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EDITORIAL

Dual-chamber pacing confers better myocardial performance and improves clinical outcomes compared to single-chamber pacing

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Abstract

The deleterious effects of long term right ventricular pacing are increasingly being recognized today. Current clinical practice favors the implantation of dual-chamber permanent pacemaker which maintains atrioventricular synchrony and is associated with better quality of life. However, despite the popular belief and common sense surrounding the superiority of dual-chamber pacing over single chamber pacing, the same has never been conclusively verified in clinical trials. Some observational evidence however, does exists which supports the improved cardiac hemodynamics, lower the rate of atrial fibrillation, heart failure and stroke in dual-chamber pacing compared to single-chamber pacing. In the index study by Haque *et al*, right ventricular pacing, particularly in ventricular paced, ventricular sensed, inhibited response and rate responsive pacemaker adversely impacted the left ventricular functions over 9-months compared to dual pacing, dual sensing, dual responsive and rate responsive pacemaker. Although there are key limitations of this study, these findings does support a growing body of evidence reinstating the superiority of dual chamber pacing compared to single chamber pacing.

Key Words: Permanent pacemaker insertion; Pacing induced cardiomyopathy; Dual-chamber pacemaker, Left ventricular ejection fraction; Atrial fibrillation; Heart failure; Global longitudinal strain; Stroke; Cardiovascular outcomes; Conduction system pacing

Core Tip: The detrimental effects of long-term apical right ventricular pacing (RVP) on left ventricular (LV) functions have necessitated the search for strategies to mitigate pacing-induced cardiomyopathy. Amongst them, allowing for a more physiological pacing and reducing the RVP burden by appropriate programming are the most clinically relevant interventions. The index study by the authors supports a net beneficial effect of dual responsive and rate responsive (DDDR) compared to ventricular paced, ventricular sensed, inhibited response and rate responsive (VVIR) mode in terms of better LV function and performance in the short-term by maintaining the atrio-ventricular synchrony. Further, as in prior studies, new-onset AF was more frequent with VVIR compared to DDDR.

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INTRODUCTION

Consistent pool of evidence supports the detrimental effect of long-term right ventricular pacing (RVP) on left ventricular (LV) systolic and diastolic functions. In particular, it is the apical pacing of the right ventricle that results in abnormal electrical and mechanical activation contributing to the worsening LV performance over the years[1,2]. Many have further explored the pathophysiology behind the same and highlighted the role of abnormal regional perfusion, adverse cardiac remodeling and mechanical dyssynchrony. This worsening LV mechanics eventually results in progressive heart failure which is associated with significant cardiovascular morbidity and mortality. Naturally, there has been an increasing focus on the strategies to mitigate the adverse impact of RVP in the short and the long-run[3-5].

PACING-INDUCED CARDIOMYOPATHY: RISK FACTORS AND PREDICTORS

The term pacing-induced cardiomyopathy (PiCM) is increasingly used to describe the development of new-onset LV dysfunction, that is a > 10% decline in LV ejection fraction (LVEF) irrespective of baseline after permanent pacemaker insertion (PPI), after excluding all other causes[6,7]. It is solely attributable to the left bundle branch block (LBBB) type activation patterns after PPI and the resultant asynchronous and delayed electrical activation which contributes to the abnormal myocardial contraction, depressed myocardial work, reduced systolic and diastolic functions and a shift in the LV pressure-volume curve to lower pressure and higher volumes[3].

While these manifestations are more pronounced and occur earlier in those with pre-existent LV systolic dysfunction, many patients with a preserved LV functions also have deterioration in both systolic and diastolic functions after PPI. As much as 6%-26% of patients with preserved LV functions prior to PPI, develop PiCM over a time period ranging from 3 months to well beyond 10 years[8-10]. Indeed, this worsening of LV functions is directly proportional to the pacing burden with highest likelihood of developing PiCM in those with RV pacing > 20%-40%. Other predictors of PiCM include a wider baseline or post PPI QRS, preexistent LV dysfunction or LBBB, advanced age, prior coronary artery disease and advanced infra hisian block[11-14]. However, our current understanding of these risk factors is largely based on a few heterogenous studies with variable patient populations and diverse individual and physician related factors. This makes a more comprehensive and robust assessment of these risk factors and the mitigation strategies a key unmet need.

