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Exercise training and atrial fibrillation: a systematic review and literature analysis

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Abstract. – OBJECTIVE: There are concerns in maintaining adequate levels of physical activity in patients with atrial fibrillation (AF). This could be related to the type of exercise delivered, different among studies, as the words used to describe it as treatment. We have analysed the state-of-art of the role of the exercise in AF by a mathematical analysis. This analysis documented the connections between topics and updated the available evidence through a systematic review of the current literature.

MATERIALS AND METHODS: A literature search was conducted using specific terms for studies published between 2000 and 2019. For the descriptive analysis of the current literature, we used the LExical Network analysed by the Graph THeory (LENGTH) method, while to perform our review we followed the PRISMA statement. Downs and Black Quality Index was also used to assess the quality of studies.

The LENGTH approach indicated nonspecific terms as "exercise", "physical" and "activity" as more representative than "rehabilitation" to describe the intervention.

RESULTS: The systematic review identified nine studies on 882 patients of moderate (n=4) to good (n=5) quality. Training consisted of a combination of supervised ambulatory and home-based outpatient programs, focused on aerobic elements (endurance and resistance training, walking, treadmill and bicycle ergometer). Significant improvements in 6-minute walking test distance and peak oxygen uptake and in quality of life were obtained, with high adherence to training and no serious/significant adverse events. Only one trial was based on cardiac rehabilitation principles.

CONCLUSIONS: Adequate exercise training can get a favourable cardiovascular outcome in patients with AF.

Key Words:
Exercise, Rehabilitation, Atrial fibrillation, Graph theory, Personalized medicine.

Introduction

Physical inactivity and low cardiorespiratory fitness have been identified as significant risk factors for many cardiovascular diseases (CVD). In the same direction, higher levels of physical activity in healthy subjects have been associated with a lower risk of adverse cardiovascular outcomes,

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with a dose-response relationship[1-3]. Recent scientific literature[4,5] has shown that general physical activity or specific training can improve cardiorespiratory fitness and quality of life, reducing risk of all-cause mortality, sudden cardiac death, cardiovascular disease, stroke and congestive heart failure. As well, the cardiovascular rehabilitation, including planned exercise training, risk-factor reduction and behavioral intervention (e.g., smoking cessation, vocational and nutritional counselling) is the most structured management for CVD[4,6-8].

Notwithstanding, a spread concern in maintaining adequate levels of physical activity in CVD exists, especially in patients with arrhythmia. Among the diseases causing arrhythmia, atrial fibrillation (AF) is the most common arrhythmia. This condition significantly increases morbidity and mortality and negatively impact the perceived quality of life because of its psychological consequences (sleep disturbances, anxiety, and depression)[9-11]. For this reason, a prompt and effective management is extremely important. Unfortunately, some concerns about exercise prescription in AF exist and they are mainly attributed to AF-related physical symptoms (palpitations, fatigue, intolerance to exercise, labored breathing, dizziness, diaphoresis, chest discomfort).

The association between several biologic determinants and AF is well recognized, but its relationship with physical fitness is uncertain[12]. Vigorous long-term exercise training and jogging (5-7 days per week) have been associated with a higher rate of AF[12]. This may be linked to changes in atrial volume, hypertrophy of the left ventricle and alteration in autonomic nervous system activity[13]. Moreover, in the Cardiovascular Health Study, a comparison between old people who walked more than 60 blocks at high speed and old people who walked less than 4 blocks at slow speed was conducted. In this study, a lower incidence of AF in the most active people was found[14].

Hence, even if no specific reservations about exercise have been declared[15,16], no specific indications for exercise training and cardiac rehabilitation have been recommended in the AF guidelines for its prevention and treatment[17,18]. Both physicians and patients maintain concerns about needs, levels, and types of exercise to perform daily in this disease and more evidence are needed.

