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Review

Chronic right ventricular apical pacing: Adverse effects and current therapeutic strategies to minimize them

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ABSTRACT

The permanent cardiac pacemaker is the only effective therapy for patients with symptomatic bradycardia and hundreds of millions are implanted worldwide every year. Despite its undisputed clinical benefits, the last two decades have drawn much attention to the negative effects associated with long-term pacing of the right ventricle (RV). Experimental and clinical studies have shown that RV pacing produces ventricular dyssynchrony, similar to that of left bundle branch block, with consequent detrimental effects on cardiac structure and function, with adverse clinical outcomes such as atrial fibrillation, heart failure and death. Although clinical evidence largely comes from subanalyses of pacemaker and implantable cardiac defibrillator studies, there is strong evidence that patients with reduced left ventricular function are at high risk of suffering from the detrimental effects of long-term RV pacing. Biventricular pacing in cardiac resynchronization therapy devices can prevent ventricular dyssynchrony and has emerged as an attractive option in this patient group with promising results and more clinical studies underway. Moreover, there is evidence that specific pacemaker algorithms that minimize RV pacing can reduce the negative effects of RV stimulation on cardiac function and may also prevent clinical deterioration. The extent of the long-term clinical effects of RV pacing in patients with normal ventricular function and how to prevent this are less clear and subject to future investigation.

1. Introduction

Permanent cardiac pacing since first implantation in man on October 8, 1958 [1] has dramatically changed the lives of millions of patients with symptomatic bradycardia, from a disease associated with high morbidity and mortality to a prognosis approximating that of the general population. In medical practice however, any given therapy rarely presents freedom from adverse effects, this also being true for the cardiac pacemaker. As early as 1925, Wiggers [2] demonstrated in mammals that ventricular pacing resulted in impaired left ventricular (LV) function. Nevertheless, the clinical relevance of the detrimental effects of long-term right ventricular apical (RVA) pacing in humans only gained recognition during the last two decades through the publication of large pacemaker and implantable cardiac defibrillator (ICD) trials, suggesting an association between long-term RVA pacing and deterioration of cardiac structure and function, in addition to the increased risk of atrial fibrillation (AF), heart failure (HF) and death [3–5]. As a result, various approaches to reduce the adverse effects of RVA pacing have surfaced: specific pacemaker programming options and algorithms that minimize RVA pacing, cardiac resynchronization therapy (CRT), and alternative right ventricular (RV) pacing sites. This article aims to review the current available literature concerning the negative effects of RVA pacing and the potential therapeutic strategies available. Towards the end of the review, the reader will find a suggested outline to practically approaching a patient with an indication for conventional pacing, and no other indication for CRT, who is expected to receive a significant amount of RVA pacing; a rather frequent clinical scenario nowadays.

2. The effects of RVA pacing: pathophysiology

Animal and human studies indicate that RVA pacing induces abnormal electrical and mechanical activation patterns (dyssynchrony), which lead to worsened hemodynamic parameters and myocardial remodeling [3,6–9]. In the normal heart, electrical propagation velocity occurs rapidly throughout the specialized conduction system at 3–4 m/s, allowing almost simultaneous myocardial contraction and relaxation. However, during RVA pacing electrical activation propagates slowly through the myocardium at about 1/4 the normal velocity, mainly from myocyte to myocyte [10]. This results in heterogeneous electrical ventricular activation, characterized by a single breakthrough at the

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interventricular septum (IVS) and latest activation of the inferoposterior base of the LV, with similarities to the abnormal activation pattern observed in left bundle branch block (LBBB) [9], although recent studies have reported certain differences between the two scenarios [11]. Animal studies have demonstrated that electrical dyssynchrony induces mechanical dyssynchrony, characterized by alterations in the onset and pattern of mechanical contraction [8]. The latter is exemplified by Prinzen et al. [7] who used high spatial resolution magnetic resonance imaging tagging to evaluate myofibril strain, stress and work during right atrial, RVA and LV basal pacing in dogs. With ventricular pacing, especially RVA pacing, myocardial strain and work were reduced with little myocardial fiber shortening near the pacing lead (IVS) and increased at sites furthest away from the pacing site (LV free wall). This resulted in redistribution in myocardial strain and work, and subsequent less effective ventricular contraction. In addition, since RVA pacing produces prolonged ventricular activation time, the systolic phase is extended with consequent reduction in the diastolic phase, leading to hampered ventricular filling and coronary perfusion. As a result, myocardial ischemia is produced which reduces both ventricular contraction and electrical conduction further [12]. In humans, the acute effects of RVA pacing in a group of patients without structural heart disease were studied by Delgado et al. [3]. In line with experimental findings by Prinzen et al. [7], pacing from the RVA acutely induced LV radial dyssynchrony, and reduced LV systolic longitudinal shortening and LV ejection fraction (LVEF), the latter secondary to a reduction in the LV end-diastolic (LVED) diameter and volume with LV end-systolic (LVES) diameter remaining unchanged. Acute mechanical dyssynchrony and adverse hemodynamic effects, characterized by decreased LVED volume and LVEF, were also reported by Liu et al. [13] in a group of 35 patients with sick sinus syndrome (SSS) receiving RV pacing, using real-time 3D echocardiography.

