR devices that may have already been outperformed by others,[41] notably in terms of updating of algorithms that are not well explained, i.e. it is unclear how HR measurement shown on the display was actually determined (sample frequency). Besides, from an operational standpoint, it is not feasible to perform a comprehensive validation of all these devices considering all their possible applications. In this context, Cadmus-Bertram et al.[45] reported that PPG-based HR monitors are accurate to measure HR at rest, but not during exercise. Also, Singh and Sittig[46] reported discrepancies in the measurements of both resting and post-exercise HR (walking and running) obtained by a HR monitor as compared with a control measurement, indicating that the device being tested lost signal when HR was over 140 bpm. Although this is not a concern for most users of HR monitors and apps, and these devices do provide good and precise measurements for daily life application, clinical cardiologists should be aware that the measurements displayed by these devices may not be accurate.

Similar results were observed by Boudreaux et al.,[47] who compared eight different models/brands of HR monitors with a gold-standard method, a six-lead ECG measurement in resting conditions, during aerobic exercise of different intensity and resistance exercise. Although all monitors tested had good validity at rest, only three showed good accuracy (r ≥ 0,75) – the Apple Watch Series 2, the Polar H7 and the Bose SoundSport Pulse, highlighting that the last two did not have a wristwatch. The higher the exercise intensity, the lower the accuracy of the measurement, with a tendency of an underestimation of HR, in both aerobic and circuit resistance exercise. In addition, some of the monitors did not measure the HR in real time, with a 3-5 second delay. This is evident since HR tends to increase slightly

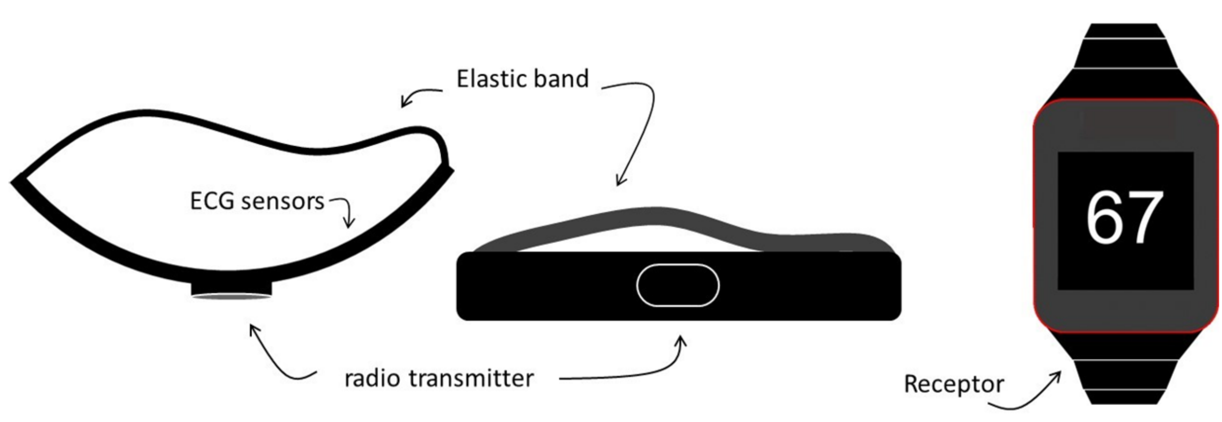

Figure 3 - Basic structural components of a radio telemetry heart rate monitor.

in the first five seconds after a very high-intensity exercise, different from what is physiological and precisely identified by an objective measurement of RR intervals at ECG.[48]

Horton et al.[49] showed that the Polar M600 is validated for HR measurements in aerobic exercises, such as cycling, walking, jogging and running, but only during steady-state exercise, i.e., with relatively constant intensity. However, HR responses to circuit resistance exercise were, again, underestimated. Other models such as the Apple Watch 1 and the FitBit Charge HR were also shown to be able to measure HR properly,[50,51] whereas the Garmin Forerunner 225 overestimated HR measurements during low-to-moderate walking and jogging on a treadmill, but obtained HR measurements similar to reference values during high-intensity exercise.[51] The authors suggested that this could be explained by the fact that the Garmin Forerunner 225 had been developed for running, and not for walking exercise. It is also possible that technical difficulties are even higher in other types of aerobic exercises, such as swimming and rowing.

The findings described in this section should be interpreted with caution, and at least in part, considered in the context of clinical practice. For some measurements, although some statistical differences were observed between the HR monitor and ECG, they may not influence the reliability of monitors, since absolute differences were not greater than 2 bpm. In addition, the device settings should be not be ignored to avoid measurement errors.[52] Therefore, in general, HR monitors may be considered sufficiently accurate to be used during physical exercise for most individuals and most daily life conditions.

Main applications in exercise

Common situations in exercise

There are many situations where a real-time recording of the HR favors the control of the exercise intensity proposed. This is somewhat commonly seen at gyms, physical activity centers or even in outdoor settings.

For example, Eddolls et al.[53] suggested high-intensity interval training (known as HIIT) to children and adolescents, based on an intensity higher than 90% of maximum HR for improvement of health indicators. Although this exercise modality includes recovery intervals, these intervals are not sufficient to perform HR measurement, be it by palpation or auscultation. In this context, the HR monitor provides an immediate feedback that facilitates the maintenance of exercise intensity within pre-established ranges.

In resistance exercises, the use of HR monitors is less frequent. However, Latella et al.[54] suggested that the establishment of recovery time between sets based on HR responses may be one of the most effective strategies to optimize the results. During circuit resistance training, HR tends to be maintained at higher levels due to its shorter and more active intervals. Alcaraz et al.,[55] though, did not find differences in performance (repetition maximum and muscle power) between high-intensity resistance circuit training and traditional strength training. HR values registered (Polar S625X monitor) at the end of each exercise bout were similar between the two types of exercises, although decrease of HR was greater in intervals between the sessions of traditional training.

Barbosa-Netto et al.[56] observed that, although the magnitude of HR responses depends on the intensity of exercise, HR kinetics was similar throughout a 10 repetitions set, with rapid acceleration in the first 10 seconds and attenuation in the last five seconds, followed by rapid recovery at the end of the last repetition. In these studies, HR monitor allowed the identification of responses that were easily obtained and interpreted.

Field conditions and team monitoring

The systematization of HR monitoring in trainings and games started in 1990 with soccer players. This strategy has been very effective in establishing training loads and compare them to physiological responses obtained during official matches and competitions. Also, it has helped the monitoring of the intensity of the training sessions (Figure 4). HR measurements were carried out using chest straps and wrist-based monitors during physical trainings, whereas in technical and tactical training and games, the signal was transmitted by telemetry, since according to the rules of the sport modality, players are not allow to wear wrist watches, rings, earrings and bracelets. The obvious reason for that was to allow the players to be as free as possible to move, and to be focused on the main goal of the training. Members of the coaching staff started to monitor players' HR in order to make adjustments in the intensity of the training and performance of matches.

Computers and tablets have become crucial instruments of biofeedback, comparably to chest straps.

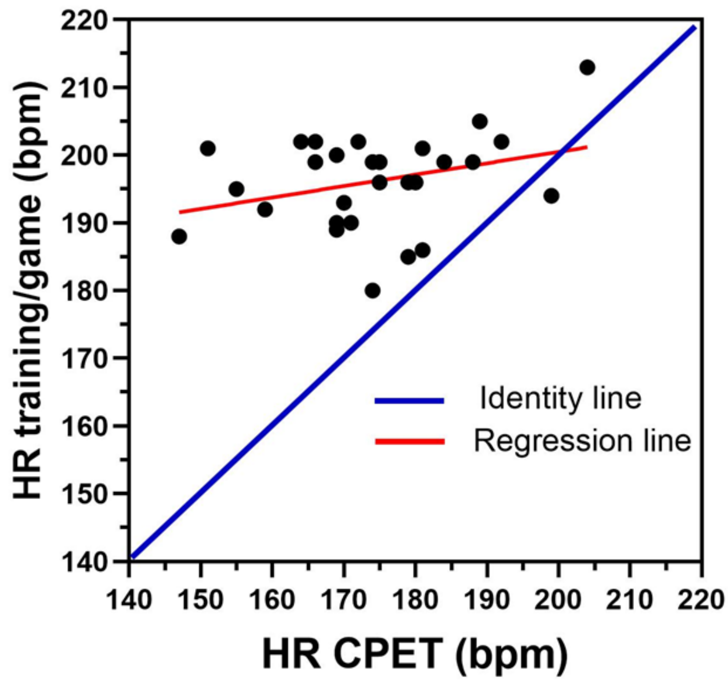

Figure 4 - Monitoring of heart rate in professional soccer players in a maximal incremental treadmill exercise test (November 2018 – end of season) and in specific soccer-related activities (training and official matches) in January, February and March 2019 (Bottino, unpublished data); HR: heart rate; CPET: cardiopulmonary exercise test.

However, it was only in 2003, during the 8th annual congress of the European College of Sports Science held in Salzburg, Austria, that HR monitoring became one of the most important variables on internal load control,[57] and the concepts of acute and chronic loads regarding stimuli and consequent adaptations emerged (Figure 5).

It is important to mention that, among all objective variables of exercise intensity, HR is, so far, the only variable that enables a real-time measurement and analysis. The other variables (hormones, metabolites, thermography etc.) require an interruption or ending of activity, training session or game for data collection and analysis.[58] Consequently, a new generation of GPS (and one of the leading brand in the area), is at final testing stage to incorporate HR measurement as one of its components.[59] This will allow an even closer integration of information with HR as a variable of training/game total load.

In field conditions, the use of apps that analyze HR alone may face some operational limitations. The signal coverage range is still small (approximately 60 m), which is very limited considering the official soccer field size. In addition, storage capacity is limited in the absence of available Bluetooth connection. This is a common situation when the team goes to the dressing rooms and become practically isolated in a Faraday shield due to the metallic structures of the beams and cladding of the facilities. Such interruption in signal transmission results in a nearly 15 minutes of recording loss, which could affect the information about the athletes' level of recovery after exercise.

This special limitation regarding Bluetooth communication does not occur when the signal is transmitted from the chest strap to the GPS, since the distance between these components is less than one meter. From the GPS unit, the signal is transmitted to external antennas in the field and then to satellites. Besides, GPS devices have enough storage capacity and, in case of signal loss during the match, the HR data can be recovered for further analysis.