Recently, a Cochrane review and a systematic review with meta-analysis documented significant improvements in terms of cardiovascular capacity and quality of life in AF patients treated with the support of cardiac rehabilitation[19,20]. However, the number and type of studies considered in the analysis beyond their low-quality, downgraded the impact of the results. Another crucial point is the type of exercise intervention, which considerably differs among the included studies. In other words, the risk of inhomogeneous approaches for the management of the same condition is real. In order to overcome the current lack of clarity, a wide literature analysis could be useful. Furthermore, the assessment of the terms used for the description of the rehabilitation approaches may allow a major understanding of the status of art about the topic. Indeed, the use of clear and shared words is fundamental for the development of a common knowledge. Therefore, the first objective of our study is the analysis of the state-of-art of exercise training in patients with AF by a lexical point of view, evaluating the importance and the frequency of the terms used in AF rehabilitation. Then, to assess specifically the effects and the harms of exercise training and cardiac rehabilitation in patients with AF, we aimed to update the available evidence by systematically reviewing the current literature and summarizing benefits and risks.

Materials and Methods

The Systematic Review Analysis

The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement for reporting systematic reviews and meta-analyses was used for performing this systematic review[21]. A systematic literature search for only randomized clinical trials (RCTs) was conducted on the electronic PubMed, PubMed CENTRAL, Cochrane database for randomized controlled trials, CINAHL (Cumulative Index to Nursing and Allied Health), Embase, Scopus, Web of Science, and PEDRo databases using the following string/keywords: "atrial fibrillation", "exercise", "exercise training", "training", "rehabilitation", "cardiac-rehabilitation", "physical activity", "cardiorespiratory fitness", "fitness", "physiotherapy" and "functional training" with Boolean terms like OR and AND were included for database search. Search strategies were modified for each database to achieve the broadest search. Finally, all the reference lists of the identified studies were manually analyzed for the search of any other potentially relevant studies.

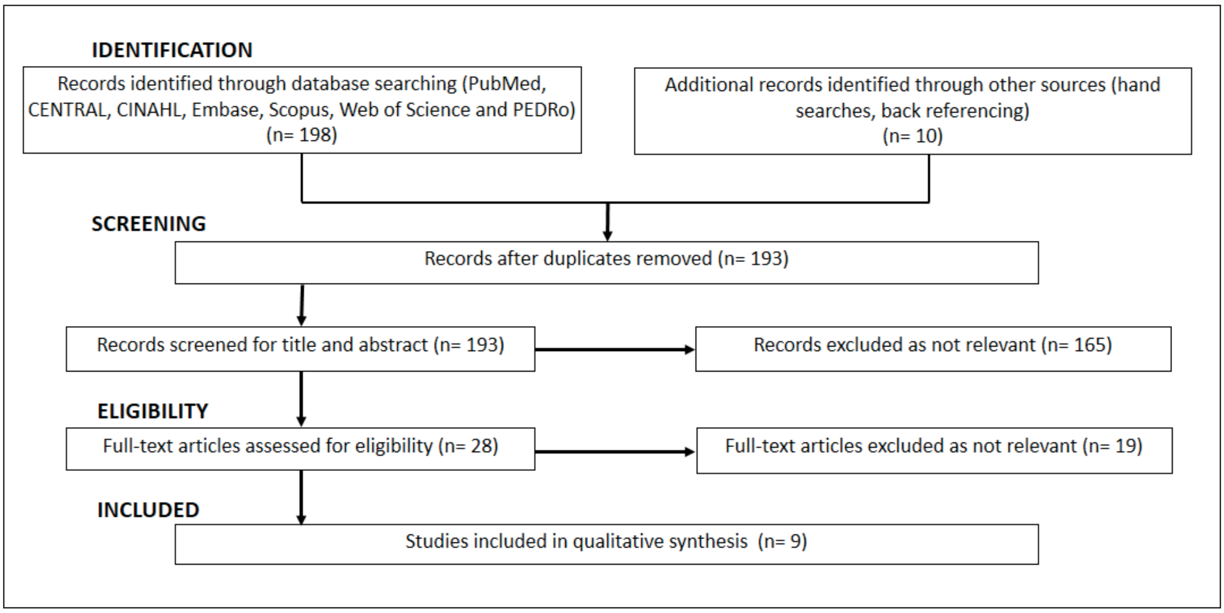

Figure 1. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart for the trial selection process.

