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Review Article

Radiofrequency ablation in patients with obstructive hypertrophic cardiomyopathy: A systematic review and meta-analysis

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ABSTRACT

Study objective: Hypertrophic cardiomyopathy (HCM) is a genetic disease that can cause left ventricular outflow tract (LVOT) obstruction. This study analyzed the efficacy of radiofrequency ablation (RA) in improving clinical and hemodynamic factors in patients receiving obstructive HCM refractory treatment. This evaluation was necessary because of the small number of studies on the effectiveness of this technique for obstructive HCM in the existing literature.
Design: We used the PubMed, Embase, and Science Direct databases to identify randomized clinical trials and observational studies addressing the clinical and hemodynamic outcomes before and after RA in patients with HCM.
Participants: We selected six articles published between 2011 and 2022, comprising 304 patients (mean age: 45 years).
Interventions: We performed a bias assessment using the ROBINS I tool, and meta-analysis processing was performed using the STATA program (v.16.0).
Results: The left ventricular outflow tract (LVOT) gradient at rest and with stimulation decreased by 58.78 mmHg ($p = 0.001$) and 70.38 mmHg (total effect $Z = 21.62$; $p < 0.0001$), respectively. Additionally, the New York Heart Association (NYHA) functional class decreased by 0.43 ($p = 0.001$), indicating symptomatic and hemodynamic improvements. Furthermore, we observed a significant reduction in septal thickness (by 4 mm; $p = 0.001$).
Conclusions: RA improved the NYHA functional class and LVOT gradient at rest and with stimulation and reduced septal thickness. These results suggest that RA is effective in patients refractory to pharmacological therapy and unsuitable for alcohol septal ablation or myectomy. However, more studies, including randomized clinical trials, should be conducted to define the role of RA in interventional therapies.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is a relatively common autosomal dominant genetic disease that causes structural deformation in the configuration of the myocardium, occurring in approximately 1 in 500 individuals in the general population worldwide [1]. Left ventricular hypertrophy is a primary clinical feature of HCM, with outflow tract obstruction occurring in up to 70 % of cases [2].

Although the American Heart Association guidelines classify beta-blockers and non-dihydropyridine calcium channel blockers as Class 1 pharmacological treatments for HCM, their effects are limited. Studies show that they only decrease the systolic gradient by 50 mmHg, resulting in many refractory patients [3,4]. Therefore, depending on how favorable the coronary anatomy is in each case, other techniques,

Abbreviations: HCM, Hypertrophic Cardiomyopathy; RA, Radiofrequency Ablation; LVOT, Left Ventricular Outflow Tract; NYHA, New York Heart Association; LV, Left Ventricular; TAVB, Total Atrioventricular Block; ASA, Alcohol Septal Ablation.

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such as myectomy (septal scraping) and alcohol ablation, are required to remove the septal tissue [5].

Radiofrequency ablation (RA) has slowly become a well-established intervention for cardiac arrhythmias in recent decades. Therefore, some researchers have explored its potential as an alternative treatment for left ventricular outflow tract (LVOT) obstruction in patients with HCM. The technique induces a local infarction in the fibrotic tissue by applying heat, decreasing the septal thickness [6].

The success of RA is independent of the coronary anatomy, and the technique is minimally invasive. Thus, medical practitioners have employed this technique in specialized centers for HCM treatment, especially when an optimal pharmacological therapy has not been identified and patients are unsuitable for alcohol septal ablation or myectomy [7,8]. However, there is an ongoing effort to determine the effectiveness of RA for HCM owing to the small number of studies on this technique in the existing literature. Thus, this study asked the following question (PICOT): can RA modify the clinical and hemodynamic outcomes in patients with HCM, thus providing effective treatment? To address this question, we performed a meta-analysis and systematic literature review.

2. Materials and methods

2.1. Search strategy

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol checklist. We used PubMed, Embase, and Science Direct as data search sources and a search period from 1992 to 2022 without language restrictions to increase the sensitivity of the results.