Potential clinical applications

Considering that some of the HR monitors have a large sample rate and large capacity of data storage, it

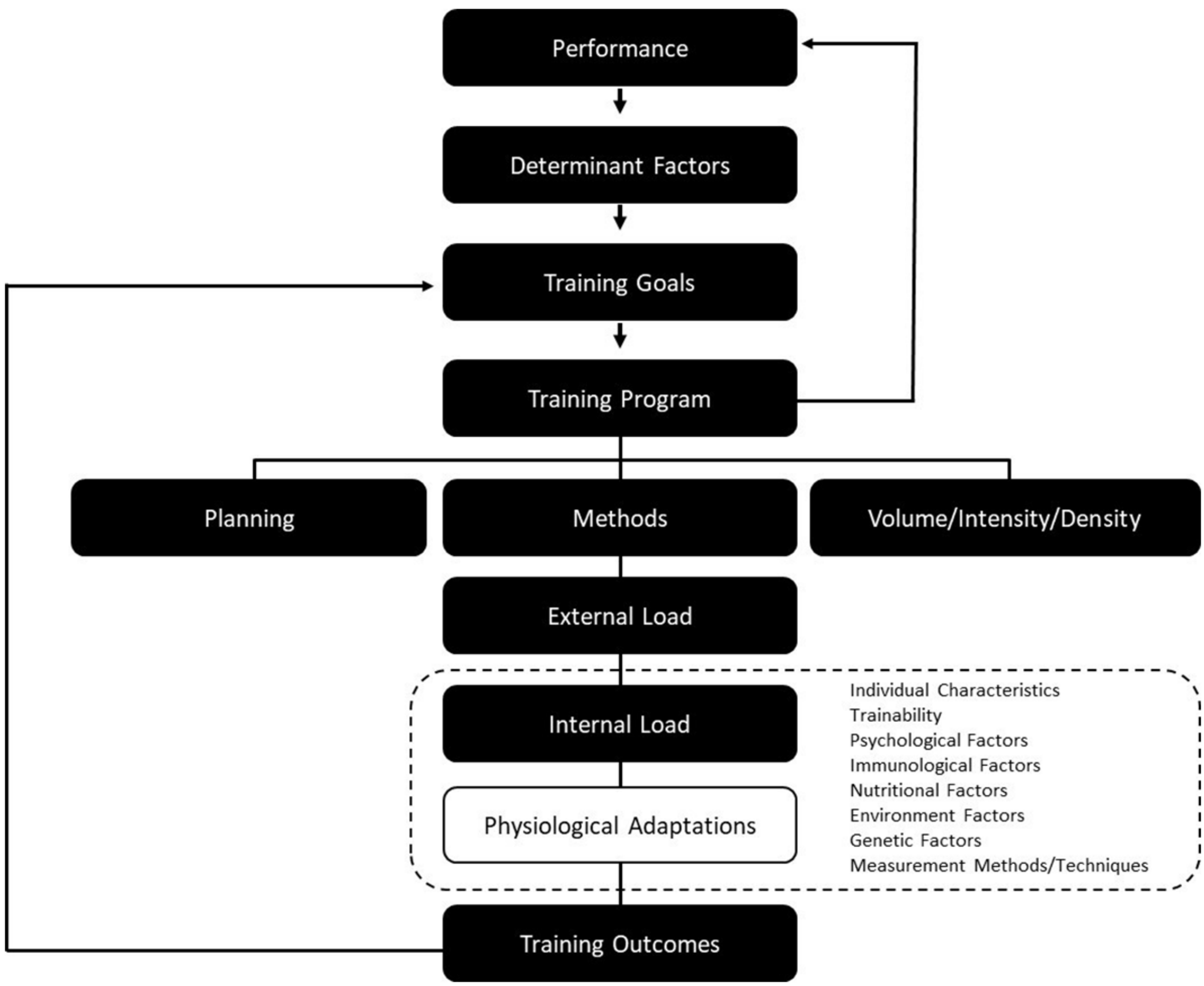

Figure 5 - Theoretical model of the sports training process. Adapted from Impellizzeri et al.[57]

became easy to obtain instantaneous HR by measuring the duration of each cardiac cycle or the RR-interval. Therefore, these devices allowed the collection of data for analysis of both cardiac rhythm and changes of HR in short intervals and HR variability by mathematical techniques.

Detection of cardiac arrhythmias

Cardiac arrhythmias may occur without symptoms and thus, may not be perceived by the patients. This is common in clinically relevant arrhythmias. Thus, with the advent of digital technology, which facilitates real-time recording and storage of a great amount of data, and allows a fast, efficient transmission and even distance and real-time monitoring, there has been a growing interest in the use of monitors (some of them in the form of watches) and mobile apps for HR reading.

This subject was initially discussed in case reports,[60,61] small studies,[62,63] and data series, and more recently has been studied in epidemiological investigations including huge samples,[64] that have benefited from machine learning and big data strategies. However, it is not the aim of this brief review to present a deeper discussion about this interesting theme.

It is worth noting that, due to a fast and encouraging progress, the possibility to correctly diagnose arrhythmias using monitors and smartphone apps has become more and more a reality in Cardiology.[65] Also, very soon, with the improvement of algorithms, it will be possible to correctly detect artifacts and interferences, and thereby the rate of false negative and false positive diagnosis will tend to zero. At that time, these devices will be safely and reliably used in routine clinical practice and become a quality standard. But for now, the detection and recording of apparently abnormal HR values (higher or lower) particularly in high-intensity exercise, deserve careful, weighed, but not alarming consideration. This is even more relevant for asymptomatic, apparently healthy athletes and practitioners with a low cardiovascular risk.[66]

HR variability

As above mentioned, the large storage capacity of HR monitors has facilitated the measurement of instantaneous HR, i.e., of each cardiac cycle or the RR-interval, and thereby enabling the acquisition of data for analysis of HR variability using mathematical techniques.[67]

One of the main contributions of exercise science about this topic occurred at the end of the 20th century. Lima and Kiss[68] proposed an indirect determination of lactate threshold by analysis of HR variability during maximal incremental exercise test. The physiological assumptions supporting this idea was based on the inverse relationship between parasympathetic autonomic activity and intensity of exercise.[23] The authors used a HR monitor Polar NV Vantage (subsequently updated by the manufacturer as S810i, RS800, V800 and currently Vantage V). HR variability was defined as the mean of six measurements (taken every ten seconds) of the variation in consecutive RR intervals. The HR variability threshold was reached when the mean of the six measurements was lower than 3 ms. This point was validated by the curve of blood lactate accumulation and corresponded to the lactate threshold.

Paschoa et al.[69] evaluated HR kinetics during resistance exercise (unilateral leg extension) and observed a marked decrease of HR variability during exercise, even the shorter ones, with a fast recovery after exercise. More recently, Barbosa-Neto et al.[56] showed that such HR variability response does not depend on exercise load. Similar RR-interval curves were found throughout the exercise performed at 50%, 80% and 100% of the load for 10 repetition maximum. Exercise cadence was controlled by a metronome, and thus all participants performed the repetitions (10 repetitions) in 15 seconds. Both studies used the Polar S810i monitor and performed the analysis of RR intervals.

Two recent systematic reviews showed that these portable devices have an acceptable margin of error[70] and provide reliable and reproducible HR variability measurements.[11] Therefore, they can be used for clinical and research purposes, especially considering its cost-benefit relationship.[70]

Four-second exercise test (T4s)

Finally, another clinical application of HR measurement during exercise is the assessment of cardiac vagal tone. Considering that the rise in HR in the first four seconds of fast movement of the lower or upper limbs,[71] be it active or passive[72] depends solely on removal of vagal tone, Araújo et al.[73,74] proposed the T4s. Briefly, the test consist in pedaling as fast as possible and without resistance a cycle ergometer from the fifth to the eighth second of a 12-second maximal inspiratory apnea. The quantification of the cardiac vagal index is determined by the ratio of two RR-intervals registered in the ECG: the longest RR-interval before exercise and the shortest RR-interval during exercise, which can be cycling[73,75,76] or stationary running.[77] Recent studies have tested whether HR monitors could be used to determine this index and shown that HR monitor can be used as a surrogate for ECG to determine the cardiac vagal tone in the T4s using a cycle ergometer,[78] but not in the T4s performed in orthostatic position.[79]

Conclusions

In summary, there is a wide range of monitors and smartphone apps to measure HR. The choice of the brand and model should be made based on the purpose of its use. Also, it is fundamental to know how to set up the device for personal, clinical or research purpose. These pieces of equipment may be helpful in the monitoring of the intensity of many types of exercises, and thereby increase the safety and efficacy of a physical exercise or sports training program. In addition, HR monitor devices and apps are in rapid development and would ultimately be useful in the detection of stress-induced cardiac arrhythmias and in the management and follow-up of physically active patients.

Author contributions

Conception and design of the research: Araujo CG. Acquisition of data: Almeida M, Bottino A, Ramos P, Araujo CG. Analysis and interpretation of the data: Almeida M, Bottino A, Ramos P, Araujo CG. Writing of the manuscript: Almeida M, Bottino A, Ramos P, Araujo CG. Critical revision of the manuscript for intellectual content: Almeida M, Bottino A, Ramos P, Araujo CG.

Potential Conflict of Interest

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Study Association

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Ethics approval and consent to participate

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

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REVIEW ARTICLE

Effects of Exercise Training on Cardiovascular and Autonomic Parameters in Stroke Survivors: A Systematic Review

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Abstract

Negative changes in cardiovascular and autonomic variables in stroke survivors have encouraged the global scientific community to focus on investigating therapeutic strategies to mitigate stroke damage. The objective of the present study was to describe the effects of exercise training on cardiovascular and autonomic variables in stroke survivors. We used the PICO (population, intervention, control/comparison, and outcome variables) model for the search of articles in PubMed and Physiotherapy Evidence Databases from 2009 to December 2018. The following data were also recorded: type of study, author, year of publication, participants (time after stroke, sample size, and age) and benefits of exercise training. A total of 544 articles were initially selected, of which nine peer-reviewed articles met the search criteria. These nine studies enrolled 611 participants (middle-aged or elderly), and pointed to positive effects of training on maximal oxygen uptake, peak aerobic capacity, 6-minute walk test and resting heart rate. However, more well-controlled studies are needed to confirm the benefits of exercise training on cardiovascular and autonomic variables in this population.

Keywords

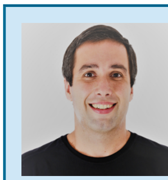
Exercise; Physical Fitness; Cardiovascular System; Autonomic Nervous System; Physiotherapy; Rehabilitation; Stroke; Review.