Two reviewers (ML, AM) independently screened the titles and abstracts for relevance. The full texts of selected manuscripts were reviewed for inclusion or exclusion using the selection criteria. Two reviewers (ML, AM) independently determined the articles to include/exclude, and data from the relevant articles were extracted using pre-defined extraction forms. Any disagreements in data extraction were discussed until consensus was reached. In the case of discrepancy during the data extraction, other authors (MGB and AF) acted as arbitrators.

The search was limited to English language articles published from 1st January 2000 to 1st May 2019, and the results were filtered by "clinical trials". From this search, we only included articles specifically addressing the effects of exercise training, physical activity and cardiac rehabilitation on cardiovascular functional outcomes (main outcome: 6 minutes walking test or peak oxygen consumption) in patients affected by AF. All RCTs published in peer-reviewed journals concerning exercise training (aerobic, resistance, inspiratory muscle training or combinations of these) as intervention for patients with AF delivered through any setting (i.e., hospital, home, community or a combination of them), were included. Only RCTs with usual care and no exercise as control group were included. To provide a broad cutting-edge outline, no other specific inclusion and exclusion criteria were adopted. Summary of the selection of articles has been reported as per the PRISMA guidelines (Figure 1).

The quality of studies was assessed using the Downs and Black Quality Index (QI) to evaluate the quality of studies[22,23]. The scale has five sub-domains, which include reporting, external validity, bias, confounding, and power being scored out of 11, 3, 7, 6 and 5 respectively. The total score obtained is scored out of 32. The studies were rated as excellent, good, moderate and poor based on the percentage of the total score achieved, as >95% (>30), 75-95% (24-29), 55-74% (18-23) and <55% (<18).

Details on training interventions were collected concerning the FITT principle (frequency, intensity, type and time). Effects of the training on outcomes as exercise capacity (i.e., six-minute walk distance, peak oxygen consumption), quality of life scores, functional class, survival, safety and cost-effectiveness were collected (Table I)[24–32].

Data were collected and the number of patients was pooled together. No meta-analysis was performed due to heterogeneity about exercise intervention.

Lexical Network

In order to broaden out the above reported literature review, we have used a specific method of analysis based on the graph theory. In particular, we analyzed the scientific literature from a lexical point of view, evaluating the use of specific words in published papers[33-35]. This analysis was performed by the support of graph theory. With this method, the graphical representation and the