Descriptor searches included "hypertrophic cardiomyopathy," "radiofrequency ablation," and their synonyms (Medical Subject Headings [MeSH]/Emtree), as well as keywords separated by the following booleans: "Hypertrophic Cardiomyopathy" AND "Endocardial Radiofrequency Septal Ablation" OR "Percutaneous Intramyocardial Septal Radiofrequency Ablation" OR "Radiofrequency Ablation." Additionally, we used MeSH as a second strategy to increase article capture by employing the terms "Hypertrophic Cardiomyopathy" and "Septal Reduction." Finally, to select relevant studies, we used the "citation matching" tool along with the keywords "Hypertrophic Cardiomyopathy" and "Percutaneous Intramyocardial Septal Radiofrequency Ablation."

We used the Mendeley (https://www.mendeley.com/) program to remove duplicates, which helped manage the references. After removal, two authors (C.C.C. and E.P.J.) independently selected the articles and analyzed the titles and abstracts. If the abstract was unavailable, the full article was accessed. In the event of a disagreement, a third author (A.S. M.J.) determined whether the article should be included or excluded.

2.2. Data extraction and result definitions

The following information was extracted from the selected studies: 1) publication details (e.g., first author's last name, publication year, and country of origin); 2) study design and period; 3) study population characteristics (e.g., sample size, sex, age, RA indication, New York Heart Association [NYHA] functional class, ventricular septum size, left ventricle [LV] outflow gradient, and follow-up duration); 4) outcome evaluations (e.g., all-cause mortality, sudden death, and intervention occurrences); and 5) peculiarities of the RA technique (e.g., temperature, power, procedure duration, and catheter type). The indication for RA was based on a history of refractory clinical pharmacological and invasive therapy (alcohol ablation or myectomy).

2.3. Inclusion criteria

We included studies that: 1) involved patients who underwent RA and had pathological obstructive HCM and 2) used the NYHA functional class and hemodynamic (e.g., LV output gradient and ventricular septum size) classifications to describe the outcomes. All extracted information was placed in spreadsheets and scrutinized for eligibility.

2.4. Exclusion criteria

We excluded studies in which patients underwent alcohol ablation and myectomy, articles focusing on pharmacotherapy and animal studies, studies with incomplete statistical data, case reports, and systematic reviews.

2.5. Risk of bias

All included articles were analyzed using the risk-of-bias ROBINS-I [9] (for non-randomized studies) tools from the Cochrane Methods Network.

2.6. Statistical analyses

This meta-analysis included only continuous variables. The statistical method for weighting the articles was based on the inverse of the variance, with its weight proportional to its precision. Thus, measuring the effect was based on the difference between the means, and the meta-analysis results were issued in the same unit of measure as the outcome variable.

After considering the methodological similarities between the studies, outcome variable, and longitudinal observations, we adopted a fixed-effect analysis model. Heterogeneity analysis was performed using the Higgins and Thompson test (I^2); however, the use of the effect was adopted considering the weight of the research with greater relevance, thus avoiding the acceptance of the nullity of homogeneity caused by the small-samples bias.

The meta-analysis was performed using the STATA program (v.16.0) [10], with a significance threshold of 5 % ($p < 0.05$). The publication-bias assessments were represented by funnel plot analyses (a scatter plot of standard error vs. effect size) and are available in the supplementary material.

3. Results

3.1. Database search

The database search identified 415 relevant references or citations (Supplementary Fig. 1). The first search strategy applied filters that only selected clinical trials, observational studies, and randomized clinical trials, identifying 32 articles in PubMed, whereas the second strategy resulted in 46 articles. Additionally, the first search strategy identified 241 articles in EMBASE and 96 in Science Direct. First, we excluded 270 duplicates and then 45 additional studies owing to topic inadequacy after analyzing the titles and abstracts. Thus, we analyzed 19 articles based on the eligibility criteria, but only six were selected for meeting these criteria.

