How to cite: Couto A, Couto A, Pereira R, Guedes DP, Madureira F, Scorcine C. Benefit of physical exercise programs for patients with permanent atrial fibrillation: A systematic review with meta-analysis. Rev Bras Fisiol Exerc 2021;20(6):655-664. doi: 10.33233/rbfex.v20i6.4727



# Revista Brasileira de Fisiologia do Exercício

Systematic review

# Benefit of physical exercise programs for patients with permanent atrial fibrillation: A systematic review with meta-analysis

Benefício de programas de exercício físico para pacientes com fibrilação atrial permanente: Uma revisão sistemática com metanálise

Angela Couto<sup>1</sup>, Áquilla Couto<sup>2</sup>, Rodrigo Pereira<sup>3</sup>, Dilmar Pinto Guedes<sup>3</sup>, Fabrício Madureira<sup>3</sup>, Claudio Scorcine<sup>3,4</sup>.

Hospital Ana Costa, Santos, SP, Brazil
Universidade Federal de São Paulo, São Paulo, SP, Brazil
Universidade Metropolitana de Santos, Santos, SP, Brazil

#### 4. Universidade do Oeste Paulista, Guarujá, SP, Brazil

#### ABSTRACT

**Objective:** The aim of the present study was to highlight the effects of physical exercise for patients with permanent atrial fibrillation trough a systematic review with meta-analysis. **Methods:** A search was performed in the main academic literature databases using the descriptors related to permanent atrial fibrillation and physical exercise. After reviewing the articles, four randomized clinical trial papers and a cross-over trial were selected for this review. **Results:** The analyzed works evidenced the safety and the benefits of different physical exercise programs on patients' mobility and quality of life with atrial fibrillation. **Conclusion:** The programs of exercise proved to be safe and beneficial in the mobility and quality of life of patients with permanent atrial fibrillation, since the literature showed that drug therapies no longer aim at cardiac control at the stage of the disease.

Keywords: atrial fibrillation; exercise; quality of life.

#### **RESUMO**

**Objetivo:** Evidenciar os efeitos do exercício físico para pacientes com fibrilação atrial permanente através de uma revisão sistemática com metanálise. **Métodos:** Foi realizada uma busca nos principais bancos de dados da literatura acadêmica utilizando os descritores relacionados a fibrilação atrial permanente e exercício físico. Após a revisão dos artigos, foram selecionados quatro trabalhos de ensaio clínico randomizado e um ensaio de cross-over para esta revisão. **Resultados:** Os trabalhos analisados evidenciaram a segurança e os benefícios de diferentes programas de exercício físico na mobilidade e qualidade de vida dos pacientes com fibrilação atrial. **Conclusão:** O exercício físico é uma forma de terapêutica não medicamentosa que potencializa a mobilidade e qualidade de vida dos pacientes com fibrilação atrial permanente, uma vez que a literatura sugere que as terapêuticas medicamentosas não objetivam mais o controle cardíaco nessa fase da doença.

Palavras-chave: fibrilação atrial; exercício físico; qualidade de vida.

Received: April 13, 2021; Accepted: August 29, 2021.

Correspondence: Angela Couto, Rua Tocantins 77, 11055-341 Santos SP. angelaa couto@hotmail.com

# Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia. Its incidence increases with age and has significant associations with morbidity and mortality [1]. This arrhythmia happens when there are electrophysiological abnormalities in atrial tissue, favoring the formation of unbalanced electrical impulse [2]. In this condition, the atriums lose their command capacity and, consequently, the atrial systole occurs chaotically and irregular [3]. The symptoms of this arrhythmia are associated with the heartbeat, which can reach 175 bpm at rest. The patient may experience dizziness, sweating, chest pressure, dyspnea, tiredness and syncope [4]. The cause of this disease is still unknown, although some factors can contribute to its development, for example: age, uncontrolled hypertension, diabetes, previous heart attack, coronary diseases and severe heart failure [5].

Its prevalence is 2%, with a high incidence in the population over 70 years old [6]. Projections for 2050 suggest that more than 50% of individuals over 80 years will present atrial fibrillation [7]. The morbidity of patients with atrial fibrillation is not just related to cardiovascular outcomes. Others comorbidities as cancer, sepsis, chronic obstructive pulmonary disease, sleep apnea, chronic renal failure are also related with atrial fibrillation [8].

Cumulative hospital's costs were considerably high; however, this difference loses meaning during the years, possibly due to the number of deaths. The mortality is significantly higher in patients with AF when compared to those without the disease, regardless of age [9]. In addition, the occurrence of a stroke is increased in five times in patients with this disease [10].

