Upgrade to biventricular pacing in patients with pacing-induced heart failure: can resynchronization do the trick?

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Dyssynchrony imposed on ventricular function by right ventricular (RV) apical pacing may lead in some cases to worsening or appearance of heart failure (HF) symptoms. This is a result of an altered pattern of activation, leading to several histological and functional adjustments of the left ventricle, including inhomogeneous thickening of the ventricular myocardium and myofibrillar disarray, fibrosis, disturbances in ion-handling protein expression, myocardial perfusion defects, alterations in sympathetic tone and mitral regurgitation. Studies of mid- and long-term effects of RV apical pacing on left ventricular (LV) function have demonstrated a progressive decline in ejection fraction and other indices of LV functional competence. Upgrading RV pacing systems to biventricular resynchronization modalities is a theoretically promising option for paced patients with worsening HF. The potentially favourable effect of upgrading on LV functional indices and patient clinical status has been demonstrated in few, non-randomized trials. Apart from the scantiness of existing clinical data, issues concerning technical aspects of the procedure and selection of eligible patients are raised. Is pacing-induced dyssynchrony equivalent to the indigenous dyssynchrony in unpaced patients with HF? What selection criteria should be applied in order to identify potential responders to cardiac resynchronization therapy in this patient population? Answers to these and more questions are still lacking.

KEYWORDS
Dyssynchrony; Biventricular pacing; Heart failure; Upgrade; Pacemakers

Pacing is a therapeutic intervention which, in most of its forms, imposes to some extent a hypo-physiological mode of function on the heart. This may lead, in some cases, to deterioration or appearance of heart failure (HF) symptoms, especially in patients chronically paced in the right ventricular (RV) apex. The mechanisms underlying the deleterious effect of pacing on ventricular function are complex.

Pathophysiology of pacing-induced HF

Pacing-induced asynchrony

RV pacing results in interventricular asynchrony, leading to a 30–180 ms delay in left ventricular (LV) activation, as well as intraventricular asynchrony resulting from the complete reversion of ventricular activation sequence (apex to base instead of base to apex). RV apical pacing leads to a heterogeneous distribution of workload (lower strain, i.e. workload, in the early-activated region than in the late-activated regions), which in turn results in regional heterogeneity of myocardial tissue mass. More specifically, it has been shown that early-activated regions tend to become thinner over time, as opposed to late-activated ones, which show a progressive increase in wall-thickness, with myocyte enlargement being the primary histological contributor to wall thickening. The regional heterogeneity of myocardial hypertrophy results in remodelling of the LV, which alters its contractile and haemodynamic conduct, reducing LV overall functional efficiency. The primary causative factor of this remodelling seems to be the alteration of force vectors, which entails an alteration of mechanical stress distribution in the ventricle; however, a role of a neuro-endocrine mechanism cannot be excluded.

Haemodynamic effects

Haemodynamic parameters have been shown to deteriorate substantially when the physiological activation pattern is not respected. More specifically, right atrial pressure, pulmonary arterial pressure, and pulmonary capillary wedge.
pressure have been shown to be significantly different in AAI, DDD and VVI pacing modes, being lowest in the first case, where both atrioventricular and ventricular activation sequences are preserved, and highest in the third case, where dyssynchrony is complete. \textsuperscript{11} LV ejection fraction (EF) and peak filling velocity of the LV have been demonstrated to be lower with pacing modes that cause a higher degree of dyssynchrony (i.e. VVI vs. AAI). \textsuperscript{11} Studies comparing paced individuals with controls over long periods of time have shown a significant progressive deterioration of ventricular function, expressed as decreased LVEF\textsuperscript{12–15} and cardiac output\textsuperscript{1} as well as decreased LV fractional area change and myocardial performance index, \textsuperscript{16} with paced QRS duration being the major independent predictor of LV function deterioration. \textsuperscript{19} It has been demonstrated in humans that even as little as 2 h of RV pacing causes a significant and persistent LVEF reduction. \textsuperscript{18} Prolongation of pacing for 1 week further reduces LVEF and it is not restored before 32 h after cessation of pacing have elapsed. \textsuperscript{19} Another contributing factor to the unfavourable effect of RV pacing on LV haemodynamics is the diminution of LV relaxation and filling times, i.e. a diastolic dysfunction which further impairs LV haemodynamic efficiency. \textsuperscript{19–21}