3.2. Study characteristics

We selected six articles published between 2011 and 2022, involving 304 patients (162 men and 101 women; one study with 41 patients did not report the sex of the sample population). The number of participants in each study ranged from five [11] to 200 [12]. Overall, the mean age of the patients was 45 years. One article exclusively evaluated children (32 patients [13]), whereas the remaining articles evaluated an adult population (men and women) [11–13,15,16]. Two studies were conducted in China, two in England, one in Germany, and one in the United States [11–16]. Supplementary Table 1 describes the patient characteristics.

3.3. RA intervention

All the analyzed studies used RA to treat obstructive HCM refractory to pharmacological measures and other procedures [11–16]. The mean procedure duration ranged from 75 min [12] to 142 min [15]. Supplementary Table 2 details the intervention characteristics for each study.

3.4. Outcomes

The primary outcomes were compared before and after RA, including the LVOT gradient at rest, LVOT gradient under stimulation, the population's NYHA functional class, and septum size.

3.4.1. LVOT gradient at rest

The LVOT gradient at rest was described in all articles. RA intervention considerably reduced LVOT obstruction by 58.78 mmHg (range: 52.96–64.6, $p = 0.001$) (Fig. 1). The heterogeneity was 60.3 %.

Evaluation of publication bias (funnel plot; Supplementary Fig. 2) clearly indicated that the analysis was well-centered on the fixed effect, representing a low standard error among the studies.

3.4.2. LVOT gradient under stimulation

The LVOT gradient under stimulation decreased by 70.38 mmHg after RA intervention, along with 91 % heterogeneity ($p < 0.0001$) (Fig. 2). By contrast, the meta-analysis had a total effect Z of 21.62 ($p < 0.0001$), demonstrating that RA effectively reduced this parameter.

Further evaluation of publication bias (funnel plot; Supplementary Fig. 3) demonstrated that the fixed-effect and heterogeneity tests did not apply to three studies ($p < 0.0001$). Therefore, we used a fixed-effect model for this outcome variable, given the weight of studies with larger sample sizes.

3.4.3. The NYHA functional class

The NYHA functional class quantifies and classifies the degree of symptoms (dyspnea). Patients classified as Class I have no symptoms in daily activities, whereas those classified as Class IV have symptoms following minimal exertion.

NYHA functional class decreased by 0.43 (range: 0.38–0.49, $p = 0.001$) (Fig. 3), with a heterogeneity of 99 % ($p < 0.0001$). Because the fixed-effect model was unsuitable for the analysis, we used the random-effect model and identified the heterogeneity of the sample size as the main factor in the heterogeneity of the distribution of the NYHA functional class (Supplementary Fig. 4).

3.4.4. Septum size

The septum size before and after intervention showed a heterogeneity of 94.39 % ($p < 0.0001$) (Fig. 4), revealing that RA reduced the interventricular septum size by 4.00 mm (range: 3.32–4.69, $p = 0.001$). Supplementary Fig. 5 shows the heterogeneous distribution according to the sample size used in each study.

3.4.5. Complications

On follow-up day 30, Zhou et al. [12] reported complications in 21 (10.5 %) patients. Of these patients, two (1.0 %) died in the hospital within 30 days; one of them owing to cardiogenic shock due to anterior mitral valve prolapse, probably caused by excessive ablation and myocardial edema, while the other patient was found unresponsive, with sudden death (monitor in asystole), possibly due to bradycardia or ventricular arrhythmia. Seven patients (3.5 %) had pericardial effusion requiring mini-thoracotomy, and 12 (6 %) had pericardial effusion requiring pericardiocentesis. This pericardial effusion rate can be reduced with pre-procedure tomography angiography planning. Other periprocedural complications included permanent right bundle branch block in five patients (2.5 %), reversed ventricular fibrillation in two (1.0 %), and septal branch aneurysm in two (1.0 %), although these did not require definitive pacemaker implantation [12].