Atrial fibrillation can be classified in five ways: first time diagnosed (not diagnose previously regardless of the duration of the disease); paroxysmal AF (also known as intermittent, with sporadic episodes); persistent AF (it last more than seven days and it is not solved without pharmacological treatment); longstanding persistent AF (continuous form, it last more than a year, interventions are taken to control the rhythm); permanent AF (it represents a therapeutic attitude, in which doctor and patient decide that the interventions to control the rhythm should stop) [4]. Specifically, permanent AF is one of the most severe forms of the disease. Individuals that present this type of AF usually do not tolerate physical effort, leading to a decrease in activities of daily life. Therefore, less global physical activity and lower overall quality of life [11].

One of the proven ways to increase day-to-day physical effort tolerance is training through physical exercise [12]. Thereby, a patient who does not tolerate a minimum effort to perform the daily life actions begins to perform them more efficiently due to the increased tolerance to physical effort [13]. There is a vast literature on the benefits of regular physical exercise in order to attenuate the risks of comorbidities that can potentialize the development of AF [14]. Among the protective factors, physical exercise is able to minimize the chance of developing obesity [15], diabetes, hypertension [16], atherosclerosis [17], acute myocardial infarction [18].

For these benefits to be achieved, the American College of Sports Medicine recommends a minimum of 150 minutes per week of moderate activities or 75 minutes per week of intense physical exercise [19]. On the other hand, sedentary lifestyle predisposes the individual to a series of factors related to the decrease in quality of life through lower functional capacity [20]. The decrease in functional capacity is linked to a lower ability to move and perform activities of daily living, making these people dependent on others [21,22].

Physical exercises for patients already diagnosed with AF promotes benefits as the increase in the amount of walking footage in the six-minute walk tests, the improvement in muscle power [23] and in the quality of life [24]. Even though researches indicate that physical exercise can improve functional capabilities and life's quality of patients with permanent AF, a systematic review with meta-analysis can direct the professionals' intervention in relation to the safety and efficiency of training.

Thereby the objective of the present study was to elaborate a systematic review with meta-analysis about the effects of physical exercise in patients with permanent atrial fibrillation.

# Methods

This study is a systematic review with meta-analysis conducted from the checklist Prisma (Prospero CRD42021248139). For a complete coverage about the subject, databases were analyzed: Medline via Pubmed, Lilacs, Cochrane e Academic Google. The descriptors used were "atrium fibrillation", "permanent atrium fibrillation", "six-minute walk test", "exercise", "cardiac rehabilitation". The search contemplated articles in English and Portuguese from 2000 to 2021. Two experienced researchers assisted by a librarian experienced in systematic reviews performed data collection.

Only original articles of randomized clinical trials were included in the review. 165 articles were identified using the first criteria. Of these articles, 42 were excluded for duplication in databases. Of the remaining 123 articles, 23 were excluded for not meeting the original article criteria (n = 13 reviews; n = 2 case studies; n = 8 articles written in other languages; n = 3 researches performed on animals). From the 97 articles selected after this filtering, titles and abstracts were analyzed and 92 articles were excluded (n = 26 patients with other comorbidities; n = 61 with no physical activity intervention; n = 5 non-randomized studies). According to the eligibility criteria, four randomized articles and one-crossover articles with patients with permanent AF who experienced physical exercise intervention to improve their functional capacity and/or quality of life.