**Effects on the tissue and cellular level**

The effect of RV pacing on LV function may be primarily due to the dyssynchrony induced by pacing on LV activation and systole, but it appears that additional mechanisms, which tend to make pacing-induced changes more lasting and not immediately reversible following the cessation of RV pacing, are at work. Pacing-induced alterations in the transient outward current (I\textsubscript{to})\textsuperscript{22} and the L-type calcium channel\textsuperscript{23} have been implicated in the process of LVEF depression during RV pacing. Additionally, it has been shown that LV dyssynchrony induces a marked dysregulation of protein expression, leading to regional heterogeneity in ion channel-handling and gap-junction proteins, which most probably contributes to LV function impairment. \textsuperscript{24}

On the tissue level, chronic RV apical pacing has been shown to cause significant histological alterations, mainly consisting of myofibrillar disarray, fibrosis, fat deposition, sclerosis, and mitochondrial morphological changes. \textsuperscript{25} In an interesting study, Hamdan et al.\textsuperscript{26} measured sympathetic nerve activity during acute RV, LV, and biventricular (BiV) pacing and were able to demonstrate significantly higher sympathetic nerve activity during RV when compared with LV and BiV pacing in patients with low EF. As increased sympathetic activity has been shown to be an important contributor to HF progression and a prognostic factor of cardiac mortality, \textsuperscript{27} if these findings are also true for long-term pacing, they are indicative of yet another association between RV pacing and LV functional deterioration. Alterations in the adrenergic innervation of the ventricular myocardium have been reported in patients with permanent DDD pacing, studied with \textsuperscript{123}I-MIBG scintigraphy, mainly in the inferior and apical wall segments. \textsuperscript{28}

**Effects on myocardial perfusion**

RV apical pacing has been shown to affect myocardial perfusion, both in animal models\textsuperscript{29} and humans. \textsuperscript{30} Several investigators\textsuperscript{31–34} have demonstrated a high incidence of perfusion defects with radionuclide scintigraphy in patients with long-term permanent RV pacing. These perfusion defects were most frequently located in an inferior or apical segment and were associated with significantly lower LVEF. \textsuperscript{31} Skalidis et al.\textsuperscript{33} further proceeded to assess coronary blood flow in the defect-related arteries, demonstrating that these perfusion defects are secondary to regional microvascular flow impairment. Nielsen et al.\textsuperscript{15} used positron emission tomography to assess myocardial blood flow in patients paced either in the AAI mode (which preserves physiological ventricular activation) or in the DDD mode (which preserves only atrioventricular synchrony) and reported a significant reduction in global as well as in regional myocardial blood flow in the inferior and septal regions (the early-activated regions) after 22 ± 7 months of DDD pacing. It is worth noting that switch from DDD to AAI mode resulted in restoration of regional and global myocardial blood flow, indicating that the effects of long-term ventricular pacing on myocardial blood flow are reversible. It is obvious that AAI pacing is associated with better myocardial perfusion and haemodynamic characteristics than DDD pacing. \textsuperscript{25} Modern pacing algorithms in dual-chamber pacemakers attempt to increase the time in AAI pacing vs. the DDD pacing mode. This pacemaker function in combination with the better accommodation of the lower pacing rate to the activity status of the paced patient may decrease the time the patients receive RV apical pacing.

**Mitral regurgitation**

Mitral regurgitation (MR) of variable severity is another common result of RV pacing,\textsuperscript{36–38} which has a direct impact on patient functional status. RV pacing causes MR through a complex mechanism. It appears that the altered sequence of activation of the components of the mitral apparatus and the dyssynchronized conveyance of force from the papillary muscles through the chordae tendinae to the mitral leaflets lead to poor coaptation and thus to regurgitation during ventricular systole. The appearance or aggravation of pre-existing MR may contribute to the development or deterioration of HF in paced patients.

**Reversing the deleterious effects of RV apical pacing**

**Alternative RV pacing sites**

The differential effects of alternative RV pacing sites on QRS duration and ventricular systolic function have been studied in the past: Takagi et al.\textsuperscript{39} showed in a normal heart canine model that haemodynamics and interventricular conduction are less disturbed by proximal RV septal pacing than apical pacing. In contrast, Peschar et al.\textsuperscript{40} have demonstrated, also using a normal heart canine model, that although septal or apical LV pacing did not affect LV systolic function, RV septal pacing was not superior to RV apical pacing. In the human heart, despite reports of preservation of LV systolic function with RV septal pacing as opposed to RV apical pacing, in patients without HF,\textsuperscript{41} this was not re-iterated by studies in the failing heart.\textsuperscript{42} Interestingly, it has been demonstrated that finding the site of the RV septal surface causing the shortest QRS when paced and implanting the pacing lead there, may result in improved LV systolic performance.\textsuperscript{43,44} However, it was postulated that the latter finding is unlikely to have a significant clinical impact, as
the effects on LVEF were relatively minor and the procedure is impractical for everyday clinical practice. The RV outflow tract was also proposed as an alternative site of RV pacing, associated with increased cardiac output when compared with RV apical pacing in acute pacing studies; however, this was not confirmed with long-term pacing. These data suggest that RV pacing at alternative sites has not demonstrated any unequivocally proven clinical benefit in terms of optimization of LV systolic function and, therefore, it is doubtful that it would be of use to consider alternative RV pacing sites for patients with pacemaker-related HF.