By contrast, Lawrenz et al. [14] reported a complete block and a high-grade atrioventricular block requiring pacemaker implantation after the procedure in 12 patients (29 %), owing to damage to the electrophysiological beam during septal ablation. Additionally, two patients experienced pericardial tamponade caused by RV pacing catheter perforation [14]. Lawrenz et al. related one death to cardiogenic shock caused by mitral regurgitation and LVOT reduction. An attempt was made to replace the valve, the leaflets of which were possibly injured during RA, but it was ineffective.

Sreeram et al. [13] reported one procedure-related death due to a paradoxical increase in the LV outflow gradient, with two patients having total atrioventricular block (TAVB) and requiring dual-chamber pacemaker implantation. Similarly, two patients developed ventricular fibrillation related to catheter manipulation in the ventricle. Minor complications included a groin hematoma ($n = 1$) and superficial burns at the ground electrode sites ($n = 1$) [13].

Furthermore, Cooper et al. [11] reported mesenteric ischemia related to retroperitoneal hemorrhage and femoral artery bleeding, leading to death. One patient developed a paradoxical increase in LVOT gradient immediately following ablation resulting in pulmonary edema.

Crossen et al. [15] presented five intraventricular conduction delays post-procedure, and two patients (17 %) required pacing support for complete atrioventricular block. Liu et al. [16] described just one complication, pericardial tamponade due to an injury to the coronary vein and abnormal blood coagulation, that required operative intervention. They recommend maintaining a safe distance of 3 mm between the border of the ablated region and the left side of the LV, with a gradual increase in ablation power to avoid affecting the conduction system. This appeared to be effective, since no patient developed a complete block. Supplementary Table 3 summarizes the complications

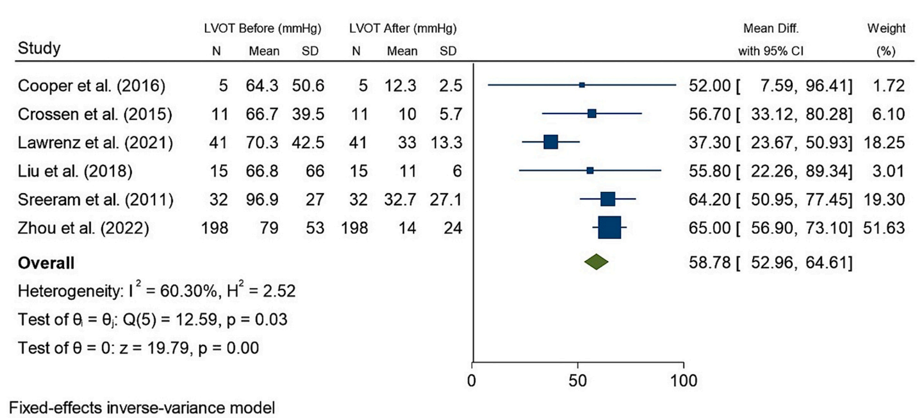

Fig. 1. The effect of radiofrequency ablation on the left ventricular outflow tract at rest.

