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A systemic review of endocardial left ventricular pacing

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ABSTRACT

Background: Endocardial left ventricular pacing is an alternative technique used in cardiac resynchronization therapy (CRT), when placement of a left ventricular lead is not possible via the coronary sinus or in non-responders to conventional CRT.
Objectives: To review the evidence regarding the efficacy and safety of endocardial left ventricular pacing.
Methods: Systematic research on Medline (PubMed), ClinicalTrials.gov and Embase with the terms "endocardial left ventricular pacing", "biventricular pacing" or "endocardial left pacing" was performed with the identification of 1038 results. Eleven studies with endocardial left ventricular pacing patients were included, independent of the technique being applied to naïve CRT patients or con non-responders to conventional CRT. The end-point of this analysis was the impact of endocardial left ventricular pacing techniques regarding New York Heart Association (NYHA) functional classification, left ventricular ejection fraction (LVEF) and QRS width, and the occurrence of complications Mean differences (MD) and confidence interval (CI) was used as a measurement of treatment.
Results: A total of 560 patients were included, with different techniques used (trans-atrial septal technique, trans-ventricular septal technique and transapical technique). Significant improvement was registered in NYHA class (MD 0.73, CI 0.48–0.98, $p<0.00001$, I^2 = 87%), LVEF (MD -7.63, CI -9.93 - -5.33, $p<0.00001$, I^2 = 69%) and QRS width (MD 29.25, CI 9.99–48.50, $p<0.00001$, I^2 = 91%). Several complications were reported after the procedure, 11 pocket infections, 22 transient ischemic attacks, 18 ischemic strokes, 41 thromboembolic events, among other complications. The mortality rate during the follow-up was 20.54%.
Conclusion: Left ventricular endocardial pacing is a feasible alternative to conventional CRT, with clinical, electrocardiographic and echocardiogrphic improvement. However, first data regarding this procedure was associated with significant complications rates.

Introduction

Heart failure is a growing pandemic in developed countries being a frequent cause of mortality. Several medical and device therapies improvement of survival rates of heart failure (HF) patients. Cardiac resynchronization therapy (CRT) is a proven treatment in patients with severe left ventricular systolic dysfunction and asynchronous ventricular contraction due to intraventricular conduction disturbance (wide QRS complex), with significant improvement in symptoms, quality of life, reduction in hospitalizations and mortality rates.[1]

Conventional CRT is perform by percutaneous access to the coronary sinus and venous tributaries. However, some difficulties can limit this approach as the inabilityto implant the left ventricular electrode due to a challenging sinus coronary anatomy, or phrenic nerve capture. Also, there is significant percentage of unsuitable lead placement and suboptimal clinical outcomes in CRT patients.[2,3]

In the case of non-responders to CRT, there is no definite alternative. A surgical approach is the most frequent solution with epicardial lead implantation, yet most of these patients present several co-morbidities and a higher risk profile, wich makes this alternative approach not an attractive solution for CRT non-responders.

A possible alternative is a lead implantation via an atrial transseptal route, acrossing the mitral valve to obtain an endocardial left ventricle lead placement. However, this is a complex procedure resulting in a lead located in the systemic circulation, increasing the thromboembolic risk, and having the potential to compromisse the mitral valve function.[3] Endocardial left ventricular pacing through the interventricular septum is another available option that may be a simple and direct procedure to obtain resynchronization. Both these techniques avoid the nedd of a surgical intervention, with th advange of a more physiological activayions from endocardial pacing.[4] Therefore, we aimed to assess the feasibility, risks and

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benefits of endocardial left ventricular pacing by a systemic review of the published data.

Methods

Systemic research on Medline (PubMed), ClinicalTrials.gov and Embase was performed, using the keywords "endocardial left ventricular pacing", "biventricular pacing" or "endocardial left pacing". The databases were last access on 21 October 2020, and the research included references published between 01 January 2000 and 21 October 2020.