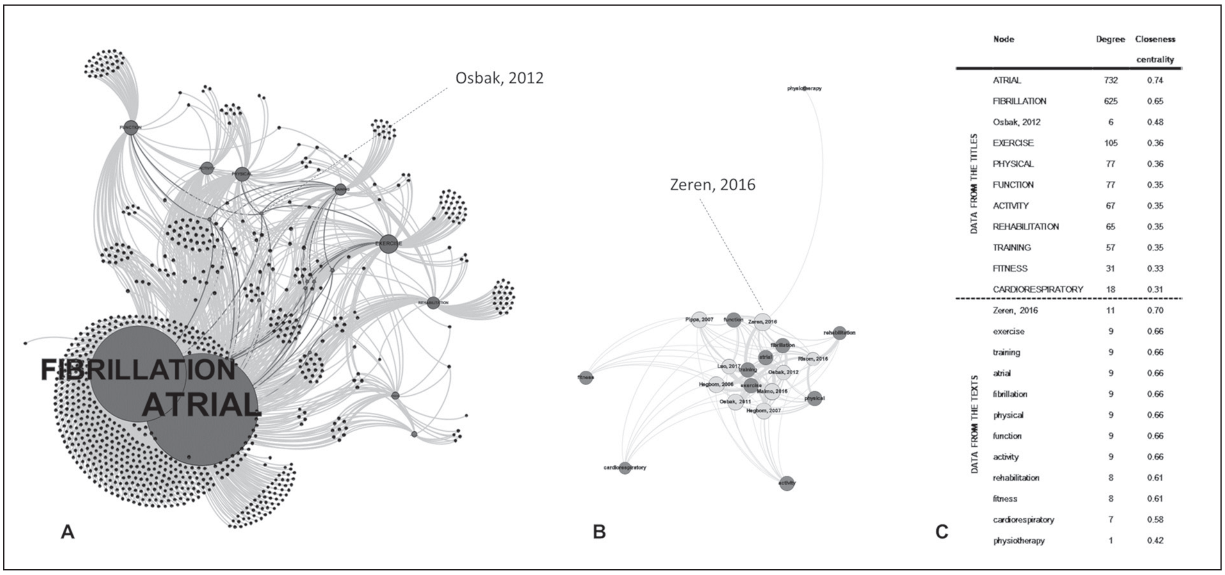

Figure 2. The Graph-Theory Model Representation based on the connection of nodes (the selected paper titles and the keywords) and edges (connections between titles and keywords). **A,** Large graph considering the whole sample of papers (titles) found by the first literature research and the keywords. The edges have the same thickness because they indicate the presence of the keyword in a title. The edges connecting the keywords and the papers selected by the systematic review are highlighted in a darker colour. **B,** Small graph considering the papers (whole text) selected by the systematic review and the keywords. **C,** In this graph, the edge thickness is different because it indicates the times when a keyword is present in the paper text.

analysis of connections between different elements is possible. More specifically, the graph is a mathematical structure made by nodes (in our case selected paper titles and keywords) and edges (connections between a paper and a keyword). The described method allowed generating a LExical Network analysed by the Graph THeory approach (LENGTH)[36], in order to assess the impact of single terms in literature (Figure 2).

A literature search for randomized clinical trials (RCTs) was conducted on the main literature database (PubMed and PubMed Central), using the following terms/keywords "atrial fibrillation", "exercise", "exercise training", "training", "rehabilitation", "cardiac-rehabilitation", "physical activity", "cardiorespiratory fitness", "fitness", "physiotherapy" and "functional training". The titles of the found papers were exported, checking the single terms contained in each paper title. For this search, no article type filters were considered, in order to obtain as more results as possible, for a more proficient analysis.

With this method, a specific matrix was built indicating, in each title, which keywords were present. This matrix was imported in the free software Gephi 0.9.2 to build a graph representing the connections between the titles and the keywords. Besides the graphical representation, the degree (the absolute number of connections for each node) and the closeness centrality (an index of the information related to a node) were calculated. A second simpler graph was created in the same way, but considering, besides the previous keywords, only the final selected papers by the following systematic review analysis. In this second graph, because of the lower number of variables, we searched the keywords in the whole text of each paper.

Results

The Systematic Review Analysis

Initial literature search resulted in 461 potentially relevant studies. A total of 9 articles were finally included in the review[24-32]: a summary of the considered studies is provided in Table I.

All the selected studies were prospective, randomized controlled trials. The study of Luo et al[24] was a further sub-analysis of a previously reported study[37]; while two studies[28,31] re-analyzed the same sample with other outcomes[29,32].

All the studies included in the Cochrane review were included in our analysis[19]. Considering the systematic review by Smart and colleagues[20], we did not include the study by Skielboe's group[38], for the presence of a different type of exercise

Table I. Summary of studies selected and included in the review.