Further, RVP has been also linked to the development of new-onset atrial fibrillation (AF). The development of AF is largely multifactorial amongst which the key players are the diastolic dysfunction, mechanical dyssynchrony with resultant mitral regurgitation and reduced systolic function both of which leads to atrial stretch and atrial electrical instability, in addition the progressive tricuspid regurgitation due to pacemaker leads also leads to atrial enlargement and eventually fibroses; all of which contribute to the development of AF[15]. The advent of AF is strongly related to worse cardiovascular outcomes with significant complications in the form of stroke, heart failure, myocardial infarction and death[16-19].

IMPACT OF PACEMAKER TYPE AND MODE ON PICM

Amongst the earlier studies, the randomized study by Andersen *et al*[20] was the first one which indicated excess cardiovascular mortality, greater decline in LVEF and New York Heart Association class, increased risk of developing AF and stroke in the ventricular paced, ventricular sensed, inhibited response (VVI) pacemaker compared to atrial pacing, atrial sensing, inhibited response (AAI) pacemaker amongst patients with sinus node disease. Later on studies by Nielsen *et al*[21] and the famous UKPACE indicated similar clinical outcomes in terms of mortality, development of heart failure and AF amongst patients with atrio-ventricular (AV) block receiving either a VVI rate responsive (VVIR) pacemaker or a dual pacing, dual sensing, dual responsive and rate responsive (DDDR) pacemaker. However, rates of stroke was higher

in the group who received a single chamber VVIR pacemaker; especially the ones functioning at a fixed rate: VVI pacemaker[22]. Another key observation amongst those receiving DDDR was that the group assigned to a short AV delay compared to those with a longer AV delay. However, the results were not replicable in the large DANPACE study wherein there was no significant across any of the clinical outcomes amongst those assigned to DDDR or VVIR stressing on the need for more robust real-world data to conclusively determine the true impact of pacemaker type on clinical outcomes[23].

Nonetheless, it is very safe to conclude that reducing RV pacing burden is one of the most important targets to mitigate PiCM and improve short and long term outcomes. The same can be achieved by choosing AAI or the DDDR mode in preference to VVIR mode, programming a longer AV delay to facilitate the native AV conduction, carefully modifying the rate responsiveness in certain groups like those with a normal sinus node function to limit unusual and higher heart rates (RV pacing) at rest or during exertion[1,24]. Another important consideration is the site of RV pacing. Pacing sites other than the apex, including at the RV outflow and septum allow for achievement of better electrical activation as reflected by a narrower QRS duration compared to apical pacing[25]. Although the PROTECT-PACE study did not demonstrate a significant difference in terms of mortality, LVEF and AF at 2 years amongst those receiving non-apical *vs* apical RV pacing, there are others which do point towards a net benefit from the non-apical compared to apical pacing [26]. Amongst these, the meta-analysis by Hussain *et al*[27] and another one by Shimony *et al*[28] indicate that those with a lower baseline LVEF and a greater baseline QRS duration are likely to benefit from non-apical pacing especially when followed over for longer durations beyond 1 year. In addition, a recent report by Samuel *et al*[29] also indicate that RV apical pacing is independently associated with development of AF post PPI which confers worse long term outcomes compared to non-apical pacing.

To this extent, biventricular pacing (BiVP) was developed as a rescue solution for those with worsening LVEF and heart failure after prior PPI. On many occasions, it could resynchronize the electrical and mechanical contraction and ultimate improve the LVEF and clinical outcomes[30]. However, there is a huge non-response rate after BiVP in this group with about 1/3rd having no change in LVEF post BiVP[6]. The most recent tool in our armamentarium is the eft bundle branch-area pacing which offers a potential solution for de-novo PiCM and those with prior response to BiVP as a means of cardiac resynchronization therapy[31-34].

IMPLICATIONS AND CLINICAL RELEVANCE OF THE INDEX STUDY BY HAQUE ET AL

The development of PiCM is in fact a continuum starting from a subtle and gradual decline in LVEF which over time adds up and qualifies as PiCM when the EF drops below the defined cut-offs. As such any decline of LVEF is clinically relevant especially early in the course after PPI. In the index study by Haque *et al*[35] the authors prospectively looked into the impact of pacing mode (DDDR *vs* VVIR) on LV functions and clinical outcomes over a period of 9 months in patients undergoing dual-chamber PPI at their tertiary-care center. They used a cross-over study design with the pacing mode being set to DDDR during the first three months followed by VVIR for the next 3 months and again DDDR for the remainder of the three months towards the end of the study.

