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EDITORIAL COMMENT

Cardiomyopathy associated with long-term right ventricular pacing: an intriguing clinical issue

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This article refers to 'Clinical features, predictors and long-term prognosis of pacing induced cardiomyopathy' by S.W. Cho *et al.*, published in this issue on pages 643–651.

The history of permanent cardiac pacing began in 1958 with the pioneering experiences of Senning and Elmqvist who performed the first implant on a 43-year-old patient, Arne Larsson, on 8 October 1958.[1] Since then, millions of patients have been implanted with a pacemaker, which is considered a life-saving treatment with an extremely favourable risk–benefit and cost–benefit profile.[2]

The conventional technique for implanting a cardiac pacemaker includes the placement of the ventricular lead at the right ventricular (RV) apex, even though this results in a non-physiological ventricular activation which may cause left ventricular (LV) dyssynchrony, more frequently in the presence of a depressed LV ejection fraction (LVEF) at baseline and enlarged LV volumes.[3] The percentage of patients in whom RV apical pacing results in an LV systolic dyssynchrony detectable with echocardiographic methods has been reported to be around 50%,[4] but it is noteworthy that also diastolic mechanical dyssynchrony is becoming a subject of investigation and research in the complex field of heart failure pathophysiology.[5,6]

The concept of 'pacing-induced' cardiomyopathy (CMP) has recently been applied to describe the condition characterized by LV dilatation and hypokinesia, often with symptoms of heart failure, associated with a high burden of RV pacing. However, pacing-induced CMP has not been specifically included in classification schemes of cardiomyopathies, nor has its definition been fully established.[7] Nevertheless, this condition has been reported in the literature with variable definitions and with variable frequencies of occurrence, according to the type of study, methods of assessment and length of follow-up. In a general view of the literature, a pattern of CMP has been reported to occur in patients treated with permanent cardiac pacing between 9% at 1 year[8] and around 20% at 3–5 years[9,10] of observation. However, the appearance of this form of CMP does not seem to markedly increase with a longer follow-up, since a study on patients treated with RV pacing for > 15 years, with no previous evidence of LV dysfunction, reported a prevalence of 15.4% after more than 30 years of pacing.[11] Since this type of CMP occurs only in a minority of the patients, the critical question is to identify what factors predispose or facilitate its occurrence and modulate its development.

In the present issue of the Journal, Cho *et al.*[12] report on clinical features and predictors of the occurrence of pacing-induced CMP, on the basis of the analysis of around 1400 patients implanted with a pacemaker in a single centre in South Korea. In the study by Cho *et al.*, pacing-induced CMP was defined as new-onset LV systolic dysfunction with LVEF < 50%, with either a > 10% decrease in LVEF as compared to previous evaluations or new-onset regional wall motion abnormality unrelated to known disease. The occurrence of this form of CMP was observed during follow-up in 14.1% of patients after a median of 3.5 years following pacemaker implant, with a mean decrease in LVEF from 60% to 40%.[12] Around 47% of patients with pacing-induced CMP had admissions for heart failure, and cardiac death was significantly increased in comparison with patients without this form of CMP. In the series by Cho *et al.*, which specifically excluded patients with depressed LVEF before pacemaker implant, the independent predictors of pacing-induced CMP were a left bundle branch block at baseline, wide paced QRS interval (> 155 ms) and a higher percentage of ventricular pacing (≥ 86%), with a 16-fold increase in the risk of CMP when all three factors were present.[12]

According to the literature, patients with pre-existing LV dysfunction, even if moderate (LVEF 41–55%), may present a higher rate of LVEF worsening with appearance of a pattern of CMP.[13] However, individual factors appear to play a major role in modulating the changes in LV function observed at long term in patients implanted with a pacemaker, with either the possibility