Authors – year	Design – Number	Setting – Intervention	Duration	Outcomes	Results
Luo et al, 2017[24]	Prospective, multicenter, randomized controlled trial (n= 193-189)	Ambulatory outpatients – Exercise training (aerobic exercise) or usual care	Supervised training for 12 weeks followed by a home-based exercise program for an additional 2 years	Peak oxygen uptake, 6-minute walking test (6MWT) distance, Kansas City Cardiomyopathy Questionnaire overall summary score, all-cause/cardiovascular mortality and/or hospitalization. 6MWT (m): T=20.01; C=4.8	Atrial fibrillation in patients with chronic heart failure was associated with older age, reduced exercise capacity at baseline, and a higher overall rate of clinical events, but not a differential response to exercise training for clinical outcomes or changes in exercise capacity.
Risom et al, 2016[25]	Prospective, multicenter, multidisciplinary 1:1 randomized clinical superiority trial with blinded outcome assessment (n= 105-105)	University hospitals – Comprehensive cardiac rehabilitation program (individualized exercise protocol and psycho-educational consultations) plus usual care versus usual care	12 weeks	Peak oxygen uptake, 6MWT distance, quality of life measured by the Short Form 36 questionnaire. 6MWT (m): T=44; C=17	Comprehensive cardiac rehabilitation had a positive effect on physical capacity compared with usual care, but not on quality of life (physical and mental components). Cardiac rehabilitation caused more non-serious adverse events.
Zeren et al, 2016[26]	Prospective randomized controlled single-blind study (n= 19-19)	Single medical center – Inspiratory muscle training or standard medical treatment only	12 weeks	Spirometry, maximal inspiratory and expiratory pressures, 6MWT distance. 6MWT (m): T=55.53; C=4.69	Inspiratory muscle training can improve pulmonary function, respiratory muscle strength and functional capacity in patients with atrial fibrillation.
Malmo et al, 2016[27]	Prospective, single-center, single-blind, randomized, controlled trial (n= 26-25)	Single medical center – Aerobic interval training or usual care (continue and maintain their usual/regular exercise habits)	12 weeks	Change in time in atrial fibrillation, atrial fibrillation symptoms, peak oxygen uptake, cardiac volumes, quality of life, lipid status, level of physical activity, number of cardioversions and hospital admissions resulting from atrial fibrillation. Steps per day: T=1,343; C=-191	Aerobic interval training reduces the time in atrial fibrillation in patients with nonpermanent atrial fibrillation and significantly improves atrial fibrillation symptoms, peak oxygen uptake, left atrial and ventricular function, lipid levels and quality of life.
Osbak et al, 2012[28]	Prospective, randomized, controlled trial (n= 25-24)	Single medical center – Aerobic training or attention control	12 weeks	6MWT, exercise capacity, muscle strength, quality of life, lean body mass, fat percentage. 6MWT (m): T=66; C=1	Muscle strength, exercise capacity and quality of life increased with exercise training in subjects with atrial fibrillation. Lean body mass was unchanged.
Osbak et al, 2011[29]	Prospective, randomized, controlled trial (n= 25-24)	Single medical center – Aerobic training or attention control	12 weeks	6MWT, exercise capacity, quality of life, cardiac output, natriuretic peptides. 6MWT (m): T=65.5; C=1.0	Exercise training increased exercise capacity, 6-minute walking test distance and quality of life and decreased resting pulse rate significantly. Cardiac output and natriuretic peptides were unchanged.

Table continued

Table. ***(Conituned).*** Summary of studies selected and included in the review.

Authors – year	Design – Number	Setting – Intervention	Duration	Outcomes	Results
Pippa et al, 2007[30]	Prospective, randomized, controlled trial (n= 22-21)	Single medical center – Treatment group (qi gong training) or wait-list control group	16 weeks	6MWT. 6MWT: T=114.0; C=9.0	Qi gong training was well tolerated and compared with baseline, showed a significant improvement in physical capacity.
Hegbom et al, 2007[31]	Prospective, randomized, controlled trial (n= 15-15)	Single medical center – Aerobic exercise and muscle strengthening or control	2 months	Exercise capacity, quality of life, symptom frequency and severity related to arrhythmias.	Exercise training significantly improved exercise capacity, quality of life and symptoms during exercise testing.
Hegbom et al, 2006[32]	Prospective, randomized, controlled trial (n= 15-15)	Single medical center – Aerobic exercise and muscle strengthening or control	2 months	Exercise capacity, quality of life and heart rate variability. Exercise duration (min): T=2.9; C=-0.3	Exercise training significantly improved exercise capacity, quality of life and heart rate variability.

intervention as comparator (out of our inclusion criteria). We also excluded the Wahlstrom's study[39] that did not report a measure of functional capacity as outcomes and for consistent pharmacological treatment reported to control the persistent AF.

The quality of the nine studies assessed using the Downs and Black Quality Index was of moderate (n= 4) to good (n= 5) quality[22], as summarized in Table II.

In the selected 9 RCTs, a total of 882 patients were randomized to exercise intervention (n=445) and control groups (n=437) (Table I). Most of the studies lasted 12 weeks[24-29], while in the oldest reports; the proposed program was two months[31,32]. In only one study, the intervention was longer, and patients performed the exercise training for 16 weeks[30]. It has to be noted that in the study of Luo et al[24] the program was followed by a home-based exercise program for an additional 2 years (Table I).