Introduction

Stroke can be defined as a neurological loss associated with abnormal vascular perfusion due to a vascular cause.[1] It affected 33 million people worldwide in 2010, of which 16.9 million experienced the first stroke.[2]

After stroke, in addition to increased mortality risk due to brain damage, there are impairments in autonomic cardiac control (ACC),[3,4] which are associated with reduced aerobic fitness due to changes in central (reduced central stimulation to the heart) and peripheral (reduction of muscle mass, changes in type II to type I fibers, and reduction of type I fibers) nervous system.[5-8] In this sense, MacKay-Lyons and Makrides[5] observed impaired aerobic capacity (peak VO_2) in stroke survivors.

Additionally, changes in ACC may indicate health impairment, including changes in blood pressure due to reduction of cardiac baroreflex sensitivity and high risk of cardiac death.[9-14] In addition, Dütsch et al.,[15]



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have observed that, regardless of the side affected by the stroke, the individuals showed impairments in the ACC, such as increased sympathetic and decreased parasympathetic system activities.[3,4,15,16]

Exercise training has been used as a non-pharmacological strategy in the management of stroke survivors. Meta-analyses and review studies have reported an increase in strength and muscle function, as well as improvement in cardiovascular variables of stroke survivors in response to exercise training.[17-23]

Although review studies on the association of exercise training and stroke have been gaining attention, the worldwide epidemic of this disease and its structural and functional consequences on cardiovascular and autonomous variables justify the need for further studies on adequate strategies to mitigate stroke damage. This would provide health professionals with more information on the most appropriate exercise prescription to prevent further stroke complications. Thus, the objective of the present study was to describe the effects of exercise training on cardiovascular and autonomic variables in stroke survivors.

Methods

Eligibility criteria

Study selection

The PICO (population, intervention, control/comparison, and outcome variables) model was used for study selection. Studies were chosen for inclusion if they met the following four criteria: (A) post-stroke (> 6 months) patients of both genders, aged over 18 years; (B) structured exercise training program (aerobic and/or resistance); (C) randomized controlled trials; (D) cardiovascular (aerobic capacity) and/or autonomic (resting heart rate in beats/min; heart rate variability) benefits of exercise. The reviewers documented the methodological quality of the studies and extracted relevant data. The following quality criteria were documented: baseline comparison of groups, randomization, all assessed outcomes, and details of participants (i.e., age, gender and time after stroke).

The screening was performed by two independent reviewers. For each article, any discrepancy between the reviewers was resolved by re-reading and further analysis. In the first screening stage (titles plus abstracts), studies were selected when both reviewers agreed they were eligible for inclusion or if there were no disagreements on whether to exclude them. In the second screening stage (full text), studies were included when both reviewers agreed that they met all the inclusion criteria.

Study identification and selection

Relevant studies were identified through computerized and manual searches. For data collection, PubMed and Physiotherapy Evidence Database (PEDro) databases were systematically searched from 2009 until December 2018 (last 10 years).

The following keywords were used in the search: stroke, cerebrovascular accident, cerebral vascular accident, exercise training, aerobic training, aerobic exercise, resistance exercise and resistance training. This review was written in accordance with some items of the Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Assessment of article quality

The methodological quality of the studies was evaluated using the PEDro scale. Two independent reviewers completed the checklist based on the PEDro scale.

The PEDro scale evaluates the following aspects of methodological quality: (1) detailed eligibility criteria, (2) random allocation, (3) concealed allocation, (4) baseline prognostic similarity, (5) participant blinding, (6) therapist blinding, (7) outcome assessor blinding, (8) more than 85% follow-up for at least one primary outcome, (9) intention-to-treat analysis, (10) between- or within-group statistical analysis for at least one primary outcome, and 11) point estimates of variability given for at least one primary outcome.

The internal validity of the randomized controlled trials was evaluated. A study with a PEDro score of 6 was considered level-1 evidence (6–8 good, 9–10 excellent) and a study with a score of 5 was considered level-2 evidence (4–5 acceptable, 4 poor).

Data extraction

The following characteristics were recorded for all articles: type of study, author, year of publication, participants (time after stroke, sample size, and age), cardiovascular and autonomic benefits. This procedure was performed by two reviewers: one reviewer collected the data and the second double-checked it.

Results

A total of 544 articles were initially selected, of which nine peer-reviewed articles met the search criteria. These nine studies enrolled 611 participants (middle-aged or elderly) stroke survivors. The retrieved studies and population characteristics, intervention, and outcomes are shown in Table 1.

After analysis of the selected studies, we found that aerobic training was the predominant exercise training modality, and the main benefits were observed in the following: maximal oxygen uptake, peak aerobic capacity, 6 minutes' walk test and resting heart rate beats/min (Table 1).

There were no accidents involving the participants during the programs (exercise training) in the nine studies selected. However, 17 patients were excluded for the following reasons: absences from training days, lack of motivation, kidney disease, alcoholism, epilepsy, knee pain, inability to perform tests, and dropping out of the study. These findings indicate that the exercise training programs used in these studies seemed to be safe.

Discussion

To our knowledge, this is the first review on cardiovascular and autonomic impairments caused by stroke and the effects of exercise training on these variables in this population.

It is widely recognized that the practice of structured exercise training program may provide several benefits for both healthy individuals and those affected by chronic degenerative diseases.[23-35] Some reviews and meta-analyses have already demonstrated positive effects of exercise training on functional parameters and on the aerobic capacity of poststroke individuals.

Table 1 - Benefits of exercise training in stroke survivors (n = 9)

Authors	Sample	Intervention	Main findings	Quality (PEDro Scale)
Quaney et al.,[36] 2009	38 subjects (17 men and 21 women) (> 6 months poststroke).	Aerobic training	↑ Maximal oxygen uptake	6/10
Globas et al.,[37] 2012	36 subjects (29 men and 7 women) (≥ 6 months poststroke)	Aerobic training	↑ Peak aerobic capacity, ↑ 6 minutes' walk test	7/10
Jin et al.,[38] 2012	133 subjects (94 men and 39 women) (≥ 6 months poststroke)	Aerobic training	↑ Peak VO_2, L/min, ↑ peak VO_2, mL/kg/min	4/10
Jin et al.,[43] 2013	128 subjects (91 men and 37 women) (≥ 6 months poststroke)	Aerobic training	↑ Peak VO_2, L/min, ↑ peak VO_2, mL/kg/min, ↓ resting HR beats/min	4/10
Gordon, Wilks, McCaw-Binns,[39] 2013	128 subjects (64 men and 64 women) (> 6 months poststroke)	Aerobic training	↑ 6 minutes' walk test	7/10
Severinsen et al.,[40] 2014	48 subjects (men) (≥ 6 months poststroke)	Resistance training	↑ Peak aerobic capacity	5/10
Lee at al.,[41] 2015	26 subjects (> 6 months poststroke)	Aerobic training + resistance training	↑ 6 minutes' walk test	7/10
Ivey et al.,[41] 2017	30 subjects (21 men and 9 women) (> 6 months poststroke)	Resistance training	↑ 6 minutes' walk test, ↑ peak aerobic capacity	4/10
Marzolini et al.,[44] 2018	44 subjects (men) (> 6 months poststroke)	Aerobic training+resistance training	↑ 6 minutes' walk test, ↑ peak VO_2, mL/kg/min, ↓ resting HR beats/min	6/10

According to Harris and Eng,[17] Mehta et al.,[18] and Wist et al.,[19] it is possible to improve functional components of poststroke individuals through the practice of resistance training. Additionally, Francica et al.,[21] have shown that aerobic exercise can benefit functional and cardiovascular abilities in poststroke individuals. Pang et al.,[22] have also observed improvement in cardiorespiratory capacity of poststroke individuals who underwent aerobic exercise training.

In line with some of the above findings, seven randomized controlled trials showed benefits on aerobic fitness provided by systematized exercise programs.[36-42] However, in the last 10 years, we found only two studies addressing ACC and exercise in stroke survivors.[42-44] Thus, once again, we emphasize the need for further randomized studies to investigate the effects of exercise training on negative changes in ACC caused by stroke.

ACC is performed by the influence of the sympathetic and parasympathetic branches on the myocardial cells promoting either increase or decrease of the heart rate, according to the needs of the organism. Such variation in heart rate moment by moment in response to the body's need is called heart rate variability. When heart rate variability is normal, it indicates the ability of ACC to respond to multiple physiological stimuli, such as exercise training, mental stress, respiration, and metabolic alterations.[45-47] Any negative change in the interaction between central and peripheral nervous systems (afferent and/or efferent pathways) reduces heart rate variability by compromising ACC with consequent health impairment.[9-11]

According to a study by Kleiger et al.,[48] there is a strong relationship between mortality risk and heart rate variability in individuals after acute myocardial infarction. A high heart rate variability represents good functioning of the autonomic nervous system, positively impacting the health status of an individual, whereas the reduction of this variable indicates losses on the ACC and higher risk of cardiac death.[12,13] According to a study conducted by Francica et al.,[49] poststroke individuals had lower heart rate variability when compared to controls. Although few studies have attempted to investigate the effects of exercise on ACC poststroke, it has been demonstrated that non-pharmacological strategies (exercise training) may increase heart rate variability in other populations and consequently reduce the risk for cardiovascular death.[50-57]

Conclusions

This review found that in the last ten years, few randomized clinical trials involving aerobic training, resistance training, and cardiovascular and autonomic variables after chronic stroke have been performed. Evidence from some studies suggests that exercise training seems effective in improving cardiovascular and autonomic variables in stroke survivors. More randomized controlled trials are needed to assess the role of exercise training in the management of stroke survivors, so that health professionals can make informed choices when prescribing exercise training to improve the impaired variables above mentioned.

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Author contributions

Conception and design of the research: Gambassi BB, Santos CP, Queiroz C, Schwingel PA, Almeida FJF, Almeida AERAF, Ribeiro JR, Novais TMG, Rodrigues B. Acquisition of data: Gambassi BB, Santos CP, Queiroz C, Schwingel PA, Almeida FJF, Almeida AERAF, Ribeiro JR, Novais TMG, Rodrigues B. Analysis and interpretation of the data: Gambassi BB, Santos CP, Queiroz C, Schwingel PA, Almeida FJF, Almeida AERAF, Ribeiro JR, Novais TMG, Rodrigues B. Writing of the manuscript: Gambassi BB, Santos CP, Queiroz C. Critical revision of the manuscript for intellectual content: Gambassi BB, Schwingel PA, Almeida FJF, Rodrigues B.

