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REVIEW ARTICLE

Effect of different modalities of exercise on cardiac autonomic modulation in patients with coronary artery disease: a systematic review

Efeito de diferentes modalidades de exercício na modulação autonômica cardíaca de pacientes com doença arterial coronariana: uma revisão sistemática

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ABSTRACT

Introduction: CAD is responsible for a substantial fraction of cardiovascular disease-related deaths and autonomic dysfunction is among the most important changes caused by this disease. **Objective:** To investigate, through a systematic review, the effects of supervised physical exercise on cardiac autonomic modulation in individuals with CAD. **Methods:** Studies originally published in English from the last 10 years were analyzed using the MedLine (National Library of Medicine) database as a reference. In order to select the studies with the greatest scientific evidence, only clinical trials and observational studies were selected. **Results:** Literature data demonstrated benefits for patients in the exercise group, as they obtained improvements in autonomic modulation. Patients with CAD who underwent physical training programs, whether aerobic land or water, showed improvement in baroreflex sensitivity index, parasympathetic modulation, HR variability (significant increase in heart rate recovery) and cardiorespiratory index. **Conclusion:** The results suggest an improvement in the autonomic modulation of patients with CAD after the introduction of the physical training program, thus constituting a good non-pharmacological intervention for the affected population.

Palavras-chave: Autonomic Nervous System Diseases; Autonomic Dysfunction; Coronary artery disease.

RESUMO

Introdução: A DAC é responsável por uma fração substancial de mortes relacionadas a doenças cardiovasculares e a disfunção autonômica está entre as mudanças mais importantes causadas por esta doença. **Objetivo:** Investigar, por meio de uma revisão sistemática, os efeitos de diferentes modalidades de exercício na modulação autonômica cardíaca em indivíduos com DAC. **Métodos:** Foram analisados estudos publicados originalmente na língua inglesa, dos últimos 10 anos, tendo como referência a base de dados MedLine (National Library of Medicine). Objetivando selecionar os estudos de maior evidência científica, foram selecionados apenas os ensaios clínicos e estudos observacionais. **Resultados:** Os dados da literatura demonstraram benefícios, na modulação autonômica cardíaca de pacientes que praticam exercícios. Os pacientes com DAC que passaram por programas de treinamento físico, sejam aeróbicos terrestres ou aquáticos, apresentaram melhora no índice da sensibilidade barorreflexa, na modulação parassimpática, na

variabilidade da FC (aumento significativo na recuperação da frequência cardíaca) e no índice cardiorrespiratório. **Conclusão:** Os resultados sugerem melhora na modulação autonômica dos pacientes com DAC após a introdução do programa de treinamento físico, constituindo, desta forma, uma boa intervenção não farmacológica para a população acometida.

Palavras-chave: Doenças do sistema nervoso autonômico; Disfunção autonômica; Doença arterial coronariana.

INTRODUCTION

Coronary artery disease (CAD) is characterized by insufficient blood supply to the heart through the coronary arteries. Insufficiency is related to the degree of blood flow obstruction caused by atherosclerotic plaques, which results in the narrowing of the coronary arteries (stenosis) with a consequent reduction in coronary blood flow and a reduction in the arrival of oxygen to the heart[16]. CAD can impair the sympathovagal balance, promoting a decrease in parasympathetic modulation and an increase in cardiovascular sympathetic modulation even at rest, which increases the risk of fatal arrhythmias and sudden death. Therefore, due to the relationship between CAD and autonomic dysfunction, the assessment of the autonomic nervous system is considered extremely important in this population[11].

The autonomic nervous system, in turn, tonically and reflexively influences the cardiovascular system, since both noradrenaline and acetylcholine released in the heart modify cardiac output by altering the strength of contraction of myocardial fibers and heart rate. In resistance vessels of the systemic circulation, the release of norepinephrine modifies the contractile state of vascular smooth muscle and, thus, peripheral vascular resistance. Furthermore, the sympathetic system can exert a trophic effect on smooth and myocardial muscle cells[10].

Although the mechanisms behind the development of cardiovascular disease are increasingly understood, it remains the leading cause of death worldwide. CAD is responsible for a substantial fraction of these deaths and autonomic dysfunction is among the most important changes caused by this disease. It has been demonstrated that, in patients with CAD, there is a cardiac parasympathetic inhibition that is triggered by a predominant cardiac sympathetic activity, partly caused by coronary ischemia and mainly by changes in the electrical properties of the myocardium, due to the destruction of the neural ventricular receptors[1].