The exercise intervention differed among the included studies. Most of the studies were performed in ambulatory settings as aerobic training program. The exercise training line-up was a combination of supervised in-hospital and home-based outpatient training programs. Most of the exercise programs included aerobic endurance and resistance training with or without treadmill (as ergometer cycling, walking, walking on stairs, running, fitness training on physio balls)[24,25,28–32]. In some studies, aerobic exercise was coupled to the muscular strengthening[31,32]. It was also included an educational part as instruction, to maintain usual daily activities. In the study by Zeren and colleagues[26] the exercise protocol was mainly directed to inspiratory muscle training on pulmonary function, respiratory muscle strength and functional capacity.

In such cases, these elements were combined all together with the supervision of the physiotherapists[29,32], while in other cases were performed alone[27]. Patients were admitted to a possible extra-training at home (once a week), when familiar with the training regimen[27] or directly encouraged to maintain themselves active by using ergometer cycle or an ordinary bicycle[32].

Only the CopenHeartRFA trial[25] was based on cardiac rehabilitation principles. In this program, a series of complex and comprehensive interventions, not only including exercise training, were performed. In addition to exercise, constitutive elements of the rehabilitation program were the education and the psychosocial management, and the behavioral modification of the patients' habits[40].

Finally, the study by Pippa et al[30] examined the efficacy of the medically assisted practice based on Qigong. This refers to a set of static exercises considered as an introduction to the renowned Tai-Ji-Quan. In Qigong, most of the protocol is related to the deep diaphragmatic breathing and the practice of postures in order to increase the muscular tone and strength and the body flexibility, inducing also the better control of patients' feelings.

As control groups, patients were requested to maintain their habitual physical activity.

Concerning outcome measures, 6-minute walking test distance was the only always-measured outcome[24-32] as tool of assessment of exercise capacity, globally showing a significant improvement in the active group respect to patients of the control groups. In the study by Zeren et al[26], in addition to the amelioration for the functional capacity, the inspiratory muscle training significantly improved the pulmonary function

Table II. Summary of quality of studies selected and included in the review.

Authors – year	Reporting (11)	External validity (3)	Bias (7)	Confounding (6)	Power (5)	Total (32)	Quality as per cut-off described*
Luo et al, 2017[24]	10	3	5	5	5	28	Good
Risom et al, 2016[25]	10	3	5	5	5	28	Good
Zeren et al, 2016[26]	9	2	4	4	3	22	Moderate
Malmo et al, 2016[27]	10	3	5	5	4	27	Good
Osbak et al, 2012[28]	9	2	4	4	4	23	Moderate
Osbak et al, 2011[29]	10	3	5	5	4	27	Good
Pippa et al, 2007[30]	8	2	4	4	3	21	Moderate
Hegbom et al, 2007[31]	10	3	5	5	3	26	Good
Hegbom et al, 2006[32]	9	2	4	4	3	23	Moderate

*>30: Excellent, 24-30: Good, 18-23: Moderate, <18: Poor.

and respiratory muscle strength (measured using spirometry and maximal inspiratory/expiratory pressures).

In addition, peak oxygen uptake[25,26,29] was frequently used in the assessment of exercise capacity, as low-cost and objective measure of the physical capacity of personal fitness, retrieving significant improvements in all active groups. The role of peak oxygen consumption is important because it is a measure of cardiorespiratory fitness, strongly predicting future CVD[41].

In one of the included study[29], aerobic training was not significantly effective on cardiac output, and natriuretic peptides remained unchanged. However, although the difference was not statistically significant, the mean N-terminal pro–B-type natriuretic peptide was lower after the training program in the active group while no change was observed in the control group. Furthermore, this study, together with the study of Hegbom and colleague[32], showed that exercise training positively influences the heart rate at rest and during exercise and the heart rate variability, indicating a possible increase of the vagal tone.

In the study by Malmo et al[27], aerobic interval training reduced the time in AF and significantly improved left atrial and ventricular function and lipid levels and quality of life. Finally, exercise training was able to significantly improve heart rate response and variability[27,31].