Potential Conflict of Interest

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

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

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REVIEW ARTICLE

Sudden Cardiac Death in Sports: Why Its Prevalence is So Different by Gender?

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Abstract

Sports competition can be a trigger to fatal arrhythmias in predisposed individuals, leading to sudden cardiac death. Athletes have 2.8 fold more risk of sudden cardiac death than non-athletes. However, female athletes seem to have some cardiac protection, dying suddenly much less than men during sports. Although the mechanisms for this protection have not been well established until now, hormonal, genetic and molecular factors may play a role in it. The so-called "fair sex" might harbour the key for sudden cardiac death prevention.

Introduction

The occurrence of sudden cardiac death (SCD) in sports competition has been described as 10-fold less prevalent in females when compared with male athletes. Literature data show that women are less prone to SCD than men during exercise at any age even among amateur athletes. A large American study analysed US competitive athletes (12-40 years old) who died suddenly over a 27-year period and described that only 11% were females.[1] Likewise, French authors demonstrated similar results performing a nationwide survey in the general population (10-75 years old), where 95% of the sports-related SCD occurred in males.[2] This is an intriguing finding which is not completely understood yet. Previously, it was believed that this would be a consequence of fewer women participating in competitive sports. Moreover, women were considered unable to perform high-intensity exercise and thus, they would not be exposed to a high risk of SCD.[3] However, during the last decades, we have witnessed a sharp increase in female participation in sports, including professional and elite athletes population. Despite this, current data do not present a different scenario in the sex-related differences in SCD occurrence, suggesting that the previous explanation may be too simple.

Sudden cardiac death

The main cause of SCD in older athletes (> 35 years) is atherosclerotic coronary artery disease whereas in young athletes (< 35 years) are inherited structural or electrical cardiac diseases such as hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC) and ion-channelopathies.[4,5] Structural cardiomyopathies seem to be less prevalent in women than men. Moreover, recent data showed that women who died suddenly usually had a structurally normal heart.[6] The development of these diseases may suffer such influence of estrogens and the female features. There are some studies describing interesting findings and proposing some theories to explain the difference in mortality between men and women.

Gender-related differences in the clinical presentation of HCM has been reported and data suggest that women

Keywords

Exercises; Sports/physiology; Women; Death, Sudden, Cardiac/prevention and control; Death, Sudden, Cardiac/prevalence; Coronary Artery Disease; Arrhythimias, Cardiac; Cardiomyopathy, Hypertrophic.

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present a slower development of the pathological features of the disease, which can explain the "lower prevalence" of HCM in females, despite the Mendelian inheritance particularly in the youngers.[7] This is a relevant finding, considering that HCM has a prevalence of 1:500 individuals and it is reported as a major cause of SCD in young athletes.

It has been known for decades that prolonged QT interval is more common in women than men.[8] Some data have demonstrated that this difference is due to shortening of the QT interval that occurs between puberty and the age of 55 years in men, whereas there is a QT prolongation in women during the reproductive years, suggesting that estrogen affects the regulation of cardiac repolarization.[9] In addition, experimental data have shown that estrogen downregulates the activity and expression of Kv4.3 channels, which may have some influence in the clinical presentation of channelopathies, although the prevalence of these conditions is low in the general population.[10] Interestingly, prolonged QT dispersion, which has been suggested as a predictive parameter of SCD and life-threatening arrhythmias in athletes, was described as shorter in female athletes than in male athletes, despite the longer QT interval.[11,12] Previous studies have demonstrated that QT dispersion is greater in post-menopausal women than in pre-menopausal women, showing that it is influenced by sex hormone secretion, and this may play a role in the prevalence of SCD in female athletes.[13]

Physiological cardiac adaptation in female athletes

Cardiac remodelling seems to occur in a different way in female athletes. The pioneer study[14] on a large cohort of elite female athletes, all Caucasians, reported that females rarely exhibit significant myocardial hypertrophy. In this cohort, left ventricular wall thickness (LVWT) had an average of 8 mm and none of the athletes showed a LVWT > 12 mm, measured by echocardiography.[14] Data including Afro-descendant female athletes are few, but probably ethnicity also influences the women's heart. Current literature shows that 3% of female athletes may have a LVWT > 11 mm, but none > 13 mm.[15] These findings suggest that the overlapping of measurements of female athletes' heart with HCM is unlike, since they do not reach values compatible with the so-called "grey's zone" for the "athlete's heart". On the other hand, electrocardiogram (ECG) in female athletes must be carefully analysed to avoid misinterpretation. Some ECG findings described as more common in cardiomyopathies, such as anterior T wave inversion (V1-3) and a flat ST segment, were reported to be more frequent in female athletes but they did not fulfil diagnostic criteria for ARVC after further investigations. As a matter of fact, this ECG pattern has been considered as non-specific in low-risk populations such as women.[16,17]

The effects of cardiac adaptation to exercise on left ventricular (LV) geometry have been studied recently. A large study with healthy elite athletes (41% female) described different LV geometry according to sex and sports discipline and demonstrated limit values for LVWT in Caucasian female athletes similar to previous data.[18] Interestingly, LV cavity dimension, indexed for body surface area, was higher in women, demonstrating that eccentric hypertrophy was more common in endurance female athletes, whereas concentric hypertrophy/remodelling was more common in male athletes. Thus, one may infer that cardiac remodelling could be related to women's "cardiac protection" for SCD.

Where is the key?

A recent review reported some mechanisms of cardiac remodelling and highlighted that hormones and genes may play a role in this process.[19] Some studies have shown the presence of androgenic and estrogenic receptors in myocytes and the hormonal effects on myocardial response. Whereas testosterone stimulates myocardial hypertrophy, estrogens inhibit the proliferation of cardiac fibroblasts.[20] This depends on hormone levels and their bindings to cardiac receptors, which is modulated by genetic expression.

The angiotensin-converting enzyme activity, which is related to blood pressure levels and myocardial hypertrophy, is also influenced by testosterone and estrogen.[21] Some data have shown the association between LV hypertrophy degree in endurance athletes and renin-angiotensin system encoding genes, suggesting that sex hormones affect the expression of these genetic polymorphisms.[22] In addition, a higher level of nitric oxide (NO), which promotes peripheral vasodilation and afterload reduction, is associated with stimulation of strogen release.[23] Consequently, women have a lower systolic blood pressure peak during exercise what is advocated to contribute to less LV hypertrophy.

Experimental studies have also shown that some enzymes involved in energy substrate (fatty acids, glucose) availability are related to prevention of cardiac hypertrophy and their activity seems to be higher in females than males.[24]

Cardiovascular responses to exercise include increase in heart rate, blood pressure and stroke volume. In the presence of abnormal substrates, which occurs in individuals carrying silent cardiac diseases, the adrenergic surges during intense exercise may lead to life-threatening arrhythmias, and hence competitive sports can be a trigger to SCD. Data suggest a higher sympathetic and/or a lower vagal activity in men compared with women. Markers of sympathetic activation after an orthostatic challenge were reported to be higher in male athletes than in females.[25] Thus, it is plausible to assume that sympathetic predominance contributes to a higher risk for SCD in men.

Recent studies[26-28] have demonstrated that veteran male athletes with lifelong high-intensity exercise may exhibit cardiac abnormalities such as coronary artery calcification (CAC), atrial fibrillation (AF) and myocardial fibrosis. These abnormalities have been described as possible deleterious effects of exercise and were rarely present in female athletes. Although a higher prevalence of CAC was observed in veteran male athletes when compared with sedentary males, such difference was not seen between female athletes and female controls.[26] Additionally, female marathoners showed a lower prevalence of coronary plaques and less CAC than sedentary women.[27] Regarding AF, studies including female athletes are few, but the 5 fold-risk of developing AF suggested in veteran male athletes has not been observed in female athletes yet.[28] Similarly, myocardial fibrosis has been described in veteran male athletes, but not in female athletes. A recent study on triathletes reported that 17% of the men but none of the women had late gadolinium enhancement in cardiac magnetic resonance.[29] Therefore, despite the small number of women studied, it can be inferred that females are protected from these complications as well.

Conclusion

The lower prevalence of SCD in women is a fact, but not well understood. The recent increase in women's participation in high-level sports competitions raises the debate on whether this occurrence is a question related only to the number of women in sports.

Female athletes exhibit different cardiac adaptation to exercise and different prevalence of cardiac abnormalities during lifelong exercise practice, including less CAC and myocardial fibrosis, both potentially substrates for life-threatening arrhythmias and SCD. There is a lack of data in humans, particularly in female athletes, but estrogens may play a role in these responses. Cardiac remodelling mechanisms depend on molecular and genetic characteristics influenced by hormones and seem to harbour the mystery of women not being the "fair sex", especially for dying suddenly in sports competition.

It is essential to expand the studies including female athletes to acquire better knowledge in this area. This understanding may improve the preventive actions for SCD in sports.

Author contributions

Conception and design of the research: Colombo C, Ghorayeb N. Acquisition of data: Colombo C, Garcia TG, Francisco RC. Analysis and interpretation of the data: Colombo C, Ghorayeb N. Writing of the manuscript: Colombo C, Ghorayeb N. Critical revision of the manuscript for intellectual content: Colombo C, Ghorayeb N.

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REVIEW ARTICLE

Physical Exercise in the Management of Erectile Dysfunction in Patients with Heart Failure

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Abstract

Erectile dysfunction (ED) is a highly prevalent problem that affects the quality of life, prognosis and survival of patients with heart failure (HF). In the management of ED, physical exercise is a therapeutic strategy that reduces disease-related symptoms and optimizes drug use. However, the repercussions of physical exercise on ED in individuals with HF still need to be elucidated. In this sense, the objective of this study was to evaluate the effects of physical exercise on erectile function (EF) in HF patients. This was a systematic review conducted according to PRISMA guidelines. Patients with HF, male and ejection fraction ≤ 45% were submitted to physical exercise of different modalities. The search for scientific articles was conducted in the electronic databases (PubMed, LILACS, Cochrane-Library, Science Direct) from the inception until October 2018, according to the MeSH dictionary descriptors, which were suitable for all databases. Results: Three studies were analyzed, includinng 99 male subjects, age ranging from 53 years (± 7.48) to 58 years (± 12). Seventy subjects were submitted to a physical exercise program and 29 were in the control group. In all studies, physical exercise showed positive results in the management of ED regardless of erectile dysfunction (ED) classification status and intensity of exercise used. It was concluded that physical exercise of different intensities was considered an effective therapeutic intervention to improve EF in individuals with HF and ED.