Biventricular pacing

LV or BiV pacing, or cardiac resynchronization therapy, has been proposed as an adjunctive treatment for patients with advanced HF complicated by discordant contraction due to intraventricular conduction delay. Both short-term and a growing number of long-term clinical trials have reported on the mechanisms and short- and mid-term efficacy of this approach, with encouraging results. A QRS duration >200 ms has been arbitrarily required to upgrade RV pacing in HF patients to BiV pacing because such a wide QRS has been suggested to correspond with notable inter- or intra-LV mechanical dyssynchrony. It should be noted, however, that improved mechanical synchrony and function do not necessarily require increased electrical synchrony, and more recent data dispute the correlation between electrical features (QRS duration) and the degree of electromechanical ventricular dyssynchrony in RV paced patients. It has also been shown that regardless of the presence of HF, the last activated LV wall is not always the free wall and the first one activated is not always the septal wall, as has already been shown in patients with spontaneous atrioventricular conduction. Pacing at mid-lateral LV sites has been demonstrated to achieve the greatest increase in systolic function when compared with any other region that could be accessed via the coronary sinus. Furthermore, more patients have RV pacing-induced intraventricular than interventricular dyssynchrony, suggesting that in these patients, the major cause of LV function impairment is likely to be the presence of intra-LV dyssynchrony. Echocardiographically documented and quantified dyssynchrony is a new approach to the issue of patient selection and also gives new insight into the possible mechanisms of improvement (Figure 1). As BiV pacing results in the improvement of intra-LV rather than interventricular synchrony, RV-paced patients who present with an abnormally increased intra-LV dyssynchrony should benefit from BiV upgrading.

Upgrading of previously implanted RV pacing systems has been attempted in the past by the use of different techniques, either using a variety of configurations of leads and connectors or by implanting additional pulse generators. Current generator systems have three dedicated ports and truly independent output to both ventricles. Although most studies involved systems tying both ventricular leads to a common internal current source with the risk of an impedance mismatch that could result in only RV or only LV pacing, rather than both, new devices have two independent channels and further add programmability of the RV-LV stimulation delay.

Unresolved issues and future perspectives

Given that dyssynchrony is the problem, or at least a prominent part of it, with pacing-induced or pacing-aggravated HF, resynchronization is a theoretically sound aim to pursue. The clinical settings and pre-conditions for conventional RV pacing to be upgraded to BiV resynchronization have not been clearly outlined because of the lack of clinical data, leading clinicians to treat paced patients with HF as equivalent to patients with indigenous conduction delay, using the same selection criteria for the prediction of responders in this patient population as in the general population of HF patients. There is a growing need to integrate new strategies of assessing the potential of an RV-paced patient with HF to respond to resynchronization treatment, such as the developing echocardiographic methods, namely tissue Doppler imaging, strain and strain-rate analysis and tissue tracking. The few non-randomized, uncontrolled studies that have been reported have demonstrated that the ‘upgrading’ approach to the treatment of already paced HF patients is at least feasible and relatively safe. Future studies should define where LV leads should be placed when upgrading a previously implanted device and which are the potential complications that may arise from the upgrading approach beyond venous occlusive phenomena or the difficulties posed by the anatomic
Figure 1  Off-line myocardial velocity curves obtained by tissue Doppler imaging at the basal septal (yellow) and basal lateral (green) segments. (A) Taking as referral point the onset of the QRS, there is a 50 ms delay in the onset and 130 ms in the peak of the sustained systolic velocity in the lateral when compared with the septal wall in this patient with RV pacing electrode. The 2D image reveals the extension of the phenomenon by the abnormal distribution of the blue colour on the lateral wall during systole. (B) No significant dyssynchrony observed in this patient on myocardial systolic velocity curves obtained by tissue Doppler imaging at the basal septal (yellow) and basal lateral (green) segments. The 2D image confirms the homogenous contraction of the LV lateral wall and septum.
variability of the coronary sinus anatomy. Furthermore, more data are required concerning the application of resynchronization therapy in those previously paced HF patients in whom an ICD is also indicated. Conclusively, better powered and controlled trials with adequate follow-up time are clearly warranted in order to determine the mid- and long-term efficacy of upgrading from RV to BIV pacing, as well as its cost-effectiveness, which is a particularly relevant issue in the era of device therapy.

References
Upgrading to BiV pacing in HF patients