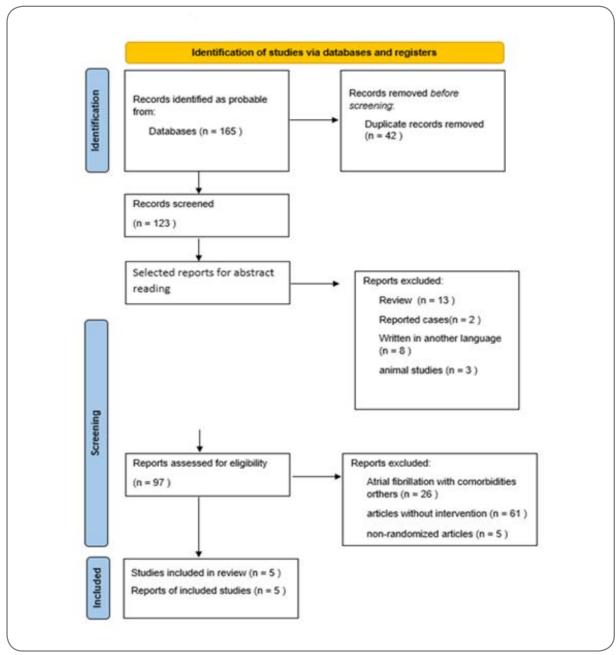


Figure 1 - Selection of articles included in the systematic review

All the selected articles were analyzed and carefully reviewed to data extractions (figure 1). To evaluate the risk of publication bias, the Cochrane Risk of Bias Tool model was used (figure 2). For statistical analysis was used measures of effect size (Cohen d). For the creation of the Forest Plot, the variables present in three or more articles were used (six minute walk test). The adopted effect size stratification was 0.2 for small effects; 0.5 moderate effects and 0.8 for large effects.



Figure 2 - Cochrane Risk of Bias Tool

### Results

Five articles were selected to the results of this systematic review, three articles for analyze meta-analysis that evaluated mobility through the walk test and two that evaluated the levels of quality of life through the SF-36 questionnaire.

Study	Correlation, confidence interval 95%	Weigth	Confidence interval 95%
Zeren, M. et al. (2016)	· · · · · · · · · · · · · · · · · · ·	30.66%	0.55 [-0.14, 1.25]
Osbak, O.S. et al.(2011)	<b>—</b>	36.56%	1.21 [ 0.60, 1.82]
Pippa, L. et al/2007)	⊧i	32.77%	1.35 [ 0.69, 2.01]
RE Model	J	100.00%	1.05 [ 0.59, 1.52]
łeterogeneidade: Tau² = 0,05; l²= 33,45%; df este para efeito geral: Z= 4,46 (p <0,001)	=2 (p=0,22); -0.5 0 0.5 1 1.5 2 2.5		
Control n			

**Figure 3** - Forest Plot Graph comparing the control and training groups in the variable distance of the six-minute walk test

**Table I** - Description of the studies included in the analysis of statistical data and/or meta-analysis that contains exercise intervention in patients with permanent atrial fibrillation

Author/Year/ Country	Type of study/Population	Interventions	Conclusions
Zeren M, et al. [28] (2016) Istanbul	Randomized clinical trial Permanent FA G. Training n = 17, age 66.1 $\pm$ 8.7 years 8 men and 9 women. G. Control n = 16, age 67.0 $\pm$ 6.3 years 9 men and seven women.	Respiratory muscle training with equipment ( <i>Threshold IMT, Respiranics, US</i> ). The training group received inspiratory muscle training at 30% of the maximum inspiratory pressure. Workout: duration 15 minutes, 2x daily, 7x a week, for 12 weeks.	test 6 minutes of walking, maximum inspiratory pressure, maximum expiratory pressure, forced vital capacity, forced
Osbak PS, et al. [29] (2011) Denmark	Randomized clinical trial Permanent FA G. Training n = 24, age $65.5 \pm 7.3$ years. Control group n = 23, age $70.9 \pm$ 8.3 years.	Training with exercise bike, treadmill walking, running, physical training with physiotherapy balls and interval training. All sessions included warm-up and cooling periods. Training: 60 minutes (30 minutes to 70% of effort). The intensity was increased during the training period total duration of 12 weeks.	Training group - Increase in muscle strength, efficiency in performing exercise, reduction of resting heart rate. Control group - no significant changes.
Hegbom F, et al. [24] (2007) Norway	Randomized trial/cross over Permanent FA G. Training n= 13, $62\pm7$ years, male. Control group n= 15 $65\pm7$ years, 13 males and 2 females. Total n=28.	Strength Training for the dorsal, MMII and abdominal muscles. Final part: 5 minutes back to calm and 15 minutes of stretching and training on exercise bike Three days a	tests by 1.4 points, improvement of exercise execution capacity ±20%. Improvement of summary and specific scores of Symptoms of SSCL, summary score of the physical
Pippa L, et al. [27] (2007) Italy	Randomized clinical trial Permanent FA G. Training n= 22, age $68.3 \pm 7.2$ years. Control group n = 21, age $68.8 \pm$ 9.1 years.	Training: 90-minute GONG IQ, 2x week. Duration: 16 weeks (total 32 sessions).	Training group - Increase in the distance covered by the 6-minute walk test in 27% Control group - no significant changes.
Osbak PS, et al. [23] (2011) Denmark	Randomized clinical trial Permanent FA G. Training n = 24, age 65.5 ± 7.3 years. Control group n = 23, age 70.9 ± 8.3 years.	The training was performed using exercise bike, treadmill walking, running, physical training with physiotherapy balls and interval training. All sessions included warm- up and cooling periods. The intensity was managed by the Borg scale, 70% of the maximum capacity for 30-60 minutes, 3 x in the week, for 12 weeks. Control patients were advised to continue their usual physical activity.	