Keywords

Cardiovascular Diseases; Heart Failure; Exercise; Physical Finess, Erectile Dysfunction; Aged; Drug Therapy.

Introduction

Heart failure (HF) is the final common pathway of cardiovascular diseases and a complex syndrome involving multiple systems.[1,2]

Recently, interest in the investigation of sexual dysfunction (SD) of these individuals has increased because it is considered a clinical problem of high severity and prevalence,[3-5] with many pathophysiological aspects similar to HF syndrome.[6,7]

Approximately 80% of patients with HF report SD and 30% report total abstinence from sexual activity.[3-5,8] In this context, the correlation between HF and erectile dysfunction (ED) deserves attention, especially considering that sexual function is an important component of quality of life (QoL).[5,9] Sexual problems are strongly related to worse QoL of HF patients, both men (52%) and women (38%).[10-13]

Recently, it has been demonstrated that men with HF, younger than 66 years, monogamous, with ejection fraction below 35% are the individuals who report more difficulties in sexual life.[12,14] ED is defined and characterized as the inability to reach out and maintain the erection of the penis for enough time to allow

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satisfactory sexual intercourse.[15,16] In men with HF, there is a high prevalence of ED, higher than in healthy men of the same age group (37% vs 17%).[14] ED has been associated with the pathophysiological mechanisms of the HF syndrome and to the side effects of drug treatment.[12,13] Additionally, the degree of ED can be used as prognosis and survival factor for these patients.[9]

In HF, based on the high level of scientific evidence, physical exercise is a highly recommended therapeutic strategy,[17-21] with several beneficial effects.[22-24] In fact, physical exercise was shown to benefit erectile function (EF),[25,26] the inflammatory profile[27-28] and the modulation of the autonomic nervous system,[29-31] promoting improvement in QoL and a reduction in the morbidity and mortality rates of these individuals.[32-36]

However, despite growing interest in the topic, with emergence of many observational studies,[3-5,9-14] there is still a lack of studies evaluating the effects of physical exercise on EF of these patients.

In the current knowledge, it seems plausible the hypothesis that physical exercise is a valid therapeutic strategy for ED, by contributing to improvement of the QoL and prognosis of these patients. In addition, physical exercise improves cardiocirculatory performance leading to reduced dyspnea and fatigue symptoms, and less need for drugs. All these variables have been recognized as aggravating factors of SD.[12-14] Therefore, this study aimed to evaluate the effects of physical exercise on EF in individuals with HF, using a systematic review.

Methods

Search strategies

This was a systematic review conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes)[37] recommendations and registered in the PROSPERO platform (International Prospective Register of Systematic Reviews), under the number CRD42018090028.

The search for articles was conducted by two independent researchers in the electronic databases (PubMed, LILACS, Cochrane-Library, Science Direct) databases from inception until October 2018. The study was structured using the PICO – acronym for Population, Intervention, Comparison (since "control" was not applicable to the goal of this study) and Outcomes – framework.[37]

For the search in the PubMed and Cochrane databases, the following MeSH (Medical Subject Heading Terms) descriptors were used: "Heart Failure" OR "Congestive Heart Failure" OR "Cardiac Failure" AND "Exercise" OR "Exercise Therapy" OR "Aerobic Exercise" OR "Physical Exercise" OR "High-Intensity Interval Training" OR "High-Intensity Interval Training" OR "Resistance Training" OR "Strength Training" AND "Erectile Dysfunction" OR "Sexual Dysfunction, Physiological" OR "Penile Erection" OR "Genital Diseases, Male" OR "Impotence" OR "Sexual Dysfunction, Physiological" (Appendix I). These words were then found suitable for the search in the other databases (LILACS and Science Direct).

In addition, a manual search was carried out for references cited in the articles. Also, a search for "gray" literature was performed in Google Scholar, and in the annals of the World Congress of Cardiology and the European Congress of Cardiology, since they are important events in the area of cardiology with strict selection criteria and representatives from all over the world. We also conducted a search for abstracts, due to the small number of papers on this topic.

Eligibility criteria

Inclusion criteria

We included in the review controlled and randomized clinical trials, quasi-randomized controlled trials, comparative studies with or without concurrent controls, case studies, case series with 10 or more consecutive cases, abstracts and articles published in Portuguese, English, or Spanish.

We selected studies with adults (18 years of age or older), with a diagnosis of HF, with reduced ejection fraction (≤ 45%) and functional classes I, II or III according to NYHA. Patients should have been submitted to intervention with aerobic and/or resistance exercise of different intensities. Evaluation of sexual function should have been performed by questionnaires or specific tests: stiffness and nocturnal penile tumescence test, drug-induced erection test, eco-doppler of the cavernous arteries, cavernosography by dynamic infusion, internal pudendal arteriography.[38] The minimum of 4-week of follow-up time was considered for the time of intervention.

Exclusion criteria

Letter to the editor, guidelines, systematic reviews and meta-analyses were not included. We also did not include studies on HF patients with comorbidities such as renal diseases, cardiac transplantation, chronic obstructive pulmonary disease (COPD), stenosis, ventricular assist devices, and patients using any type of supplementation or experimental medication that could affect sexual function.

Selection of studies

The selection of studies was conducted by two independent investigators. Studies were initially screened by titles, then by abstracts, and those considered potentially eligible were selected for full reading. The divergences were resolved by consensus.

Data extraction

Data extraction was performed using a dataset constructed by the researchers; data were added to the dataset by one researcher and then checked by the other researcher. When necessary, the corresponding authors of the studies were contacted to clarify methodological issues or results when necessary or to provide relevant data missing from the abstract or full text.

Assessment of study quality

For assessment of methodological quality, we used the TESTEX (Tool for the assessment of study quality and reporting in exercise) tool. This instrument was developed specifically for use in exercise training studies.[39]

Results

Search results

The flow chart of the search process and results of the search is shown in Figure 1. A total of 318 studies was identified in PubMed, LILACS, Cochrane-Library, Science Direct, and in the Annals of the main scientific conferences in the area. Then, studies were excluded due to duplicity and analysis of the title, abstract and full reading. Finally, three studies met the eligibility criteria.

A total of 99 individuals with HF was included in this review, with mean age ranging from 53 years (± 7.48) to 58 years (± 12). Of these, 70 individuals were submitted to a supervised aerobic exercise program three times per week, and 29 were controls. In all studies, only males were included, and all patients were in NYHA functional class II (n = 37) or III (n = 62) and had left ventricular ejection fraction (LVEF) ≤ 45%.

Of the selected studies, only one randomized clinical trial, conducted in Italy, was published in the format of scientific paper,[25] while the other two studies[26,40] were published in Annals of international scientific conferences. The other two studies, in the form of abstracts, were developed in Brazil by the same research group; the first study was a randomized, controlled clinical trial40 and the second one was a uncontrolled, non-randomized prospective clinical trial.[26]

Intervention Protocols

Regarding the intervention protocols of the selected studies in this review, in the study by Belardinelli et al.,[25] the intervention was supervised exercise training with a cycle ergometer, 3x/week for 8 weeks; each session had a total duration of one hour, divided into 15 minutes of initial stretching, 40 minutes on a cycle ergometer at 60% of peak oxygen consumption (VO_2peak) and five minutes of recovery. This study was the only one that used a control group that was not submitted to any type of physical exercise and asked to refrain from exercise during the study period.

Sties et al.,[26] in a prospective study, applied a supervised exercise on a treadmill 3x/week for 12 weeks, with sessions of 40 minutes of aerobic training in which individuals should remain between the anaerobic threshold and the point of respiratory compensation determined by the cardiopulmonary test.

In the randomized clinical trial, Sties et al.,[40] evaluated two groups submitted to different intensities of supervised exercise training on a treadmill. The activity was performed 3x/week for 12 weeks, with sessions of 50 minutes divided in 5 minutes of stretching, 40 minutes of aerobic exercise in the target training zone and 5 minutes of stretching exercises. In this study, the first group (n = 11) performed continuous aerobic exercise of moderate intensity and instructed to remain close to the first threshold (aerobic threshold), determined by cardiopulmonary test. The second group (n = 9) was submitted to interval aerobic exercise on a treadmill, in a high-intensity protocol, and instructed to remain as long as possible near the second respiratory compensation threshold.

Sexual Function

For assessment of sexual function, all studies used specific questionnaires. The "Sexual Activity Profile