A recent international case-control study identified not only well-known risk factors for the development of CAD, such as smoking, obesity, diabetes, and lack of physical activity, but also some psychosocial ones, such as stress and depression[2]. Furthermore, Wu SK et al found that the autonomic nervous system (ANS) plays a central role in regulating cardiovascular function in both health and disease. It is suspected that ANS abnormalities have a strong influence on the mechanisms of sudden cardiac death.

The analysis of heart rate fluctuations, called heart rate variability (HRV), is one of the most widely used methods to measure cardiac autonomic modulation in humans, as it is a non-invasive measurement. HRV has been routinely performed using linear and non-linear methods and can be seen as an important tool, in addition to the lipid profile, hemodynamic variables, monitoring and treatment of patients with CAD, as they provide relevant information on the sympathetic and parasympathetic aspects, whose dysfunction is a key factor in the pathophysiology of CAD[1]. It is also known that autonomic dysfunction adversely affects the clinical outcome in patients with cardiovascular disease and physical training has been shown to modify the sympathovagal heart rate control[3].

The concept of cardiac rehabilitation (CR) and secondary prevention has been defined as the effort toward cardiovascular risk factor reduction designed to decrease the chance of a subsequent cardiac event and to slow and, perhaps halt, the progression of the cardiovascular disease process. Thus, CR has been hypothesized to favorably impact heart rate recovery through modulation of autonomic function[3]. Therefore, the aim of the present study was to investigate, through a systematic review, the effect of supervised physical exercise on cardiac autonomic modulation in individuals with CAD.

METHODS

Search Strategies

The most relevant studies originally published in the English language in the last 10 years were analyzed, using the MedLine (National Library of Medicine) database as a reference. To select studies with the greatest scientific evidence, only clinical trials and observational studies were selected.

The search strategy used the following keyword combinations: “Autonomic Nervous System Diseases”, “Autonomic Dysfunction” AND “Coronary Artery Disease”. To identify study designs, the following terms were used: Observational Study and Clinical Trial. To select the studies, the inclusion and exclusion criteria presented in Chart 1 were applied.

Chart 1. Inclusion and Exclusion Criteria applied in the selection of studies.

Inclusion criteria		
Design	•	Clinical trials and observational studies
Patients	•	Adults with Coronary Artery Disease
Language	•	English
Exclusion Criteria		
Design	•	Unclear or poorly explained methods
Patients	•	Inappropriate patients.
Publication Methods	•	Abstract only
Main Clinical Outcomes		
Effect of exercise on the autonomic nervous system		

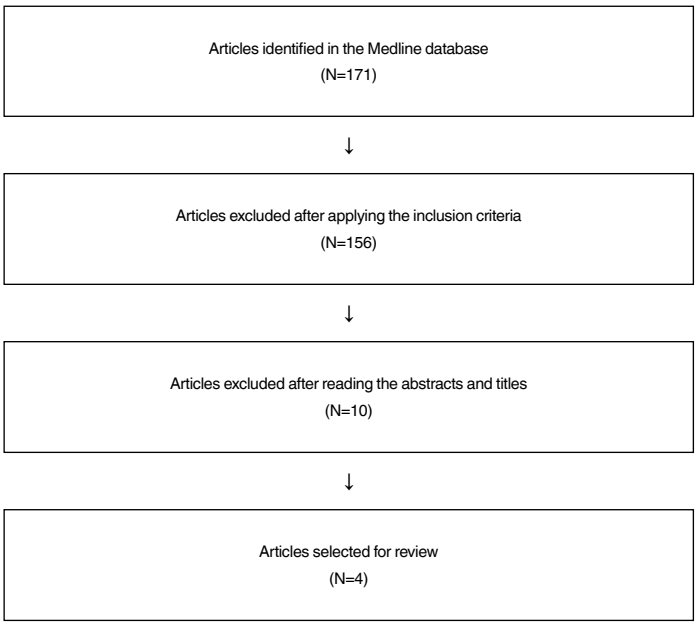

Figure 1. Flowchart of the study selection process.

RESULTS

Initially, 171 studies were identified that investigated the association of physical exercise with the improvement of Autonomic Dysfunction in patients with Coronary Artery Disease. However, after applying the inclusion and exclusion criteria and reading the abstracts and titles, only five were included in the scope of this review. This systematic review was performed in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology. The flowchart for the selection of articles that compose this review is shown in Figure 1.