Study	Variable	Pré	Post	d
Hegbom F, et al. (2007) [24]	Physical functioning	82 ± 14	86 ± 10	0.33
Osbak PS, et al. (2011) [23]	Physical functioning	72 ± 18	77 ± 16	0.30
Hegbom F, et al. (2007) [24]	Physical appearance	77 ± 29	86 ± 25	0.33
Osbak PS, et al. (2011) [23]	Physical appearance	49 ± 45	62 ± 44	0.29
Hegbom F, et al. (2007) [24]	Pain	82 ± 17	92 ± 14	0.65
Osbak OS, et al. (2011) [23]	Pain	73 ± 23	76 ± 24	0.20
Hegbom F, et al. (2007) [24]	General health	73 ± 14	77 ± 16	0.27
Osbak OS, et al. (2011) [23]	General health	57 ± 19	69 ± 19	0.64
Hegbom F, et al. (2007) [24]	Vitality	61 ± 14	68 ± 13	0.52
Osbak OS, et al. (2011) [23]	Vitality	60 ± 23	69 ± 21	0.41
Hegbom F, et al. (2007) [24]	Social functioning	92 ± 12	95 ± 13	0.24
Osbak PS, et al. (2011) [23]	Social functioning	87 ± 19	92 ± 15	0.30
Hegbom F, et al. (2007) [24]	General mental health	85 ± 28	94 ± 20	0.37
Osbak PS, et al. (2011) [23]	General mental health	64 ± 44	77 ± 37	0.32
Hegbom F, et al. (2007) [24]	General mental health	86 ± 9	85 ± 14	0.08
Osbak PS, et al. (2011) [23]	General mental health	82 ± 17	83 ± 17	0.06

**Table II** - Quality of life indexes measured using the SF-36 questionnaire stratified in eight distinct domains in the two studies statistically analyzed. The data are expressed in the form of mean and standard deviation and the size of effect through the Cohen d (d)

# Discussion

The results of the present review suggest that physical training can be an efficient strategy to improve the mobility of patients with AF. However, this fact should be considered with caution, as consistent studies specifically related to the topic are scarce. Systematized and well-oriented physical exercise can be an efficient strategy to improve the physiological parameters of these patients. The therapeutic recommendation suggested by the national guidelines for atrial fibrillation in patients with permanent AF does not include the attempt to change the patients' heart rate. Therefore, therapies that can enhance greater tolerance to small efforts, such as activities of daily living, can significantly change the quality of life of these patients.

The results of this study about the significant improvement in mobility in the six-minute test demonstrate that patients are capable to better tolerate efforts when they are physically active [23,25-28].

In a pilot study performed in 2007, the researchers found that after 12 weeks of training the heart beats at rest significantly decreased and the patients with permanent AF increased their tolerance to physical effort and improved the life quality scores [25]. Physical exercise can significantly improve the chronotropic and inotropic function of the heart [29]. Therefore, physical exercise is an effective, low-cost form that has the potential to improve the functional capacity of these patients. In relation to quality of life, it is usually measured subjectively, through instruments that measure the perception of the interviewed individuals about different parameters. The two studies that investigated this variable demonstrated a positive fact size (mild to moderate) for all the domains related to life quality.

Therefore, despite little evidence, it is possible to suggest that physical exercise can alter the patients' perception of effort on these parameters [24,30]. The physical exercise considered efficient and safe to this population is of moderate intensity (60-70% of the peak  $VO_2$ ) with duration of 20-60 minutes per training session at least three sessions per week [19,26].

These recommendations aim to achieve all the goals that the physical exercise can potentialize in this population, among these: reduction of pressure levels, blood glucose control, improvement in cardiac function, mainly due to changes in the left ventricle, decrease in fat percentage, improvement of physical, functional abilities and stress levels.

### Conclusion

The results of this review allow us to infer that physical exercise significantly and positively can alter the functional capacities of patients with permanent AF. However, the data must be viewed with caution due to the paucity of high-quality evidence.

#### Academic affiliation

This article represents a scientific initiation by Angela Couto, a resident physician at Hospital Ana Costa, supervised by Professor Dr. Claudio Scorcine at the Metropolitan University of Santos.