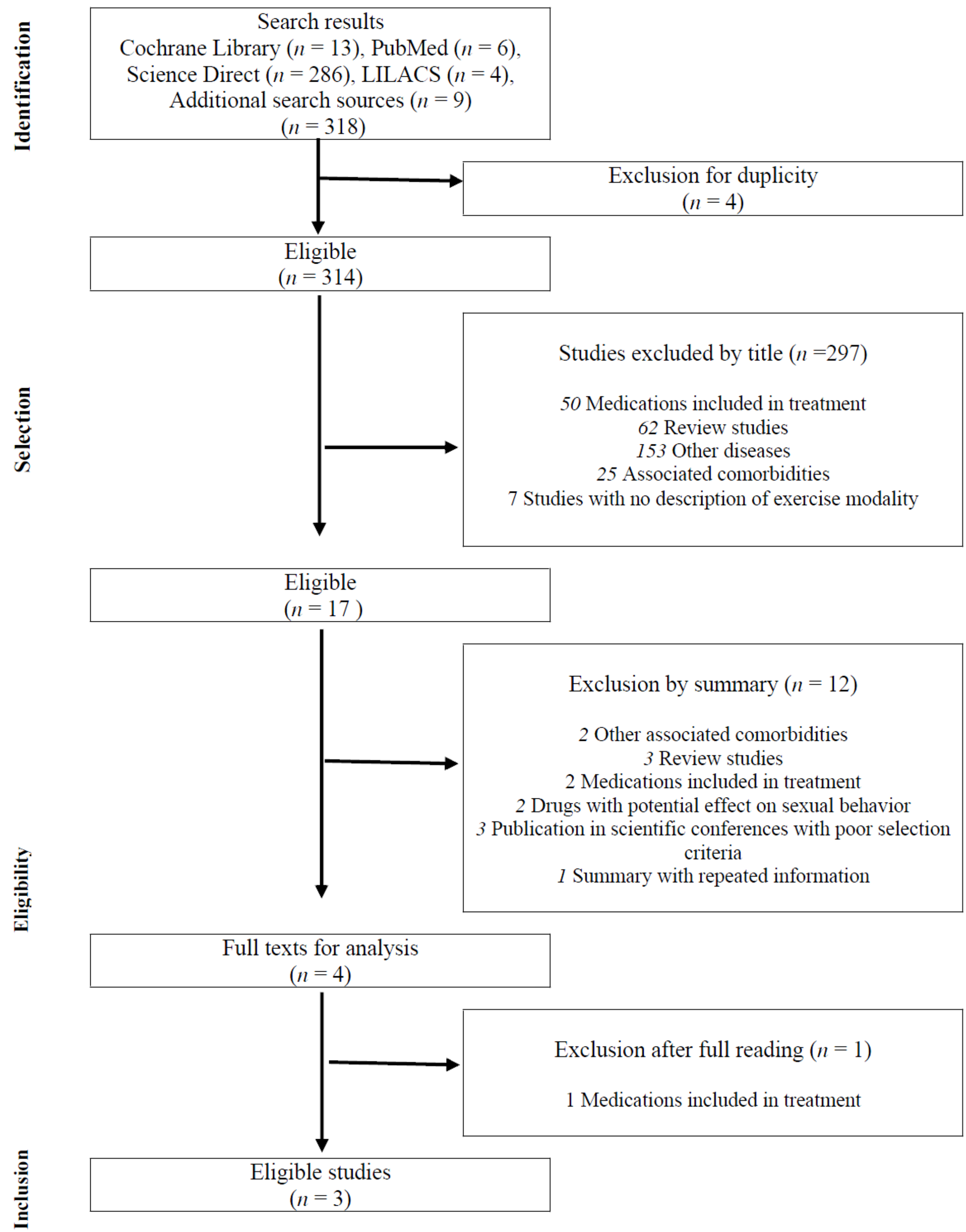

Figure 1 - Flowchart of the search strategy.

Questionnaire" was used by Belardinelli et al.,[25] and the International index of erectile function (IIEF) in the studies by Sties et al.,[26,40] Belardinelli et al.,[25] investigated only married patients, while in the studies of Sties et al.,[26,40] individuals with an active sex life were evaluated regardless of marital status or monogamy.

Regarding EF, the study by Belardinelli et al.,[25] showed that the exercise group with an intervention of 8 weeks demonstrated a significant improvement in the quality of the erection and in the relationship with the partner. In the study by Sties et al.,[26] the EF domain showed significant improvement after 12 weeks of intervention. In the study by Sties et al.,[40] the significant improvement in the EF score was evidenced only in the group submitted to high-intensity physical exercise training. However, when the results related to the EF classification were verified, both individuals submitted to both high-intensity and moderate training showed significant score increases.

Functional capacity

In the cardiopulmonary test, Belardinelli et al.,[25] and Sties et al.,[26] demonstrated a significant improvement in VO_2peak. In the study by Sties et al.,[40] the improvement in VO_2peak was evidenced only in the high-intensity interval exercise group. Only in the study by Sties et al.,[26] the six-minute walk test (6MWT) was used and verified that all individuals showed a significant improvement in the walked distance after the intervention.

Endothelial function

Regarding the endothelial function results, only two studies[25,40] performed the evaluation of this variable. In the study by Belardinelli et al.,[25] it was possible to observe a significant improvement in the flow-mediated dilation (FMD) of the brachial artery in the group submitted to physical exercise for 8 weeks, at the same time that the FMD was the strongest independent factor of improvement of the sexual function in these patients. For Sties et al.,[40] FMD of the brachial artery did not show a significant improvement in any of the study groups (moderate and high-intensity) after 12 weeks of intervention.

Quality of life

Assesment of quality of life was performed in two of the three analyzed studies.[25,40] Both studies used the Minnesota Living with Heart Failure (MLHFQ) questionnaire, validated for patients with HF. There was a significant improvement in the QoL score after physical exercise training in different intensities (high and moderate).

Evaluation of methodological quality

The eligible studies were fully read and scored based on (Table 2) a structured spreadsheet for data extraction previously designed for the study.

Of the three studies analyzed, two[25,40] got the maximum scale score (12 points) (Table 2), showing good methodological quality. Only one study showed a low score of 6 points, due to its design nature (uncontrolled, non-randomized longitudinal clinical trial).[26] The lack of intention-to-treat analysis was verified in all studies, indicating a methodological limitation.

Discussion

All studies from this review evaluated sexual function through validated and self-reported questionnaires. Physical exercise led to improvements in EF regardless of the degree of dysfunction.

Sexual dysfunction is an increasingly common problem in the middle-aged world population, strongly associated with cardiovascular disease.[5,8,15] Its high prevalence in HF patients is understandable, since SD and HF have common risk factors and pathophysiological characteristics.[3] Also, some drugs used in the treatment of HF seem to impair sexual function.[41]

Between 58% and 87% of patients report problems in sexual function after the diagnosis of HF.[12,42,43] These problems may vary from a decrease in the interest and frequency of sexual activity to total abstinence, reported by 25% of these individuals.[13] Despite the high prevalence of SD in subjects with HF with concomitant worsening in the QoL indexes, few studies or relevant data on the topic[44] have been published.

In this context, ED stands out as the most prevalent sexual alteration in patients with HF[3,14,15] and it influences not only the QoL but also the prognosis and the survival.[9] of these patients. Therefore, it is imperative that health professionals do not neglect this condition, and be prepared to discuss sexual function with patients and their partners, providing them with adequate counseling and pertinent information.[13,41,42,45] According to the

Table 1 - Summary from the studies designs and outcomes

Author/Year Contry of Study	Purpose of the study	Study Design	Sample Description	Intervention	Evaluation of Erectile Function	Functional capacity	Endothelial Function Quality of life	Conclusion
Belardinelli 2005[25] ITALY	To evaluate the effects of physical exercise on sexual dysfunction in individuals with HF	RCTs	59 men EG (n = 30) CG (n = 29)	EG: Supervised exercise on cycle ergometer, 3x/week, 8 weeks; 60% of the VO_2peak CG: The volunteers were instructed not to perform any physical activity during the study	Men with partners Sexual activity profile questionnaire ↑EG*	Cardiopulmonary test ↑VO_2peak = EG*†	FMD = ↑ EG* MLHFQ = ↑ EG*	In HF, exercise training using cycle ergometer significantly improved endothelial function of the brachial artery, suggesting a systemic effect of leg exercise. This benefit was correlated with improvements in sexual activity.
Sties 2014[41] BRAZIL	To evaluate the effects of moderate and high-intensity physical training on sexual function and quality of life (QoL) in patients with HF	RCTs	20 men MIG (n = 11) HIG (n = 9)	MIG: Supervised activity on treadmill, 3x/week, 12 weeks; Aerobic exercise Moderate continuous close to L1. HR target determined by cardiopulmonary test. HIG: Supervised activity on treadmill, 3x/week, 12 weeks; High-intensity interval exercise with the HR being maintained between second L2 threshold / point alternating with the L1 HR. HR target determined by cardiopulmonary test	Sexually active men IIEF ↑ HIG*	Cardiopulmonary test ↑ VO_2peak = HIG*	FMD MLHFQ = ↑MIG* ↑HIG*	High-intensity exercise promoted significant benefits in erectile function, desire, sexual satisfaction and peak aerobic power, while in the moderate intensity exercise no changes were found in these outcomes. Improvements in the walked distance in the 6-minute walking test and QoL occurred in both groups, with no differences between them.
Sties 2013[26] BRAZIL	To determine whether aerobic physical training can improve the sexual function of men with HF	Non-randomized Clinical Trial	20 men	Supervised physical exercise on treadmill, 3x/week, 12 weeks. Exercise between the anaerobic threshold and the respiratory compensation point, 40 minutes per session	Sexually active men IIEF ↑p = 0,02*	Cardiopulmonary test ↑VO_2peak* 6MWT ↑ walked distance*	NE	In stable HF, physical exercise training on treadmill significantly improved VO_2peak, and walked distance in the 6MWT and sexual function.

*Subtitle: RCTs: randomized controlled clinical trial; IIEF: International index of erectile function; QOL: quality of life; HF: heart failure; EG: exercise group; CG: control group; MIG: moderate intensity group; HIG: high intensity group; MHFLQ: Minnesota Living With Heart Failure Questionnaire; 6MWT: Six-minute walking test; L2: respiratory compensation point/ ventilatory threshold; HR: heart rate; L1: respiratory compensation point aerobic threshold; * - significant difference $p < 0,05$ post-intervention intragroup; † – significant difference $p < 0,05$ intergroups; FMD: flow-mediated dilatation; NE: non evaluated.*

Table 2 - Studies classification according to the Testex scale (maximum score of 15 points)

TESTEX Items	Authors		
	Belardinelli et al (2005)[25]	Sties et al (2013)[26]	Sties et al (2014)[40]
1 – Eligibility criteria specified	Yes	Yes	Yes
2 – Randomization specified	Yes	Not	Yes
3 – Allocation concealment	Yes	Not	Yes
4 – Groups similar at baseline	Yes	Not	Yes
Blinding of all participants*	Not	Not	Not
Blinding of all therapists*	Not	Not	Not
5 – Blinding of assessor (for at least one key outcome)	Not	Not	Not
6 – Outcome measures assessed in 85% of patients#	Yes	Yes	Yes
7 – Intention-to-treat analysis	Not	Not	Not
8 – Between-group statistical comparisons reported[a]	Yes	Not	Yes
9 – Point measures and measures of variability for all reported outcome measures	Yes	Yes	Yes
10 – Activity monitoring in control groups	Yes	Not	Yes
11 – Relative exercise intensity remained constant	Yes	Yes	Yes
12 – Exercise volume and energy expenditure	Yes	Yes	Yes
Total score TESTEX	**12**	**6**	**12**

*Subtitle: * – items of the scale TESTEX that are not scored; #items of the TESTEX scale which scores up to 3 points; [a]items of the TESTEX scale with escores up to 2 points.*

European Society of Cardiology (Guideline ESC 2016), management of sexual dysfunction of patients with HF should consider the educational status of the patients, who should be informed about sexual behavior, its relationship with HF, and how to treat ED when it exists.[46]

For this purpose, physical exercise should always be recommended.[17-21] According to the results obtained in this systematic review, a physical exercise program is considered effective in the treatment of ED in HF patients, promoting a significant improvement in erectile function scores[25,26,40] and QoL[25,40] in individuals with functional class II and III (NYHA). Studies have shown that physical exercise is a safe and effective therapy for ED, even for patients with more severe impairment, which may be an additional motivation to exercise for HF patients.