Table 1 presents a summary of the studies and their main outcomes involving the proposed theme.

DISCUSSION

It is known that autonomic dysfunction is among the most important changes caused by CAD, as cardiac parasympathetic inhibition occurs and is triggered by predominant sympathetic activity. The main finding of this study demonstrates that there are exercises capable of generating beneficial changes in autonomic balance in CAD patients since a sedentary lifestyle is associated with hyperactivation of sympathetic modulation and a greater number of risk factors for cardiovascular diseases are associated with increased HR at rest, characterizing greater stress on the cardiovascular system[19].

The heart is a central organ in maintaining homeostasis and receives autonomic influences to achieve such a state. In this sense, one of its main characteristics is the constant modification of the frequency of its beats. Through medullary and vagal afferent pathways, the information reaches the central nervous system (solitary tract nucleus), is modulated, and returns to the heart through fast vagal efferent fibers (which may manifest in the first subsequent beat) and slow sympathetic efferent fibers (which may occur in intervals up to 20 seconds). The effect of these autonomic influences is beat-to-beat variability of instantaneous heart rate[13].

The magnitude of cardiovascular responses during physical exercise depends on the muscle mass involved, muscle tension, duration, and intensity of the exercise. For these rapid adjustments, the cardiovascular system reacts to maintain its homeostasis and these responses are produced by the action of the autonomic nervous system in the heart[8].

Heart rate (HR) is constantly subject to fluctuations in autonomic tone, determined by sympathetic and parasympathetic activation and/or inhibition. Different stimuli, such as breathing, muscle contraction, and varying degrees of stimulation of arterial baroreceptors are responsible for this dynamic pattern of autonomic activity[17]. Thus, there are some ways to measure cardiac autonomic modulation in humans, such as the use of HR variability (HRV), in addition to methods that seek to improve the dysfunction, such as increasing cardiovagal baroreflex sensitivity (SBR), a marker of the ability to increase vagal reflex activity and decrease sympathetic activity[1].

Spontaneous HR fluctuation, which is related to sensitive and early indicators of pathological states, can be applied to indirectly evaluate the Autonomic Nervous System[7]. It is assessed by

Table 1. Summary of studies involving the association of physical exercise in improving autonomic dysfunction in patients with Coronary Artery Disease.