A preferred reporting item for systematic reviews and meta-analyses statement was applied (Fig. 1). Duplications were removed, and the abstract was reviewed by the authors. Studies that included endocardial left ventricular pacing patients were included, apart of the technique applied, whether it was used in naïve CRT patients or non-responders to conventional CRT. The selection criteria included between non-CRT responders' and patients with an endocardial CRT implantation, studies with at least 16 patients, a minimum follow-up period of least 6 months and the presence of complications reports. The absence of these criteria and the lack of at least one of the main end-points reports was used as exclusion criteria.

The end-point of this review was the comparison between groups regarding New York Heart Association (NYHA) functional classification, left ventricular ejection fraction (LVEF) and QRS width. We cross-referenced the research papers to identify additional studies that comply with the inclusion criteria. Full articles that were identified after screening were reviewed by the authors and the data extracted.

The data variables extracted from the publication were: author name, year published, the country where the study was performed, number of patients, follow-up period, selection criteria and composite endpoints, as well, NYHA class, LVEF and QRS width. The meta-analysis was conducted with the calculation of mean differences (MD) and 95% confidence interval (CI) for all the endpoints. NYHA class, LVEF and QRS width were entered as continuous variables. Heterogeneity was determined using the I^2 test, with values $>$ to 60% considered to be of substantial heterogeneity. Significance was set to $p = 0.05$.

Results

Our systemic electronic search resulted in 34 publications after the initial screening of titles and abstracts. Subsequently, 23 studies