Although ED treatment in these patients may involve the use of PDE-5 inhibitors, this class of drugs is safe only in patients with functional class I and II (NYHA) and is contraindicated in high-risk patients or patients taking nitrates.[47]

In relation to the pathophysiology of ED and HF, two pathways of neurovascular activation have been suggested to be responsible for the association between these conditions.[25,48-51] These pathways would explain the reduced capacity of penile arterial dilation caused by inadequate blood inflow to the corpus cavernosum, making penile stiffening and enlargement impossible for a satisfactory erection in HF patients. This could contribute to the greater activation of the sympathetic nervous system, which would increase smooth muscle tone of the penis and consequent vasoconstriction of the penial vessels.[5,11,48] In this view, we showed that therapies that can modulate neurovascular activation pathways in patients with HF and ED are promising, including physical exercise.

By evaluation of endothelial function, the study developed by Belardinelli et al.,[25] demonstrated that there was a significantly greater improvement in FMD to the brachial artery in the group of patients with ED submitted to the 8-week exercise protocol compared to controls. In this study, FMD was the strongest independent factor related to the improvement of the sexual function of these patients, who showed a significant improvement in the quality of penile erection. In the study of Sties et al.,[40] the FMD of the brachial artery showed no significant change after 12 weeks of intervention. The difference in these results may have occurred due to differences in the methods used for endothelial function evaluation.

Belardinelli et al.,[25] evaluated FMD by application of 240mmHg of pressure in the cuff for 4.5 minutes in the dominant upper limb of the patient. The measurements were performed after the use of sublingual nitroglycerin, 30s, and 90s after deflation. In the study by Sties et al.,[40] the pressure used was 250mmHg, for 5 minutes, in the left upper limb and the image obtained was captured 50 seconds after the deflation.

The presence of peripheral hypoperfusion in HF patients with impaired LVEF[3,5,48,52] contributes to aggravate ED,[4,10,11] worsening functional status and exercise tolerance.[5,53-55] The symptoms of HF (dyspnea, fatigue, and exercise intolerance) are among the main factors responsible for impairing sexual function.[5,13]

The results of this review demonstrated that physical exercise in different intensities was able to promote significant improvement in functional capacity and tolerance to exercise in patients with HF and ED when evaluated by cardiopulmonary test. In the study by Sties et al.,[40] the improvement of exercise tolerance in cardiopulmonary exercise test was evidenced only in subjects submitted to high-intensity interval exercise in comparison to those submitted to moderate-intensity exercise. These findings are in agreement with the studies that recommend the use of high-intensity physical training for patients with HF.[22,24] However, all the patients with ED assessed by the 6MWT showed a significant improvement in the walked distance after the intervention, regardless of exercise intensity.

Limitations

Among the limitations of this study, there is the small number of participants. Only one study included a physically inactive control group, and only one complete article was included in the review. These limitations make it difficult to carry out a quantitative analysis and show a large gap in the literature.

Additionally, because of the scarcity of data about this relevant topic in the clinical area, further studies should be encouraged to confirm the findings.

Conclusion

In this systematic review, physical exercise was recommended as a safe and effective therapy to improve EF, endothelial function, quality of life and functional capacity of individuals with ED and heart failure.

Author contributions

Conception and design of the research: Gonzáles AI, Carvalho T, Andreato LV, Sties SW, Souza AC. Acquisition of data: Gonzáles AI, Carvalho T, Andreato LV, Sties SW, Souza AC. Analysis and interpretation of the data: Gonzáles AI, Carvalho T, Andreato LV, Sties SW, Souza AC. Critical revision of the manuscript for intellectual content :Gonzáles AI, Carvalho T, Andreato LV, Sties SW, Souza AC.

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

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Appendix I: Search Strategy at PubMed and Cochrane-Library

[("Heart Failure" OR "Congestive Heart Failure" OR "Cardiac Failure") AND ("Exercise" OR "Exercise Therapy" OR "Aerobic Exercise" OR "Physical Exercise" OR "High-Intensity Interval Training" OR "High-Intensity Interval Training" OR "Resistance Training" OR "Strength Training") AND ("Erectile Dysfunction" OR "Sexual Dysfunction, Physiological" OR "Penile Erection" OR "Genital Diseases, Male" OR "Impotence" OR "Sexual Dysfunction, Physiological")]

CASE REPORT

Sudden Cardiac Arrest in Athletes: Do not Miss Suspicious Details

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Introduction

Sudden cardiac death (SCD) related to sports activities is an unexpected and rare event, usually occurring in young and apparently healthy athletes. The main cause of SCD in young athletes (< 35 years old) is ventricular arrhythmia (VA) associated with arrhythmogenic disorders (e.g. hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy – ARVC, channelopathies). Some of these conditions can be suspected by routine pre-participation clinical evaluation, while others remain undetectable even after careful screening.[1-3] This paper presents the case of a professional athlete with undiagnosed ARVC, whose first manifestation was malignant VA and biventricular dysfunction.

Case report

A 19-year-old white male professional handball player participated in a regional league since he was 16. He had unremarkable medical or family history. His pre-season medical examination showed electrocardiogram (ECG) with sinus rhythm, inverted T wave in right precordial leads and occasional premature ventricular contractions (PVC) (Figure 1). For more information, his physician ordered 24-hour Holter monitoring, transthoracic echocardiography (TTE) and an exercise test. The 24-hour Holter monitoring revealed periods of sinus bradycardia and 3713 PVC occurring as isolated, pairs or triplets, independently of exertion. TTE and exercise test were described as normal and he was allowed to play.

Keywords

Spots; Athletes; Physical Endurance; Risk Assessment; Sudden Death; Cardiac Arrest; Arrhythmias Cardiac; Arrhytmogenic Right Ventricular Dysplasia.

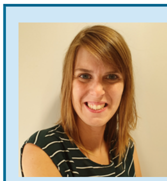
Two years later, the athlete collapsed due to cardiac arrest during a handball match, while he was defending an attack. His colleagues started cardiopulmonary resuscitation (CPR) immediately. The prehospital medical emergency team arrived 10 minutes later and detected ventricular fibrillation. After one shock, the patient showed signs of return to spontaneous circulation on the field. Afterwards, the young athlete presented another collapse in the emergency transport, with shockable rhythm. Advanced life support with defibrillation and mechanical compressions were started again and the patient recovered after a total of 20 minutes of CPR. The first ECG (figure 2A) at the emergency room showed sinus rhythm, right axis deviation, dominant R waves in V1 and elevation of ST segment in precordial leads.

Bedside TTE revealed dilated right chambers with biventricular global systolic dysfunction. Emergent coronary angiography showed normal coronary arteries. Lab tests showed high sensitivity troponin I elevation with no other relevant alterations.

Three days after the event, invasive mechanical ventilatory support and vasopressors were suspended and the patient recovered without neurological or cognitive deficits. Serial ECGs showed inverted T wave in right precordial leads (Figure 2B).

TTE was repeated and confirmed dilatation of the right chambers with marked trabeculations in the right ventricle (RV) and biventricular global systolic dysfunction (Figure 3A-D).

For further investigation, cardiac magnetic resonance (CMR) was performed, showing left ventricular (LV)



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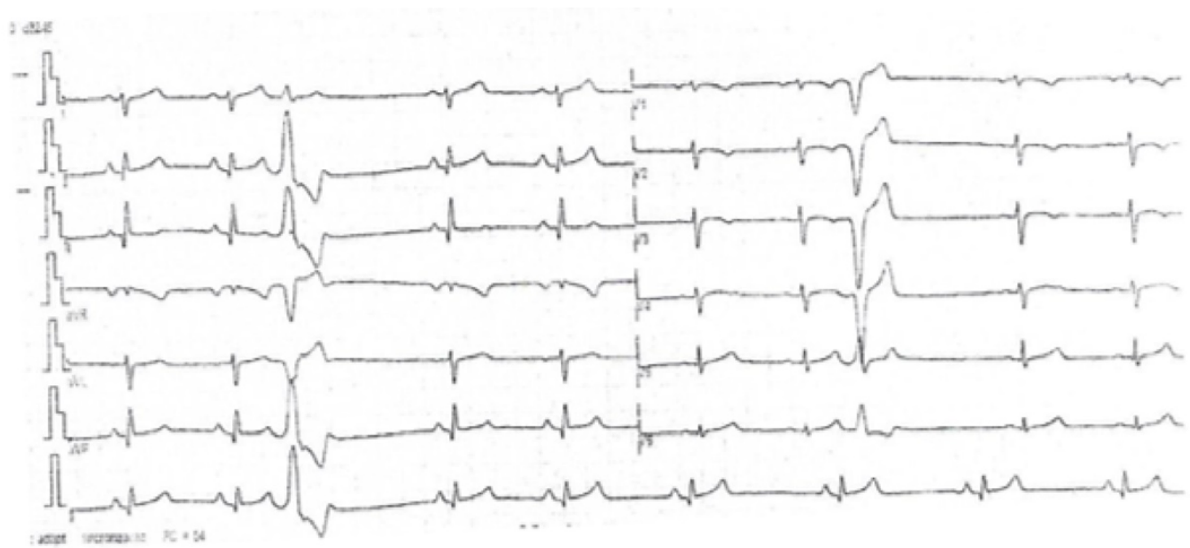

Figure 1 - Pre-seasonal routine electrocardiography.