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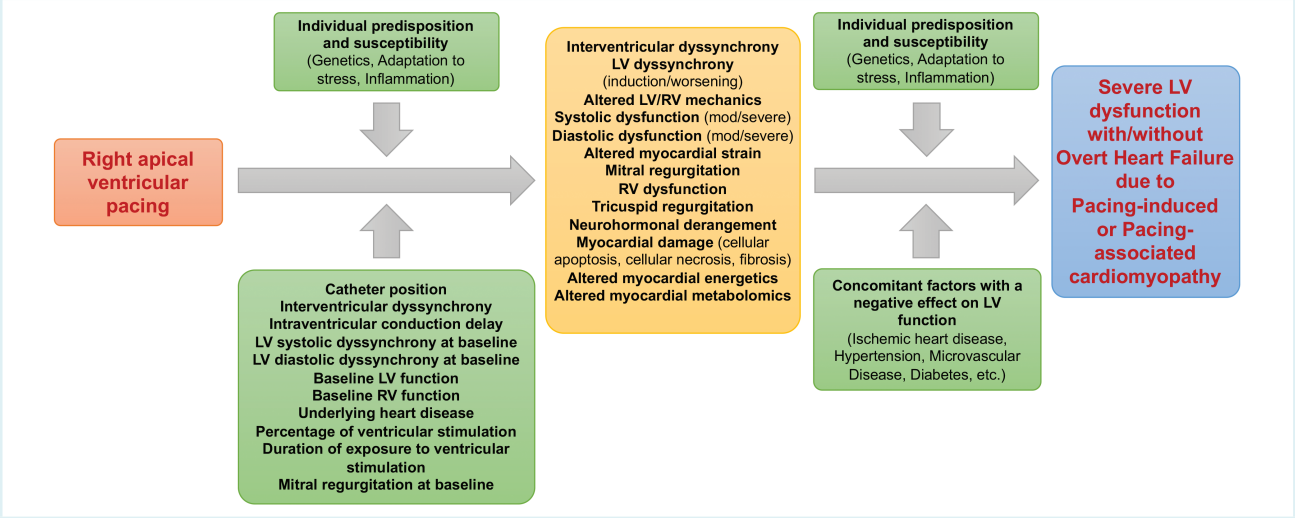

Figure 1 Factors involved in the complex pathophysiology of pacing-induced or pacing-associated cardiomyopathy, with variable influence in conditioning, modulating or causing the onset of left ventricular (LV) dysfunction with or without overt heart failure. mod., moderate; RV, right ventricular.

of worsening or, less frequently, of improvement of a mildly depressed LV function.[13] Indeed, it is noteworthy that follow-up studies clearly show that individual patients did not develop LV dysfunction despite being pacemaker-dependent with 100% RV pacing for years.[11] The important role of individual factors possibly conditioning a pre-disposition to the potentially deleterious effect of RV pacing is historically stressed by the case of Arne Larsson, the recipient of the first permanent cardiac pacemaker who survived for 43 years with ventricular pacing systems (22 pulse generators were implanted over the years) and died at the age of 86 without any major episode of heart failure.[1]

The observation that the occurrence of heart failure and CMP in patients treated with permanent RV pacing for congenital atrio-ventricular block and with a structurally normal heart is predicted by antinuclear antibodies, highlights how factors independent of the pattern of ventricular electrical activation may play a major role in the development of LV dysfunction after cardiac pacing.[14] In this complex interaction of factors, genetics can also certainly play a major role, by determining an inherited predisposition that will lead to a pattern of CMP and to overt heart failure when exposure to risk factors for heart failure occurs.[15] The incomplete knowledge of genotype–phenotype interactions that characterizes our current approach to heart failure[15] also involves our attempts to explain the individual factors involved in the appearance of a pattern of CMP after exposure to RV pacing for variable periods of time. In this perspective, taking into account the complexity of the pathophysiology and of the cause–effect relationship, it might be more cautious and appropriate to approach this problem by considering this entity as a 'pacing-associated' CMP rather than as a 'pacing-induced' CMP.

As shown in *Figure 1*, the electrical dyssynchrony that RV pacing can induce at ventricular level is an important factor involved in the pathophysiology of this form of CMP, but it does not fully explain *per se* the occurrence of LV dysfunction and heart failure, since many factors can be involved in influencing and modulating the onset and progression over time of this syndrome. Further, individual susceptibility and predisposition have an important influence, due to variable factors whose impact is still not well defined.

Different strategies for reducing and even avoiding the negative effects of RV apical pacing have been proposed, ranging from algorithms to minimize unnecessary ventricular pacing, to alternative pacing sites, LV pacing, biventricular pacing, and more recently His-bundle pacing.[16,17] Although the benefits of cardiac resynchronization therapy are well established in specific settings,[18–20] the search for physiological pacing is currently characterized by a growing interest in His-bundle pacing.[9] In a new perspective that takes into account the dynamic characteristics of a pattern of dilated CMP,[15] with LV remodelling as a target for treatments, with important prognostic implications, it becomes important to improve our knowledge on the determinants of partial or complete regression of a CMP associated with long-standing RV apical pacing in the case of upgrade to a more physiological pacing modality.

Although strategies targeted to obtain more physiological pacing modalities may play an important role for care improvement in daily practice, with specific selection criteria that are still subject of investigation, it is still necessary to better understand what are the factors predisposing to the onset and worsening of LV function in association with RV pacing, what are the links with the complex pathophysiology of heart failure and what specific factors can be actual aims of preventive or corrective interventions, with a favourable risk–benefit profile, at specific phases of the 'unnatural' history of patients treated with cardiac pacing.

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