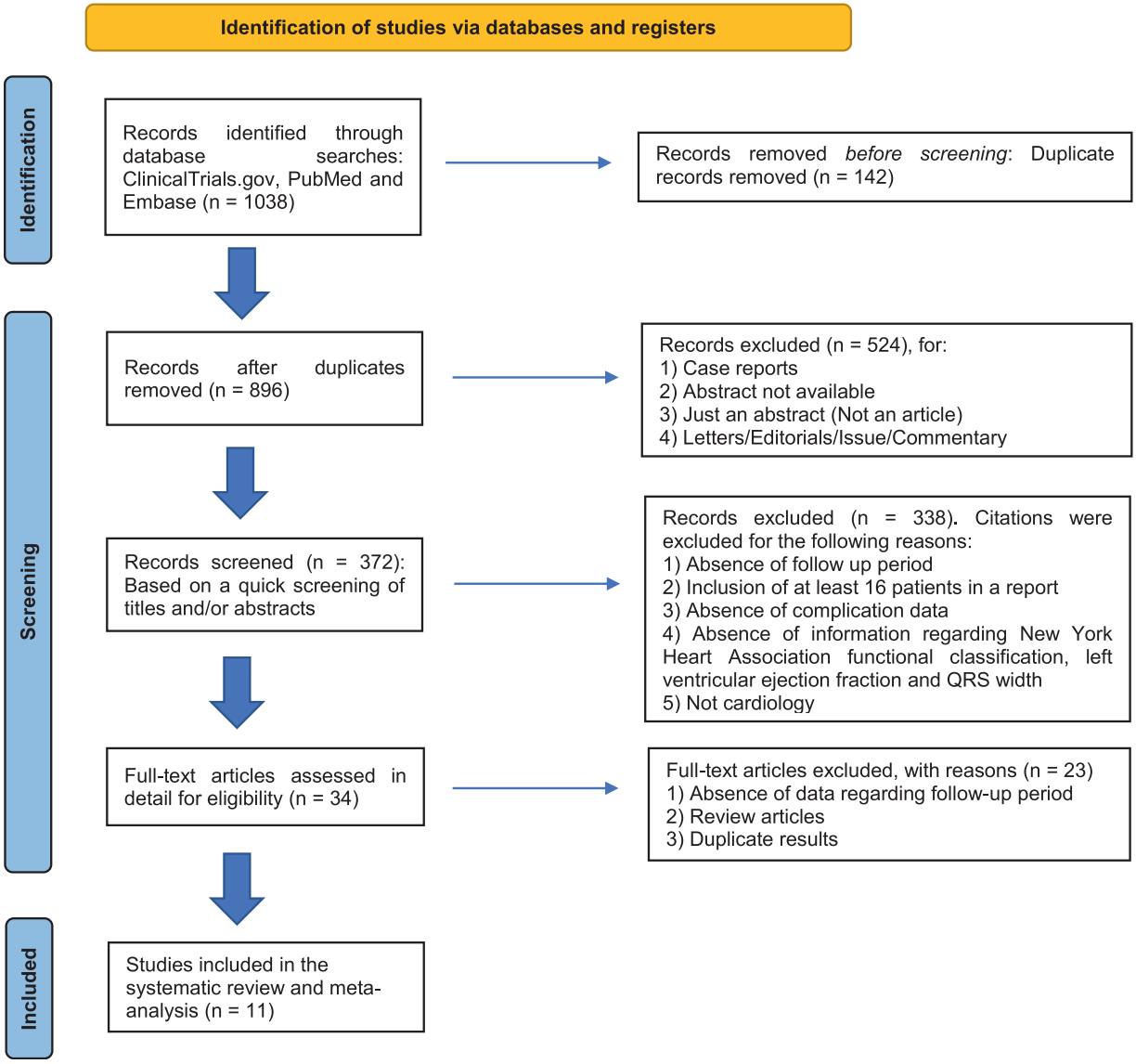

Fig. 1. PRISMA flow diagram of the systematic review process conducted in this study.

Table 1
The details regarding the eleven publications included in this systematic review.

Study name and year	Country and follow up	Technique approach	Sample size CRT non responders	LVEP	Outcomes
Kassai, 2011	Hungary, 15.3 months	Transapical	20	20	Feasible and security of Transapical placement of LV endocardial pacing lead
Rademakers, 2014	Netherlands, 24 months	Atrial transseptal, transapical	50	50	Cerebral thromboembolic complications
Morgan, 2016	7 countries, 18 centres, 17 months	Atrial transseptal	138	118	Safety of left ventricular endocardial pacing
Kis, 2017	Hungary, 40 months	Transapical	26	26	Long-term outcome of transapical endocardial resynchronization therapy
Reddy, 2017	5 countries, 6 centres, 6 months	Wireless left ventricular endocardial pacing	35	34	Safety of wireless left ventricular endocardial pacing
Gamble, 2018	United Kingdom, 6 months	Interventricular septum	20	20	Feasible and security endocardial left ventricular pacing
Sawhney, 2018	United Kingdom, 4 centres, 20 months	Atrial transseptal, Interventricular septum	68	68	Safety and efficacy of endocardial left ventricular pacing
Guerrero, 2019	Spain, 36 months	Atrial transseptal, Interventricular septum	35	35	Feasible of LV endocardial pacing
Geller, 2019	Hungary, 29 months	Atrial transseptal	54	54	Feasible and security endocardial left ventricular pacing
Sidhu, 2020	7 countries, 12 centres, 6 months	Wireless left ventricular endocardial pacing	22	20	Symptoms improvements of endocardial left ventricular pacing
Sieniewicz, 2020	7 countries, 14 centres, 6 months	Wireless left ventricular endocardial pacing	90	85	Safety and efficacy of wireless left ventricular endocardial pacing

were excluded since they did not fulfillthe inclusion criteria, leaving 11 studies to be analyzed in this systemic review. Table 1 specifies the eleven publications included in the analysis, with a total of 560 patients.

Not all the studies included the primary end-points of this systemic review, however, these publications included a follow-up period that allows a comprehensive and global understanding of the safety and feasibility of this technique. The primary indication for endocardial left ventricular pacing was coronary sinus lead implantation failure, and non-responders to the conventional CRT.