In addition, the quality of life was frequently assessed[27-32] by the specific use of scales and as self-rated health status[24,25]. In general, the reported results were positive, even if in the study of Risom and colleagues[25], the mental and physical component SF-36 did not show significant improvements respect to control group.

In terms of the arrhythmia symptoms' frequency and severity, as assessment of exercise training safety, we generally observed high compliance and adherence to proposed programs with no serious/significant adverse events compared with usual care and no need of any particular intervention. Noteworthy, in the study of Malmo and colleagues[27], the mean time of AF significantly increased from 10.4% to 14.6% in the control group while it reduced from 8.1% to 4.8% in the exercise group, with a mean difference in change between groups of 7.6%. Non-serious adverse events as musculoskeletal injuries and pain related to physical performance were noted in the active groups versus usual care[25].

The HF-ACTION trial sub-analysis evaluated all-cause/cardiovascular mortality and/or hospitalization[24]. After the adjustment for the different pharmacological and clinical factors, patients with AF were not significantly associated with worse outcomes and to an increased risk for mortality/hospitalization.

No information was reported about the cost-effectiveness of performing exercise intervention and cardiac rehabilitation by the selected studies.

Lexical Network

The results of LENGTH are shown in Figure 2.

The first graph displayed a cloud of paper titles concentrated around the two most common keywords "atrial" and "fibrillation", indicating that many titles contained these two terms.

Interestingly, in terms of intervention, the non-specific terms as "exercise", "physical" and "activity" are more represented than "rehabilitation". Considering the closeness centrality of the titles, the study by Osbak and colleagues[28] presented the overall third-highest value, even major than some keywords, indicating a strict relationship between this paper and the most represented keywords. It was noteworthy as the term "physiotherapy" is completely absent in the titles.

The second graph showed the study by Zeren and colleagues[26] was the only one with all the keywords contained in the paper, included the term "physiotherapy", only once represented. This term is graphically located in a very far distance from the graph center, to indicate its rarity. Finally, the keywords "cardiorespiratory" and "fitness" were less common, similar to the situation displayed in the first graph.

Discussion

Our systematic review strengthens the role of exercise training as possible complementary treatment in AF. Patients significantly and safely improve functional cardiorespiratory outcomes, in terms of exercise capacity, symptoms' frequency and severity and quality of life. Furthermore, there were significant improvements in pulmonary function and respiratory muscle strength. Other documented improvement concerns the global muscular reinforcement, an ameliorated left atrial and ventricular function, heart rate response and variability and reduced lipid levels. At the same time, our analysis shows an apparent dissociation between the concept of cardiorespiratory fitness and the words used to define it. This could be an important reason for the popular reservations about the use of structured exercise training in the management of patients with AF.

We have used an innovative method to analyze the connection between terms and disease. The suggested graph-based approach, indicated as LENGTH[42], adds some peculiar information about the status of the art of cardiorespiratory fitness in AF. While the term "exercise" is common and largely integrated into titles and texts, the impact of the term "rehabilitation" is relatively low. The term "training" appears well represented only in the selected papers. Interestingly, the term "physiotherapy", the most describing intervention in rehabilitation, is almost unused. This situation is very stimulating and deserves further investigations.

One of the possible explanations is related to the way to deliver the exercise intervention. Physiotherapy includes the use of several methods to restore the function from a wide plethora of different conditions. In cardiorespiratory field of application[1,2,6,43], studies use various protocols of exercise training. Most of the studies mix elements of an aerobic training program by using ergometer cycling, walking, stair climbing, running with or without treadmill. In some studies, aerobic exercise was coupled with muscle strengthening[31,32]. Also, the principles of qi gong exercises were referred to aerobic training[29]. The use of several models of training, the relative short period of intervention and short-term follow-up assessment could be the basis for the uncertainty about type, intensity and frequency of exercise training. All these parameters (FITT principles: frequency, intensity, type and time) should be prescribed in patients with AF.