Author/year	Sample	Design	Underlying disease	Intervention	Duration	Outcomes
Elie Fiogbé *et al.* (2017)	• N = 26 • Age: 50 to 70 years • Gender: (M) • GE: 14 • GC: 12	Randomized Controlled Clinical Trial	Coronary Artery Disease (CAD)	Evaluated: effects of aquatic aerobic training (WAET) on autonomic modulation of the heart, through Heart Rate Variability (HRV), and body composition, through percentage of body fat (PBF) in the rehabilitation of patients with CAD. • GE: initial assessments and the WAET protocol were performed in a heated pool that consisted of 3 weekly 1-hour sessions for 16 weeks • GC: assessments were performed and they did not participate in an exercise program during the study period.	16 weeks	• The proposal based on water exercises improved cardiac autonomic modulation, but failed to cause a significant decrease in PBF in patients with CAD. The improvement in cardiac autonomic modulation induced by WAET involves better parasympathetic modulation and reduced sympathetic modulation. • Therefore, only participants in the training group showed an improvement in HR variability indices and body composition variables remained unchanged.
Dimitra Mameletzi *et al.* (2011)	• N = 20 • Age: < 80 years • Gender: (M) • GE: 10 • GC: 10	Randomized Controlled Clinical Trial	Coronary Artery Disease (CAD)	Evaluated: whether a mixed-type, moderate-intensity, long-term structured exercise training program affects baroreflex sensitivity in patients with coronary artery disease. • GE: tilt test to assess baroreflex sensitivity and a graded treadmill test with spiroergometry to assess cardiorespiratory efficiency at the beginning and end of the study. In addition, GE performed a training program three times a week in the gym for 7 months consisting of a warm-up (15 minutes); aerobic (30 minutes); cooling (5 minutes). • GC: slope test to evaluate baroreflex sensitivity and a graded treadmill test with spiroergometry to evaluate cardiorespiratory efficiency at the beginning and end of the study.	7 months	• The physical training program had favorable effects on the baroreflex and cardiorespiratory sensitivity index. Thus, the main finding of this study was that a structured, long-duration, moderate-intensity exercise training program favorably changes autonomic balance in patients with coronary artery disease, with increased baroreflex sensitivity and baroreflex efficacy index, in addition to increased aerobic capacity. This suggests that long-term exercise training decreases sympathetic modulation and increases vagal modulation. • The physical training program had favorable effects on cardiorespiratory and baroreflex indices. Specifically, exercise time and anaerobic threshold were significantly increased by 21.9% (P50.001), 19.8% (P50.001) and 18.6% (P50.05), respectively, in group A after the training program. Additionally, there were significant increases in baroreflex sensitivity by 21.2% (P50.01), baroreflex efficacy index by 23.9% (P50.01), event count by 45.1% (P50.01) and ramp count in 13.2% (P50.05), in group A at the end of the study.
Wu *et al.* (2006)	• N = 54 • Age: • Gender: 54 (M) • GE1 (RC):18 • GE2: 18 • GC: 18	Randomized Controlled Clinical Trial	Patients undergoing CABG surgery	To investigate the effect of cardiac rehabilitation on heart rate recovery in patients who received coronary artery bypass grafting (CABG) and compare the effect with that of a home exercise program. • Rehabilitation program: aerobic exercise training for 30 to 60 minutes (riding a stationary bike or running on a treadmill) with an intensity corresponding to 60-85% of the peak heart rate achieved during the initial exercise stress test. There were approximately 10 minutes of stretching or calisthenics exercises to warm up and cool down; • Exe program. Home: Patients were instructed to exercise at least three times a week. Each exercise session included a 10-minute warm-up, 30 to 60 minutes of aerobic training (brisk walking or running), and a 10-minute cool down. • Control group: maintained their normal levels of daily physical activity without specifically instructed exercise programs.	12 weeks	• Results indicate that a cardiac rehabilitation exercise program has a positive effect on heart rate recovery in patients undergoing CABG and is consistent with autonomic improvement. • Patients in the cardiac rehabilitation group had significant increases in heart rate recovery (19.1 +/- 6.2 vs. 14.0 +/- 5.4 beats/min, P=0.022) compared with those from control group. • There were no significant differences in heart rate recovery between the cardiac rehabilitation and home exercise groups (16.2 +/- 4.8 beats/min) or between the home exercise and control groups. • All three groups had significantly improved heart rate recovery compared to their baseline data (P <0.001, <0.001, and 0.007).
Adamopoulos *et al.* (1992)	• N = 25 • Age: 62 (+-2 years)	Randomized Controlled Clinical Trial	Congestive heart failure (CHF) Moderate to severe stable ischemic	To evaluate the ability of different methods to characterize autonomic tone in chronic CHF. Sympathetic-vagal balance was assessed by: • Heart Rate Variability in the time domain, assessed by the SD of the RR intervals; • Heart rate variability in the frequency domain, assessed by low (0.03 to 0.14 Hz) and high (0.18 to 0.40 Hz) frequency components of heart rate variability by autoregressive power spectral analysis; • 24-hour heart rate, day and night; • Submaximal heart rate during exercise on an upright bicycle, with analysis of respiratory gases to obtain maximum oxygen consumption; • Radiolabeled norepinephrine extravasation	8 weeks	• After 8 weeks of physical training at home, all methods showed improvements in autonomic balance • Despite improvements in all individual measures of autonomic control after training, reflecting beneficial changes in autonomic balance or cardiopulmonary baroreflex-receptor activity, or both, there was no correlation between training-induced changes in these parameters, indicating difficulty in obtain accurate measurements of autonomic function. • The lack of correlation between methods allows us to conclude that, in CHF, individual measures of autonomic balance represent different aspects of circulatory control. Therefore, a comprehensive description of autonomous status may require a panel of complementary methods.

spectral analysis of HR time series, known as HRV, a method that consists of the analysis of different parameters based on the time variation between successive heartbeats[9], and which represents a non-invasive and selective assessment of sympathetic and parasympathetic contributions in cardiac autonomic regulation. Through HRV, we can observe the natural consequence of aging and physical fitness on cardiovascular function[6].

Low HRV is an independent predictor of mortality and incidence of cardiovascular diseases in adults. In children and adolescents, low HRV is associated with higher blood pressure levels and abdominal obesity, indicating its potential as a tool to assess cardiovascular risk among young people[12].

Sympathetic activation triggers physiological reaction responses, which cause an acceleration of the heartbeat. Sympathetic inhibition or parasympathetic excitation promotes a decrease in heart rate. A high heart rate can lead to a reduction in heart rate variability (HRV), which, at rest, indicates poor or insufficient adaptation of the autonomic nervous system to the environment[20]. The slow reduction in heart rate (HR) after exercise interruption has been associated with lower cardiac parasympathetic autonomic modulation, associated with higher mortality[21].