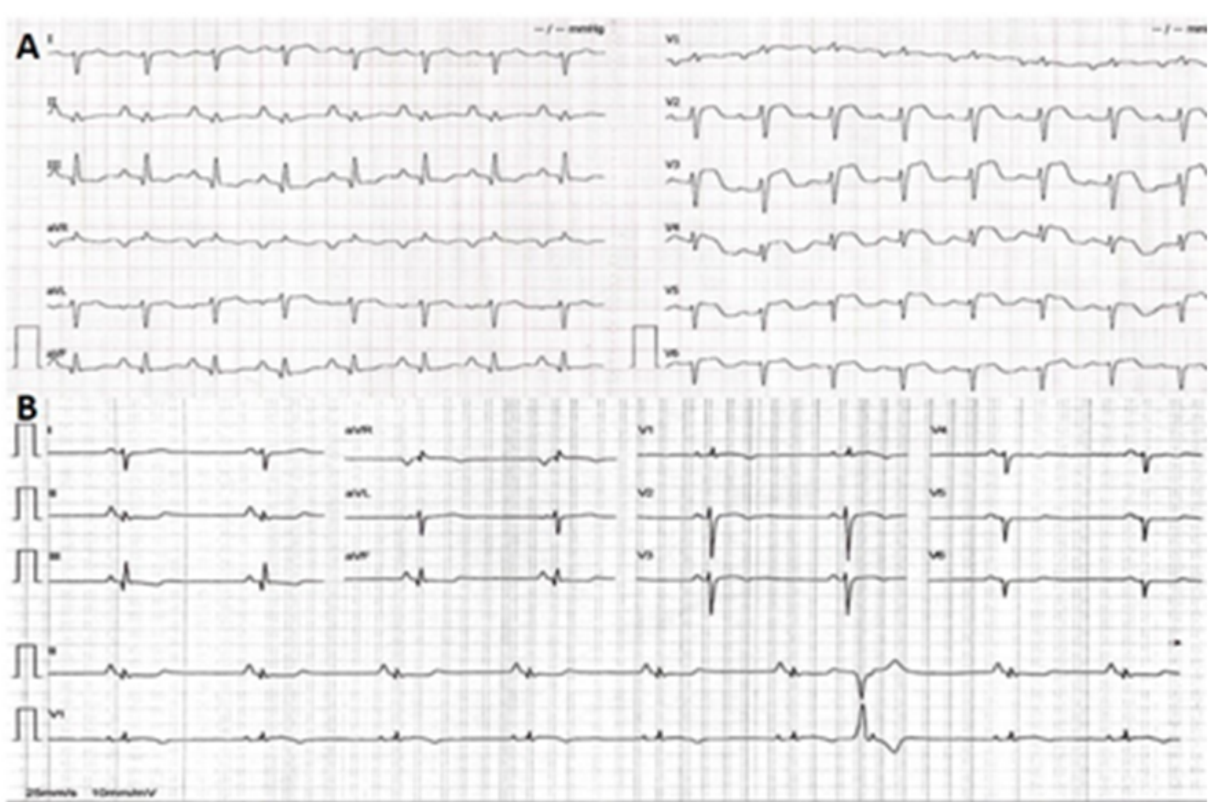

Figure 2 - A) First ECG after return of spontaneous circulation showing sinus rhythm, right axis deviation, dominant R waves in V1 and elevation of ST segment in the precordial leads. B) ECG after total recovery and at hospital discharge. ECG: electrocardiography.

end-diastolic volume in the upper limit of normality (104 ml/m^2) and mild global LV systolic dysfunction (LV ejection fraction 41%); RV was severely dilated (148 ml/m^2) with dyskinesia in the outflow tract and severe systolic dysfunction (RV ejection fraction 28%). Late gadolinium enhancement was found in the RV outflow tract (transmural) and in the LV inferolateral wall (subepicardial). These findings suggested diagnosis of ARVC with biventricular involvement (Figure 3E-G). Genetic test revealed desmoglein 2 gene variant of uncertain significance (c.874C > T).

Due to frequent PVC and runs of nonsustained ventricular tachycardia (NSVT) with inferior axis and left block morphology non-responsive to beta-blockers, sotalol was started with success. Implantable cardioverter defibrillator (ICD) was implanted for secondary prevention.

The patient was discharged home on sotalol 160 mg twice a day and lisinopril 5 mg daily. He was advised not to engage in competitive and/or endurance sports.

Discussion

ARVC is a heritable heart muscle disorder characterized by VA, heart failure (HF) and SCD.[4] ARVC is usually diagnosed in adolescence-young adulthood and is more frequent in male patients. Known disease-causing genes mostly encode desmosomal proteins, although the true prevalence of these genes has yet to be determined. Therefore, a negative genetic test does not rule out the ARVC diagnosis.[5]

The histopathological hallmark of ARVC is the replacement of myocardium by fibrofatty tissue, predominantly in the RV wall. It occurs mostly in the RV inflow tract, outflow tract and apex ("triangle of dysplasia"), from the epicardium to the endocardium. These changes lead to wall thinning and aneurysm formation. More infrequently, though not rare, there is LV involvement, as in our case.[6] Physical exercise may aggravate mechanical uncoupling of myocytes; therefore, exertion is a trigger of disease onset and progression, as well as VA.[4]

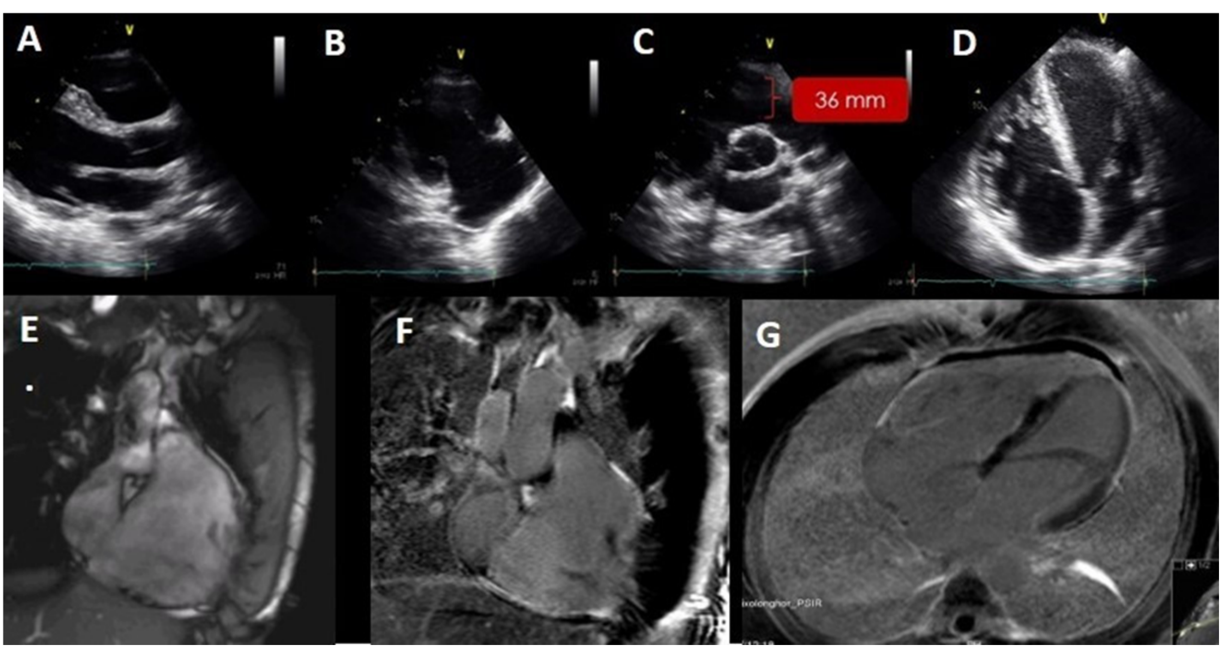

Figure 3 - Top: TTE with dilated right chambers (A: parasternal view; B: right chambers parasternal view; C: short axis view showing RV outflow tract), hypertrabecular RV (D: four-chamber view) and biventricular systolic dysfunction. Bottom: CMR revealed LV end-diastolic volume in the upper limit of normality with mild systolic dysfunction, severe RV dilatation, dyskinesia in outflow tract and severe RV systolic dysfunction (E). Late gadolinium enhancement was visible in the RV outflow tract (transmural) and in the LV inferolateral wall (subepicardial) (F and G). TTE: transthoracic echocardiography; CMR: cardiac magnetic resonance; RV: right ventricle; LV: left ventricle.

Clinically, three phases have been described in ARVC. In the "concealed phase," patients are often asymptomatic. In the overt "electrical phase," they present symptomatic arrhythmias with/without structural abnormalities in imaging tests. Progressive disease may result in RV, LV or biventricular HF combined or not with VA.[5]

Cardiac arrest can be the first manifestation, as in our case, even in the concealed phase.[4,5] Our patient had some abnormalities on the previous ECG and on the 24-hour Holter that could suggest the diagnosis, such as inverted T wave in V1-V3 leads and frequent PVC. Indeed, in recent international recommendations for electrocardiographic interpretation in athletes, anterior inverted T wave in non-black athletes and > 2 PVC per 10 seconds tracing are considered ECG abnormalities.[7] However, these abnormalities are nonspecific and, after normal TTE, our patient was cleared to sport practice.

CMR is the preferred imaging method for ARVC diagnosis. It is useful not only in RV morphological and function evaluation, but also in tissue characterization. Late gadolinium enhancement can be visible predominantly in subepicardial RV wall and/or LV inferolateral (observed in this case) or inferoseptal regions, contributing to the early diagnosis of left-sided disease.[8]

Current task force criteria for ARVC diagnosis[9] includes major and minor criteria concerning morphological RV abnormalities (by TTE, CMR or angiography), pathological abnormalities in RV endomyocardial biopsy (EB), depolarization and repolarization changes in ECG, VA, and family history. In the presence of 2 major criteria, 1 major and 2 minor criteria or 4 minor criteria, ARVC diagnosis is considered definitive.

Our patient fulfilled 2 major and 2 minor criteria: 1 major criteria of morphological RV abnormalities (RV dilatation and RV systolic dysfunction with regional dyskinesia in TTE/CMR), 1 major criteria of repolarization abnormalities (inverted T waves in precordial leads) and 2 minor criteria of VA (NSVT with RV outflow morphology and > 500 PVC in 24-hour Holter monitoring). He had no depolarization abnormalities or family history of ARVC or SCD. Given the results of non-invasive investigation, EB was dismissed.

Advising against competitive/endurance sports is the first step in the treatment of ARVC. Beta-blockers prevent exertion-induced VT/VF and are recommended in the presence of HF, as well as the remaining standard HF therapy. Antiarrhythmic drug therapy has a role in patients with symptomatic frequent PVC/NSVT or many other appropriate ICD therapies.[10] ICD therapy is recommended in patients with history of aborted SCD and hemodynamically poorly tolerated ventricular tachycardia.[10]

Conclusion

This case presents a malignant ARVC presentation in a young athlete with previous subtle abnormalities in medical exams. It highlights the missing details on clinical evaluation even when a comprehensive medical examination is performed. All patients' data need to be carefully analyzed in order to early detect cardiac disease, like ARVC, and reduce SCD in this population. Disqualification of affected patients from competitive sports might be life-saving.

Authors Contribution

Conception and design of the research: Braga M. Acquisition of data: Braga M, Araújo P. Analysis and interpretation of the data: Braga M. Araujo P. Writing of the manuscript: Braga M, Dias P, Vasconcelos M, Almeida R, Maciel MJ. Critical revision of the manuscript for intellectual content: Braga M, Dias P, Vasconcelos M, Almeida R, Maciel MJ.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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

Ethics approval and consent to participate

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

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NEWS

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