After an acute heart disease (myocardial infarction and percutaneous coronary intervention) or in patients with chronic CVD (heart failure, pulmonary and systemic hypertension), a structured program of training provides beneficial effects. In fact, it has been documented that exercise training can improve physical, mental, cognitive, and social function; is able to reduce the risk of mortality, hospitalization and, finally, the healthcare costs[1,2,6,40,43–45]. The included study of Luo and colleagues could be a valid example of structured program[24], being an exercise training tailored for patients with heart failure with reduced ejection fraction, also effective in AF. This is the only longest study in terms of time of intervention. Even if the gain was related to peak oxygen consumption and 6-minute walk distance, the sample included elderly patients with reduced exercise capacity at baseline and multimorbidity. Hence, the lack of a differential response to exercise training for clinical outcomes or changes in exercise capacity can be considered a significant result.

A possible forward step could be the adoption of a more structured cardiovascular rehabilitation as in heart failure and other CVD. This is a model based on comprehensive interventions, including exercise training, education and psychosocial management, behavioral modification of the patients' habits[40]. This model is suitable and effective in other home-based chronic conditions[46], and it is preferentially delivered in hospital settings. A comprehensive rehabilitation program is present in the CopenHeartRFA randomized clinical trial[25]. This trial was designed to investigate the effects of the addition of an individualized exercise protocol and psycho-educational consultations to usual care on physical capacity and mental health in patients with AF following ablation. The program consisted of a set of exercises and psycho-educational component, performed face-to-face or by telephone. The exercise program was delivered in different locations according to the patients' preference. The study did not report values according to the patients' preference. This could be the reason for a possible lack of efficacy in terms of quality of life.

Recently, Tang et al[47] highlighted as self-management home-based and supervised centre-based exercise programs seem to provide similar cardiovascular benefits, in a sample of patients with heart valve surgery and radiofrequency ablation for AF. The authors also noted, as the preference of patients to participate in home-based or center-based treatment was equivalent, even if the home-based group appeared to have better physical health and higher exercise capacity at baseline[47]. These results in patients with AF confirmed analogous preliminary reports for more complicated CVD[48,49]. At the same time, the self-managed exercise training contrast with the principles of cardiovascular rehabilitation and turn away the development of the structured programs of physical training, of particular relevance especially in a pandemic period[50].

Notwithstanding, our results could help the current evidence for considering exercise in the global treatment of AF, integrating the acute management of acute conversion to sinus rhythm, protection against thromboembolic events, eventual improvement of cardiac function and, finally, the long-term administration of antiarrhythmic drugs[18,51]. This is particularly important considering that patients with AF present a lower functional class and multimorbidity[24,37], often assuming many drugs[52-54], and with many age-related problems[55,56]. Even if poorly analyzed, in a relatively small number of participants, exercise training reduces the arrhythmic burden patients with associated improvements of AF symptoms[25,27].

Our analysis needs to be interpreted at the light of the publication bias and studies' limitations existing in the current literature. The main drawbacks are the heterogeneity in study designs and the inclusion of underpowered studies, reinforcing the need for further RCTs on cardiorespiratory fitness and AF.

Moreover, in this study we did not investigate the effects of the exercise on incident AF. In some studies, the exercise training may have a protective role against the development and the recurrence of AF[27]. Interestingly, none of the selected studies was designed to specifically evaluate the relationship between physical activity and incident AF. This is possibly related to the short period of intervention and follow-up. Only the sub-analysis of the HF-ACTION trial permitted to observe a long period follow-up. Exercise training did not lead to AF events increase in patients with heart failure[24].

Conclusions

This systematic review confirms that exercise training appears to be effective in functional cardiovascular capacity in AF patients. This could be also integrating the correct management of AF to prevent other CVD as heart failure. Exercise training has a good safety – and adherence/compliance – profile with few serious adverse effects; it should be encouraged as part of a multidisciplinary treatment program. The concerns in its prescription could be relative to the limited literature and to the lack of unique terms to describe the type of intervention. Our findings have implications for future research to confirm the benefits and risks of physical activity in this disease. Further studies with longer follow-up duration are needed.

In summary, despite some discordances in literature, the exercise training seems useful to improve the physical function in patients with AF.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contributions

ML, AG, DC contributed to the conception and design of the work. AV, GF, CL, ES, SG, AM contributed to the acquisition, analysis, or interpretation of data for the work. ML, AF, DC CD drafted the manuscript. LP and SG critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy..

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