#### **Conflict of interests**

The authors of this study have no conflicts of interest related to the theme, development and publication of this article.

#### Financing source

Not applicable.

#### Authors' contribution

**Conception and design of the research:** Couto A, Pereira R; **Data retrieval:** Couto A, Couto A; **Data analysis and interpretation:** Scorcine C; **Statistical analysis:** Scorcine C; **Writing of the manuscript:** Scorcine C, Couto A; **Critical review of the manuscript for important intellectual content:** Madureira F, Guedes DP.

#### References

1. Santos EB, Salles ALF, Tavares LR, Lima MV, Santos WB, Silva GP, et al. Características clínicas e demográficas e perfil terapêutico de pacientes hospitalizados com fibrilação atrial: Estudo EPIFA. Rev SOCERJ [Internet]. 2009 [cited 2021 Nov 17];22(1):9-14. Available from: http://sociedades.cardiol.br/ socerj/revista/2009\_01/a2009\_v22\_n01\_a01eduarda.pdf

2. Guyton AC, Hall JE, Zocchi L, Aicardi G. Fisiologia médica. Madrid: Elsevier; 2017.

3. Cintra FD, Figueiredo MJO. Fibrilação atrial (Parte 1): fisiopatologia, fatores de risco e bases terapêuticas. Arq Bras Cardiol 2021;116(1):129-39. doi: 10.36660/abc.20200485 4. Magalhães L, Figueiredo M, Cintra F, Saad E, Kuniyoshi R, Teixeira R, et al. II Diretrizes brasileiras de fibrilação atrial. Arq Bras Cardiol 2016;106(4):1-22. doi: 10.5935/abc.20160055

5. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart Study. Jama 1994;271(11):840-4. doi: 10.1001/jama.1994.03510350050036

6. Wilke T, Groth A, Mueller S, Pfannkuche M, Verheyen F, Linder R, et al. Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. Europace 2012;15(4):486-93. doi: 10.1093/europace/eus333

7. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the An-Ticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. Jama 2001;285(18):2370-5. doi: 10.1001/jama.285.18.2370

8. Ferreira C, Providência R, Ferreira M, Gonçalves L. Fibrilação atrial e doenças não cardiovasculares: uma revisão sistemática. Arq Bras Cardiol 2015;105(5):519-26. doi: 10.5935/abc.20150142

9. Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB. Impact of atrial fibrillation on mortality, stroke, and medical costs. Arch Intern Med 1998;158(3):229-34. doi: 10.1001/archinte.158.20.2265

10. Marianelli M, Marianelli C, Lacerda Neto TP. Principais fatores de risco do avc isquêmico: Uma abordagem descritiva. Braz J Health Review 2020;3(6):19679-90. doi: 10.22533/at.ed.07621090215

11. Saad EB, d'Avila A. Fibrilação atrial (parte 2) Ablação por cateter. Arq Bras Cardiol 2021;116(2):334-43. doi: 10.36660/abc.20200477

12. Oliveira JC, Vinhas W, Rabello LG. Benefícios do exercício físico regular para idosos. Braz J Development 2020;6(3):15496-504. doi: 10.34117/bjdv6n3-429

13. Couto LHN. Comparação da autonomia funcional de idosos praticantes e não praticantes de atividades físicas [TCC] [Internet]. Cruz Alta: Universidade de Cruz Alta; 2018. [cited 2021 Nov 17]. Available from: https://home.unicruz.edu.br/wp-content/uploads/2019/02/COMPARA%C3%87%C3%83O-DA--AUTONOMIA-FUNCIONAL-DE-IDOSOS-PRATICANTES-E-N%C3%83O-PRATICANTES-DE-ATIVIDA-DES-F%C3%8DSICAS.pdf

14. Kesaniemi YA, Danforth E, Jensen MD, Kopelman PG, Lefèbvre P, Reeder BA. Dose-response issues concerning physical activity and health: an evidence-based symposium. Med Sci Sports Exerc 2001;33(6):S351-S8. doi: 10.1037/e603442007-001

15. Jesus LAS, Gravina EPL, Neto MNF, Miguel CRCE, Ribeiro JR, Talma AJM, et al. Exercício físico e obesidade: prescrição e benefícios. HU Rev 2018:269-76. doi: 10.34019/1982-8047.2018.v44.13953