In an intact autonomic nervous system, it is expected that, at rest, cardiac parasympathetic modulation predominates. On the other hand, in individuals with heart disease, there is greater sympathetic modulation and less cardiac parasympathetic modulation. Thus, HRV emerges as an important indicator of changes in the regulation of the cardiovascular system and can provide information about the behavior of the cardiac autonomic nervous system in different populations[9].

The exercise program for coronary artery disease patients is based on traditional prescription to obtain training effects in healthy individuals. However, it undergoes modifications according to the patient's general clinical and cardiovascular status and involves an individually appropriate program in terms of types of exercises, as well as frequency, duration, intensity, and progression[18]. Guidelines involving physical exercise as a form of treatment for CAD respect a balance between safety and training effect, and recommend that resistance training (RT) be performed in combination with aerobic physical training (AT)[14].

The recovery of cardiovascular parameters after aerobic exercise provides adequate information about coronary heart disease and incidents of cardiovascular disease. Furthermore, cardiovascular variables assessed after exercise provide evidence that may not be recognized at rest[15]. Thus, after analyzing several studies, it was possible to observe the beneficial effects of physical training under autonomic modulation. Land-based aerobic exercises such as cycling and walking are capable of improving autonomic modulation, however, it is worth mentioning that some of these exercises have low adherence and a high dropout rate[4]. Therefore, aquatic aerobic training (WAET) and its role in improving modulation was also evaluated. It was possible to observe that programmed long-term mixed-type terrestrial aerobic exercise in patients with coronary artery disease is well tolerated, feasible, and safe, in addition to being effective in improving baroreflex sensitivity[4]. Likewise, WAET promoted new cardioprotection in patients with CAD as it generates a decrease in sympathetic modulation and an increase in parasympathetic modulation[1]. Therefore, regardless of whether the exercise is land or water, the physical training program is responsible for generating improvements in autonomic dysfunction, which includes benefits in cardiovascular and skeletal muscle functions, resistance, inflammation, quality of life, cognitive functions, and symptom relief of clinical symptoms (dyspnea, sleep disorders, stress and depression)[14].

Existing studies have demonstrated that there are several strategies to improve cardiac autonomic function and achieve sympathovagal balance and that physical training has shown increasingly promising results due to the improvement of all individual measures of autonomic control after training, reflecting beneficial changes in autonomic balance or baroreflex activity[5].

It is worth noting that in some studies baroreflex sensitivity was unchanged after exercise training or even reduced, while more recent studies have revealed that exercise training is effective in improving baroreflex sensitivity. This discrepancy appears to depend on the methods used to measure baroreflex sensitivity and on the characteristics of physical training. Therefore, it appears that changes in baroreflex sensitivity depend on the training mode, the exercise dose, and the duration of each study[4].

It is important to understand the importance of improving autonomic modulation and baroreflex sensitivity for clinical practice, as there is a strong relationship between cardiac autonomic modulation, assessed by heart rate variability (HRV), and cardiovascular risk factors[22].

The decrease in vagal activity and relative sympathetic predominance play an important role in the occurrence of malignant arrhythmic events during myocardial ischemia or infarction(4). Consequently, adherence to physical training may improve prognosis, as increased parasympathetic modulation is known to be an independent protector against fibrillation, ventricular arrhythmias, and death.

The results analyzed after the training exercises demonstrated an increase in HRV, which is important, as it promotes an improvement in autonomic modulation, and an increase in baroreflex sensitivity,

responsible for prioritizing the action of the parasympathetic system in order to reduce the chance of side effects arising from sympathetic predominance[1].

CONCLUSION

The results suggest that the supervised physical exercise program in patients with CAD is well tolerated, viable, safe, and generates beneficial results on autonomic modulation. Patients demonstrated improvement in individual measures of autonomic control, resulting in an improvement in the balance of autonomic dysfunction, with a decrease in sympathetic activity and an increase in parasympathetic modulation. Therefore, it is understood that patients who undertake this training program have reduced chances of malignant events that arise due to sympathetic predominance and protection against fibrillation, ventricular arrhythmias, and death due to increased parasympathetic modulation. It is therefore concluded that supervised physical exercises can constitute a non-pharmacological treatment for patients with CAD.

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