In their cohort of 56 patients, the authors demonstrated significant impairment of both systolic and diastolic functions after PPI. The worsening diastolic functions were represented by the increase in isovolumic relaxation time (IVRT) from 85.27 ± 9.54 ms to 93.07 ± 10.38 ms at the end of study period (9 months). This increase in IVRT was most pronounced in the 3 to 6 months window when the pacemaker was kept in the VVIR mode. In regards to systolic functions, the gradual impairment was reflected in the form of decline in LVEF and increase in mean LV end-diastolic diameter. The worsening of LV systolic functions were seen with both DDDR and VVIR modes. In addition they also demonstrated reduction in stroke volume and global longitudinal strain (GLS) over the 9 months in both the arms. In addition, occurrence of new-onset AF was more common in the VVIR group compared to DDDR group. However, despite the various adverse effects of either pacing mode on myocardial functions, the overall quality of life improved throughout in either of the arms.

The study findings are crucial and in line with a growing body of evidence surrounding the superiority of dual-chamber over single chamber pacemakers. Generally, a dual-chamber pacemaker is believed to enable more physiological pacing largely attributable to the maintenance of AV synchrony[1]. Theoretically this translates into a maintained preload and stroke volume. However, the evidence from real world setting remains conflicting with no clear benefit in terms of mortality and quality of life with dual chamber pacemaker compared to single chamber. The only net benefit obtained from meta-analysis is in terms of a lower AF rate and lesser pacemaker syndrome in certain subsets receiving DDDR compared to VVIR[36].

The differences in outcomes between the 2 pacemakers is even less conspicuous in the elderly patients beyond 70 years [22]. Nonetheless, there is evidence from multiple other studies which do support the superiority of DDDR compared to VVIR in terms of perseverance of LV function and reduced heart failure related morbidity and mortality. In the dedicated prospective study by Dawood *et al*[37], DDDR was shown to be associated with a better cardiac output, a higher GLS and LVEF with 3D echocardiography and strain imaging compared to VVIR. There results were conquered by an independent recent analysis by Laksono *et al*[38], wherein DDDR was able to better maintain LV functions in patients with AV block compared to VVIR mode. Adoubi *et al*[39] also highlighted a higher heart failure related mortality in their Sub-Saharan African cohort with VVIR compared to DDDR. In another large registry by Ebert *et al*[40], though decline in LVEF was infrequent in those with normal bassline LV function, it was more prevalent in the cohort receiving VVIR compared to DDDR. More recent evidence in support of a favorable impact of DDDR compared to VVIR comes from the large meta-analysis by Shah Syed *et al*[41] comprising of 8953 patients. Although the rate of LV dysfunction on follow-up was similar in the two groups, DDDR was associated with a significantly lower incidence of AF compared to those in

VVIR mode. In the recent prospective study by Blessberger *et al*[42], DDDR was associated with improved hemodynamics and stroke volume compared to VVIR mode.

The above arguments and the findings from the index study by Haque *et al*[35], do support a net beneficial effect of DDDR compared VVIR mode in terms of better LV function and performance. However, it is crucial to understand and acknowledge the key limitations and the pitfalls of the index study before accepting the results on the face value. Firstly, the study was conducted in a tertiary care center with a small number of patients and may the cohort may not be representative of the general population. Secondly, the decline is LVEF is more prominent and discernible after 3-5 years of PPI and hence a follow-up period of 9 months may not be ideal to draw such conclusions. Thirdly, the results may not apply to those with sinus node dysfunction as none of the patient in the cohort had it. The lack of assessment of ventricular pacing burden, a key player of PiCM, is yet another major limitation. The authors have implanted all ventricular leads at the RV apex which is not ideal and not the standard practice at most center for obvious reasons as highlighted above. The authors could have further used pharmacological or exercise based echocardiography assessment to more conclusively support their findings. Hence, given the key limitations, the results of the index study should be taken with due caution and dedicated future studies are needed to validate the findings of the index study.

CONCLUSION

The detrimental effects of long-term apical RVP on LV functions have necessitated search for strategies to mitigate PiCM. Amongst them, allowing for a more physiological pacing and reduction in RV pacing burden by appropriate programming are the most relevant clinically. The index study by the authors supports a net beneficial effect of DDDR compared to VVIR mode in terms of better LV function and performance in the short-term. Further, as in prior studies, new-onset AF was more common in the VVIR group.

FOOTNOTES

Author contributions: Mohan B and Batta A designed the editorial, supervised the study and provided key feedback and suggestions; Batta A performed the literature review and data collection, analyzed the data and wrote the manuscript and subsequently revised it. All authors have read and approved the final manuscript.

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