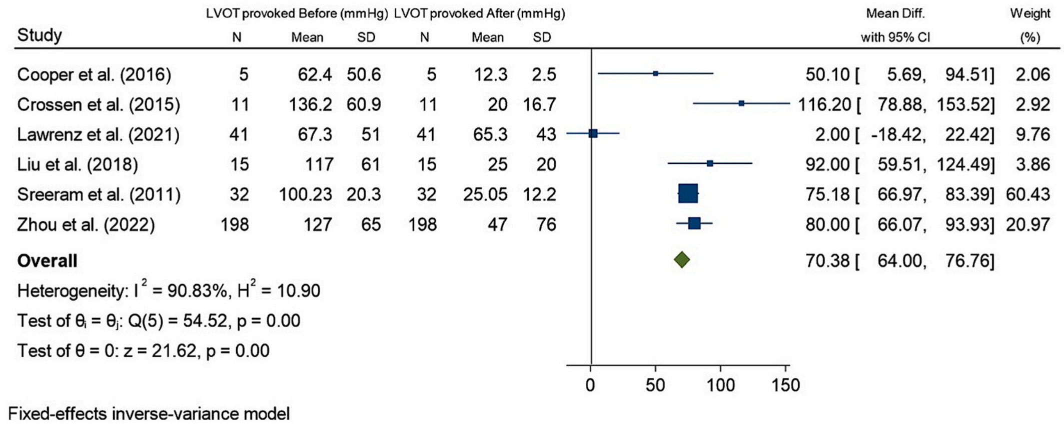

Fig. 2. The effect of radiofrequency ablation on the left ventricular outflow tract after stimulation.

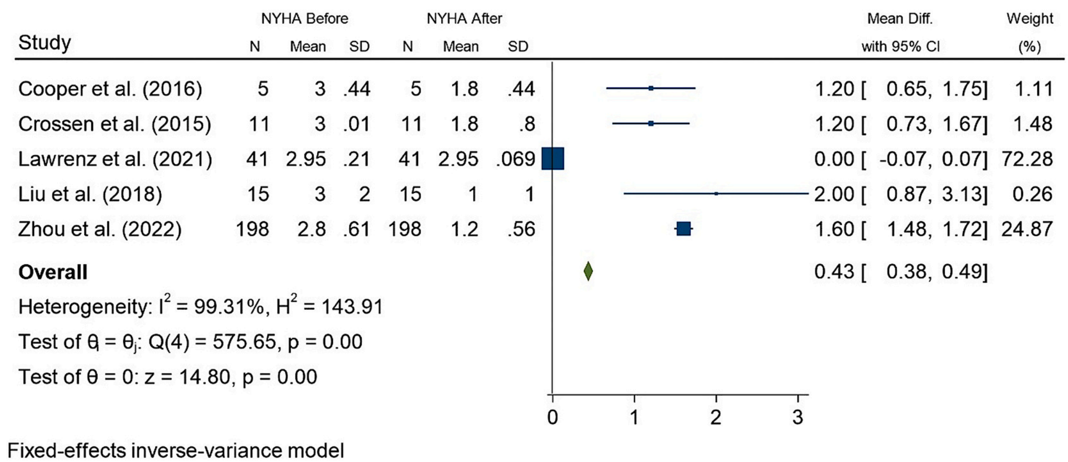

Fig. 3. The effect of radiofrequency ablation on the New York Heart Association functional class.

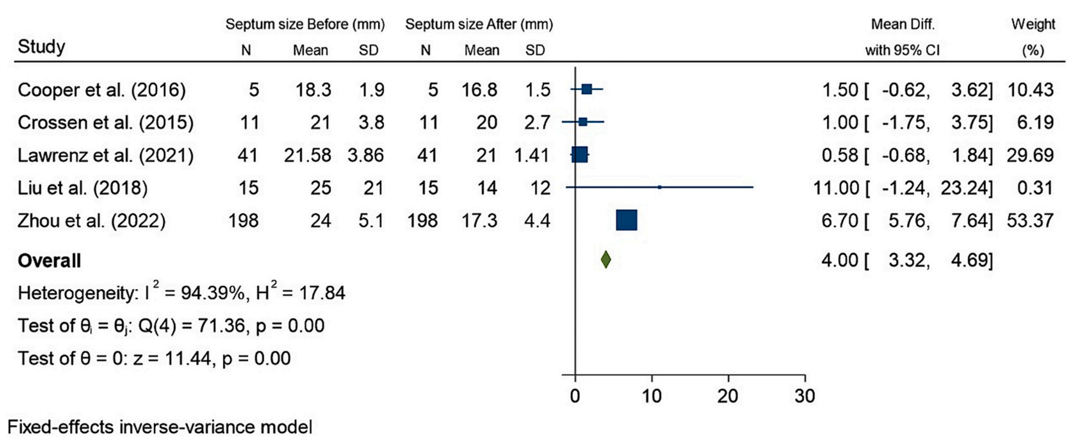

Fig. 4. The effect of radiofrequency ablation on septum size.

of the articles evaluated.