The patients included in this analysis presented a mean age of 66.93 years old (90.54% male), median LVEF of 28.86%, NYHA class of 3.03, QRS width 167.50 ms,ischemic etiologic in 43.88%, atrial fibrillation in 45.35% and left bundle branch block in 55.20%. From this data, we understand the complexity and the higher burden of comorbidities and complications presented in these patients, which is unappealing for a surgical approach and apparently more favorable to the endocardial approach. The studies included in this review were performed with different techniques - atrial transseptal approach, wireless left ventricular endocardial pacing, interventricular septal technique and transapical technique - yet all of them with the same final goal of endocardial left ventricular pacing.

Seven studies reported improvement of functional NYHA class outcomes with the endocardial pacing, with a basal NYHA class and a subsequent analysis of NYHA class during the follow-up. The studies presented different follow-up periods. Nevertheless, five of them exhibited a significant improvement on this end-point. The mean differences for the seven studies regarding NYHA class are summarized in Fig. 2. The analysis concluded that left ventricular endocardial pacing significantly improves the NYHA class (MD 0.73, CI 0.48–0.98, $p<0.00001$). The heterogeneity of the studies was found to be relatively high (I^2 statistic 87%).

The successful implantation of resynchronization therapy with left ventricular endocardial pacing increased the LVEF (MD −7.63, CI −9.93 - −5.33, $p<0.00001$, 8 studies), in all the studies that performed this evaluation. Fig. 3 displays the LVEF in the patients submitted to endocardial left ventricular pacing, also with a high heterogeneity between the studies (I^2 statistic 69%).

QRS shortening was also reported with the endocardial left ventricular pacing (MD 29.25, CI 9.99–48.50, $p<0.00001$, reported in 5 studies, Fig. 4). Like the previous evaluations in this review, significant heterogeneity beetween the studies were found (I^2 statistic 91%).

Regarding complications, thromboembolic events were reported in all studies, yet, as previously mentioned, with a very diverse follow-up period, ranging from 6 to 40 months. There were a considerable numbers of thromboembolic events registered, with a total of 41 reported cases, 18 of them classified as ischemia strokes (reported in 11 studies) and 22 cases of transient ischemic attacks (reported in 10 studies). tHowever, it is worth mentioning that just a few events can

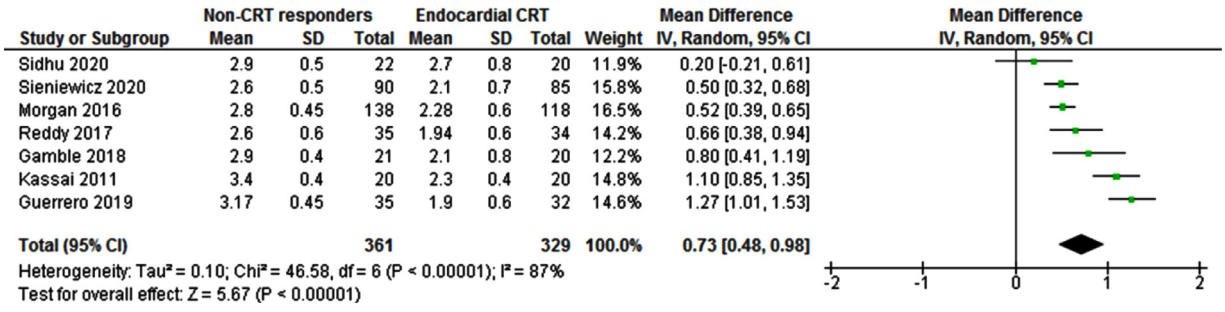

Fig. 2. Systematic review with the mean difference and 95% confidence interval (CI) for NYHA class in the patients with an endocardial left ventricular pacing.