16. Maia RHS, Navarro AC. O exercício físico leve a moderado como tratamento da obesidade, hipertensão e diabetes. Revista Brasileira de Obesidade, Nutrição e Emagrecimento [Internet]. 2017 [cited 2021 Dec 23];11(66):393-402. Available from: http://www.rbone.com.br/index.php/rbone/article/view/535

17. Gonçalves MPM, Anjos JC, Lemos ACG, Gonçalves RD, Silva VN. Nutrição e exercício físico como forma de prevenção ou regressão da aterosclerose. Revista Saúde UniToledo [Internet] 2017 [cited 2021 Nov 17];1(1). Available from: http://www.ojs.toledo.br/index.php/saude/article/view/26

18. Costa FC, Silva AFT, Macedo BFS, Silva GVN, Silva TMMF, Brito MVH. Efeitos do exercício físico na prevenção e tratamento de lesões por isquemia: uma revisão de literatura. Rev Med 2020;99(5):480-90. doi: 10.11606/issn.1679-9836.v99i5p480-490

19. Morey MC. Physical activity and exercise in older adults. UpToDate, Waltham; 2019. doi: 10.1093/ oxfordhb/9780195394313.013.0018

20. Ribeiro DBG, Silva ASC, Ferreira GLS. Análise da capacidade funcional em idosas praticantes de hidroginástica. Braz J Developm 2020;6(5):27206-11. doi: 10.34117/bjdv6n5-246

21. Oliveira DV, Nascimento J, Lima MCC, Leme DEC, Antunes MD, Bertolini S. Capacidade funcional e qualidade de vida em mulheres idosas praticantes e não praticantes de hidroginástica. Rev Rene 2017;18(2):156-63. doi: 10.15253/2175-6783.2017000200003

22. Lozado YA, Barbosa RS, Silva Caires S, Bomfim BSM, dos Santos L. Implicações do elevado comportamento sedentário à saúde de idosos: uma revisão de literatura. Práticas e cuidado. Rev Saúde Coletiva 2020;1:e9994-e. https://www.revistas.uneb.br/index.php/saudecoletiva/article/view/9994

23. Osbak PS, Mourier M, Henriksen JH, Kofoed KF, Jensen GB. Effect of physical exercise training on muscle strength and body composition, and their association with functional capacity and quality of life in patients with atrial fibrillation: a randomized controlled trial. J Rehabil Med 2012;44(11):975-9. doi: 10.2340/16501977-1039

24. Hegbom F, Stavem K, Sire S, Heldal M, Orning OM, Gjesdal K. Effects of short-term exercise training on symptoms and quality of life in patients with chronic atrial fibrillation. Int J Cardiol 2007;116(1):86-92. doi: 10.1016/j.ijcard.2006.03.034

25. Plisiene J, Blumberg A, Haager G, Knackstedt C, Latsch J, Norra C, et al. Moderate physical exercise: a simplified approach for ventricular rate control in older patients with atrial fibrillation. Clin Res Cardiol 2008;97(11):820-6. doi: 10.1007/s00392-008-0692-3

26. Giacomantonio NB, Bredin SS, Foulds HJ, Warburton DE. A systematic review of the health benefits of exercise rehabilitation in persons living with atrial fibrillation. Can J Cardiol 2013;29(4):483-91. doi: 10.1016/j.cjca.2012.07.003

27. Pippa L, Manzoli L, Corti I, Congedo G, Romanazzi L, Parruti G. Functional capacity after traditional Chinese medicine (qi gong) training in patients with chronic atrial fibrillation: a randomized controlled trial. Prev Cardiol 2007;10(1):22-5. doi: 10.1111/j.1520-037x.2007.05721.x

28. Zeren M, Demir R, Yigit Z, Gurses HN. Effects of inspiratory muscle training on pulmonary function, respiratory muscle strength and functional capacity in patients with atrial fibrillation: a randomized controlled trial. Clin Rehabil 2016;30(12):1165-74. doi: 10.1177/0269215515628038

29. Santos M, West E, Skali H, Forman DE, Junior WN, Shah AM. Resting heart rate and chronotropic response to exercise: Prognostic implications in heart failure across the left ventricular ejection fraction spectrum. J Card Fail 2018;24(11):753-62. https://doi: 10.1016/j.cardfail.2018.09.015

30. Osbak PS, Mourier M, Kjaer A, Henriksen JH, Kofoed KF, Jensen GB. A randomized study of the effects of exercise training on patients with atrial fibrillation. Am Heart J 2011;162(6):1080-7. doi: 10.1016/j.ahj.2011.09.013