3.5. Risk of bias

We performed a risk-of-bias analysis for each included study (Supplementary Figs. 6 and 7), with only one study meeting a criterion for risk [16]; therefore, it was considered a high-bias risk study due to the lack of certain details statistical analyses and tests. The remaining studies were considered low-bias risk studies.

4. Discussion

HCM is a genetic disease with a clinical presentation comparable to that of congestive heart failure, which confers a high risk of sudden death, especially in young people [8]. Approximately 70 % of patients with HCM develop anterograde flow obstruction defined by a peak systolic gradient of >30 mmHg. Its pathophysiology is associated with the displacement of the anterior leaflet of the mitral valve, which comes into direct contact with the hypertrophied septum, thereby hindering blood flow and generating an obstructive condition [17].

Thus, a recent systematic review and meta-analysis by Jiang et al. [24] compared myectomy with RA, showing that the cost and length of hospital stay for RA were lower than that for myectomy (RA: 2 days vs Myectomy: 7.7 days). On the other hand, with regard to hemodynamic outcomes, myectomy is still superior (resting LVOT Myectomy: −3.03 vs RA: −1.95; septal thickness Myectomy: −1.82 vs RA: = −0.43). Clinical outcomes (NYHA) were similar in the two groups [24].

Indications for interventional HCM treatment include clinical, hemodynamic, and anatomical criteria. Moreover, interventional treatment is primarily reserved for patients with considerable heart failure symptoms (NYHA Class III or IV) and those refractory to medication, those with an LVOT gradient >50 mmHg at rest or under stimulation, and those with an anterior septal thickness deemed safe for treatment by the interventionist. Myectomy is the gold standard surgical treatment for obstructive HCM, and percutaneous modalities are recommended when surgery is not possible [4,8,17,24].

The following studies described the outcomes of five, forty-one, one, and four patients that underwent RA after alcohol septal ablation (ASA) or a myectomy attempt (either by patient choice, unfavorable septal branch anatomy, or because of the impossibility of surgical risk to myectomy) indicated RA as an alternative when other techniques were unsuitable [11,13–15].

RA can be performed using transthoracic echocardiography, computed tomography, or angiography. Thus, it is well established for treating arrhythmias, such as atrial fibrillation, as it does not depend on the coronary anatomy for its success [18]. Therefore, studies have targeted RA as a promising therapy for obstructive HCM treatment when an optimal pharmacological treatment cannot be found [18,19].

Lawrenz et al. [14] evaluated RA's effectiveness and safety, observing that morbidity and mortality were the same in patients undergoing RA and ASA [14], which involves injecting ethanol into the artery to irrigate the tissue being reduced [20]. However, the success of ASA depends on the coronary anatomy, as the perforating arteries of the septum may not supply the hypertrophied septum, often resulting in low resolution [14].

All patients included in this systematic review presented with reduced LVOT obstruction and septal thickness, significantly improving the outflow gradient after RA [11,13–15,17]. Additionally, a review of case reports by Poon et al. [20] revealed that RA significantly reduced left ventricular obstruction, which corroborated the present findings. Furthermore, Li et al. [21] observed an 11-mm decrease in septal thickness in 15 patients [21], whereas the present study demonstrated RA effectiveness according to a 4-mm decrease in septal thickness. Moreover, some reports indicated that the systolic gradient during exercise decreased from 117 mmHg to 25 mmHg [16,22], and another study reported NYHA class improvements and decreased pro-B-type natriuretic peptide levels (from 924 pg/mL to 137.5 pg/mL) over a 6-month follow-up period [18].