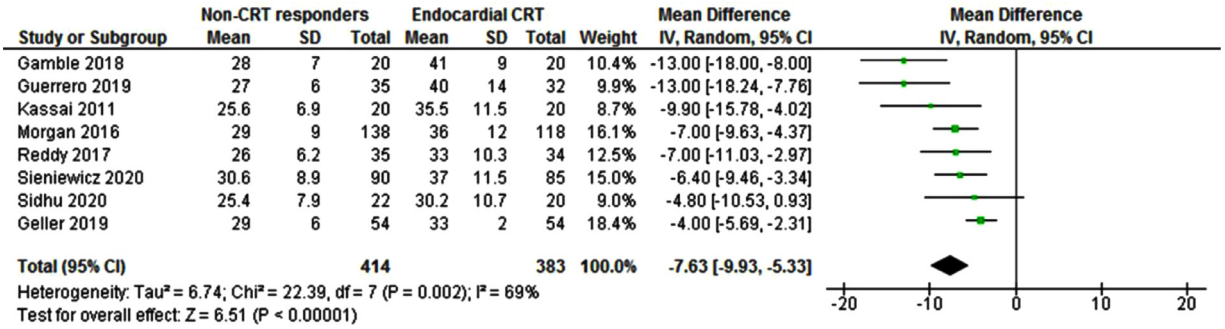

Fig. 3. Systematic review with the mean difference and 95% confidence interval (CI) for left ventricular ejection fraction in the patients with an endocardial left ventricular pacing.

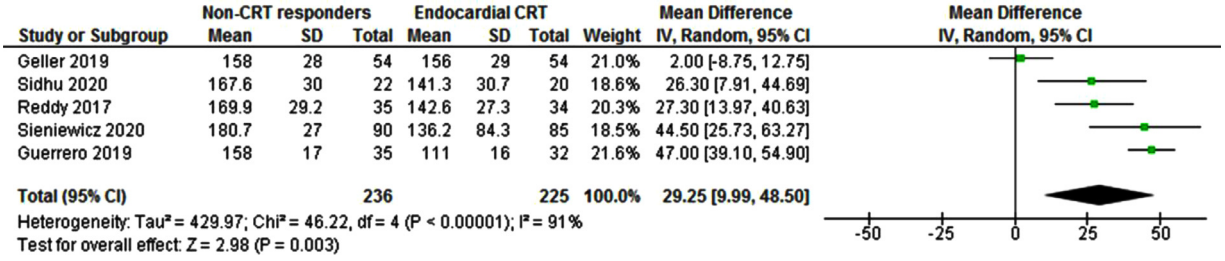

Fig. 4. Systematic review with the mean difference and 95% confidence interval (CI) for QRS width in the patients with an endocardial left ventricular pacing.

be directly related to the procedure (for example ischemic events), since they occurred during the hospitalization for the left ventricle lead implantation.

Infectious, considered a serious complication in device implantation, were also reported in the published series of this reviewThere were 11 documented pocket infections across 475 patients (in 9 studies), and 8 cases of endocarditis or bacteremia (reported in 6 studies) implying removal of the device and leads.

There were also 17 documented cases (reported in 6 studies) of lead dislodgement. Finally, considering the prognosis of these population with severe HF, a 20.54% (115 patients) mortality rate during the follow-up was observed.

Discussion

We performed a systematic review of studies to assess whether endocardial left ventricular pacing – in non-responders to conventional CRT or when the conventional left ventricular lead implantation via the coronary sinus was not successful - was an efficient and safe technique. We concluded that left ventricular endocardial pacing is a viable alternative, with a significant improvement in electrocardiographic, echocardiographic and clinical outcomes in all the endpoints.

Based on animal evidence, left ventricular endocardial pacing appears to have an hemodynamic response[5] that justifies the implementation of this procedure. Some of the patients included in this analysis were non naïve CRT patients, which can influence the results, and the significant improvement in the left ventricular endocardial pacing group.By this analysis, we found that the endocardial left ventricle pacing is not only an alternative to resynchronized therapy, but can also, accordin with some authors[5,6] have higher response rates comparing to the conventional CRT therapy.

Clinical response was demonstrated in all the studies,[6–11] except one[12] leadless left ventricular endocardial. The absence of clinical response in this particular study can be justified by the small number patients with a follow-up period of only just 6 months. These data showed that resynchronization therapy may still offered to patients with unsuccessful conventional CRT implantation or in non-responders to previous CRT. In fact, left ventricular endocardial pacing should be attempt in these cases, because, even with a higher burden of comorbidities, these patients can have a good clinical response.

The successful implantation of resynchronization therapy was able to achieve a positive impact on the LVEF in all the studies,[2,6–12] with a significant improvement. This fact reinforces the role of this alternative approach for resynchronization as an efficient option, with potential to improve prognosis. Without this technique, patients would remain symptomatic with a rapid worsening of LVEF The successful resynchronization therapy also reduces the QRS width,[7,10–12] in all the studies except one. Geller et al.[2] did not found a significant difference in the QRS duration after the procedure, but the authors did not point out a possible explanation for this finding and QRS width was not the endpoint of the study. Left ventricular endocardial pacing was associated with thromboembolic risk, possibly due to the lead location in the systemic circulation. Intracardiac leads had a propensity to thrombus formation, a fact well documented with ultrasound in right-sided leads. Considering the high risk of thromboembolic events, patients in these studies were on warfarin therapy before and after the left ventricular lead implantation. Novel oral anticoagulants were not used due to the lack of experience using these type of drugs in this context and therefore were excluded in most studies.[6]

The thromboembolism rates were higher than expected. Other publications suggested a strong association between the presence of HF, particularlywith reduced LVEF and stroke occurrence. HF is frequently associated with other comorbidities, which contributs to a higher risk of stroke.[13,14] As previously demonstrated,[6] the addition of a left ventricular endocardial lead increases significantly the thromboembolic risk, however the prevalence in this analysis was higher than expected.

A significant number of pocket infectious also ocurred. Nine of the studies reported pocket infections, without anyjustification. Since this techniquesare recent and there is a learning curve, the procedures had certainly a longer duration, wich could be associated with higher infection rates.

New developed procedures have some inherent complications. In these studies, there were left ventricular lead dislodgements

reported, although without major complications described. It is expected that with an increasing experience complications rates resulting from the intervention, will decrease.

Other exciting techniques, known as physiologic pacing, like the His-bundle and left bundle branch pacing, can also have an impact on the variables evaluated in this systematic analysis. However, there is not a direct comparison between left ventricular endocardial pacing and physiologic pacing. Further investigation and larger experience with these techniques are fundamental to understand its long-term efficacy and security.

Patients with severe HF have mortality rates at one yearat one year of the diagnosis ranging from 7% to 17%.[1] Considering the population included in this review, and the high prevalence of comorbidities, the authord expected an even higher mortality during the follow-up. The 20,5% mortality rate reported in this studys weas similar to heart failure HF populations submitted to the conventional CRT.[14] Nonetheless, the follow-up duration and the studies sample size influence the results, and of course, the applicability of this technique.

Limitations

The main limitation of this review is the number of patients included, since this is an innovative procedure still little used. The heterogeneity registered between the studies restricted the potential conclusions and its applicability to all the patients. Also it is difficult to understand the impact of different techniques of left ventricular pacing on the results.

Another difficulty was to establish the real risk of complications in this population. In fact, only a comphreensive evaluation of the individual comorbidities, complexity and risk of the procedure itself can contribute to predict the individual risk of adverse events and outcomes.

Conclusions

This systematic review indicates that endocardial left ventricular pacing is a feasible procedure, allowing highrates of resynchronization therapy, with clinical, eletrocardiographic and echocardiographic benefits. However, this pacing alternative is still associated with a high adverse events rate, namely thromboembolism.

Till now, only small series studied this technique, with heterogeneous results and different approaches, being important to explore further investigation to ascertain the potential of this therapeutic modality.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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