RA generates localized "therapeutic infarctions" with minimal tissue damage, thereby eliminating or reducing the LV systolic gradient immediately after the procedure [12]. However, hypokinesia of the LV wall is possible, which induces uncoordinated movement caused by heat and myocardial necrosis. Nevertheless, local remodeling occurs through fibrosis, causing the septal lesion to shrink [12].

A comparison by Liu et al. [16] of RA and surgical myectomy revealed similar results regarding clinical and hemodynamic outcomes [16]. However, RA did not involve sternotomy or its complications and based on their experience, they believed that it didn't damage the conduction system during or after the procedure. This is because, as mentioned, Liu et al. [16] maintained a safe distance of 3 mm between the border of the ablated region and the left side of the LV to avoid conduction system injury, which might have contributed to better long-term results [16].

RA is prone to complications. Previous studies described a paradoxical increase in the output gradient in six patients because of tissue edema [11,13,14], with Sreeram et al. [13] and Cooper et al. [11] also observing this complication using 60 W of power, whereas Lawrenz et al. [14] described this result using 75 W. Thus, this outcome might be RA-specific, as it was not observed with ASA or myectomy [14]. Additionally, other studies reported cardiac tamponade due to coronary vein injury [18].

By contrast, in alcohol ablation, some electrical complications, such as TAVB and the need for permanent pacemaker implantation, as well as extensive myocardial infarction, may occur. Aksu et al. [23] reported that 1.4 % of patients died following alcohol ablation, 3 % experienced sustained ventricular arrhythmias, 3 % experienced cardiac tamponade, and 20 % required pacemaker implantation [23]. Radiofrequency septal ablation is reportedly safe and less invasive, requires a shorter hospital stay, and can be used on cardiac tissue showing a high degree of hypertrophy [15,16]. Furthermore, if necessary, new ablations are possible, and the procedure is suitable for individuals with diverse comorbidities and symptoms and resistant to pharmacological therapy [15,16].

The patients included in all of the studies in this review reported a significant reduction in symptoms and the NYHA functional class [11,12,14–16], except in the case of Sreeram et al. [13], in which these outcomes were not addressed. Our meta-analysis demonstrated that the NYHA functional class decreased by 0.43. The most recent study in this analysis (Zhou et al. [12]) reported that 29 % of patients were classified as NYHA Class II, 63 % as NYHA Class III, and 8 % as NYHA Class IV. Moreover, the number of patients with symptoms decreased from 71 % to 4 %, and 93.4 % of patients dropped at least one functional class [12]. Thus, 52 of 58 NYHA Class II patients reported milder symptoms and were reclassified as NYHA Class I, demonstrating improved clinical parameters after RA [12].

This study was limited by one article that did not analyze some of the evaluated outcomes chosen for this meta-analysis. Therefore, these data might be considered incomplete along with the presence of high-bias risk in one study; however, the standard deviations were low.

5. Conclusion

This systematic review found that RA improved the NYHA functional class, reduced septal thickness, and decreased the LVOT gradient at rest and when stimulated. However, more studies, including randomized clinical trials with more patients, are required to incorporate this technique as the standard interventional therapy.

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Protocol registration

This review was registered on the PROSPERO platform and can be publicly accessed by the access code CRD42022329807.

CRediT authorship contribution statement

Camila Cássia Canzi: Conceptualization, Methodology, Software.
Edivalde Ribeiro do Prado Júnior.: Data curation, Writing- Original draft preparation.
Antonio da Silva Menezes Junior: Visualization, Writing-Reviewing and Editing.
Aline Lazara Rezende: Supervision; Investigation.
Silvia Marçal Botelho: Software, Validation.
Luciana Ressureição Santos: Writing- Reviewing and Editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement

The authors declare that the data generated and/or analyzed in this research are available from the corresponding author on reasonable request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2022.100229.

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