Long-term RVA pacing may also result in ventricular dyssynchrony and deterioration of LV function [14,15], as well as structural changes of the myocardium over time [16]. Thambo et al. [15] retrospectively compared echocardiographic LV parameters of 23 young adults, who underwent DDD pacemaker implantation due to complete congenital AV block (CCAVB), with 30 healthy control subjects. After 10 years of follow-up significant dyssynchrony as well as lowered cardiac output were reported in the pacemaker group. Furthermore, the same study group presented thinning of the early-activated segments and hypertrophy of the later-activated segments. Structural changes of the myocardium have also been confirmed histologically in a study of RV biopsies in patients paced for CCAVB who presented significant myofiber size variation, fibrosis, fat deposition, sclerosis and mitochondrial morphological changes [16].

Although there is substantial amount of evidence that supports the detrimental effects of RVA pacing, further clarification of its pathophysiological mechanisms is still needed. Although believed to be related to the presence of LV dysfunction at baseline [17], it still remains unclear why only half of the patients with long term RVA develop ventricular dyssynchrony [15,18]. Additionally, it is still not understood whether mechanical dyssynchrony in the acute phase is the basis for the progression to LV dysfunction and heart failure with long-term RVA pacing [19]. Mechanisms such as functional mitral regurgitation [20], perfusion abnormalities [6], and endothelial dysfunction [21], are believed to have a role in the pathophysiology of RVA pacing, although probably as a downstream consequence of ventricular dyssynchrony.

3. The effects of RVA pacing: clinical evidence

3.1. Absence of heart failure at baseline

The majority of information of the effects of RVA pacing in patients without baseline HF comes from subanalyses of large pacemaker randomized clinical trials (RCTs) of elderly patients suffering mainly from SSS, designed to evaluate the difference between atrial- (AAI or DDD mode) and ventricular-based (VVI mode) pacing strategies [22–28]. Although numbers are small, a significant proportion of the patients studied presented a New York Heart Association functional class (NYHA) III–IV. Moreover, echocardiographic evaluation of LV function, and percent RVA stimulation were not always reported, although the latter is believed to be high, as relatively short AV intervals were utilized. Despite the limitations, the results of these RCTs still represent the best approximation currently available of the clinical long-term effects of RV pacing in patients with normal cardiac function.

The Danish trial was a single-center study that randomized 225 patients with SSS to either single-chamber atrial pacing (AAI) or single-chamber ventricular pacing (VVI) [22]. In 1997, after a mean of 5.5 years of follow-up, the trial reported a significant increase in total and cardiovascular mortality, HF and AF in the ventricle-based pacing arm. Furthermore, they found that VVI pacing caused an increased left atrial (LA) diameter and a decreased LV fractional shortening. On the basis of these results, the initial principal interpretation was that conserving atrioventricular (AV) synchrony is beneficial, and as a consequence several RCTs were conducted to compare DDD vs. VVI pacing modes [23–26,28]. One of them was the Mode Selection Trial in Sinus-Node Dysfunction (MOST), a multi-center randomized study that recruited a total of 2010 patients with SSS who received either VVIR or DDDR pacing [24]. After a median of 33.1 months of follow-up there was a small, but significant, increased incidence of AF and hospitalization for HF in the DDDR pacing group, but no difference in all-cause mortality between the two treatment arms. A subanalysis [4] of 1339 patients, with normal baseline QRS duration, showed that the cumulative percentage of RVA pacing was significantly greater in the DDDR group compared to the VVIR group (90% vs. 58%, respectively) and that this was a strong predictor for AF (hazard ratio [HR], 1.36 [95% CI, 1.09–1.69] for each 25% increase in cumulative RV pacing) and HF hospitalization (HR 2.99 [95% CI 1.15–7.75] for >40% of cumulative RV pacing) (Fig. 1). Another study reported on the effects of the different proportions of RVA pacing in 177 patients with SSS randomized to three pacing modes: AAIR, DDDR with a short rate-adaptive AV delay (≤150 ms), and DDDR with a programmed fixed long AV delay (300 ms) [26]. The study results were in line with those previously reported by the Danish trial [22]: after a mean follow-up of 2.9 years the DDDR group with a short AV delay and a very high proportion of RV pacing (90%), presented increased risk of AF (23.3% vs. 7.4%, $p = 0.03$), increased LA diameter and decreased LV fractional shortening, when compared with the AAIR group. As expected, the long AV delay group received markedly less RVA pacing (17%) associated only with increased LA diameter and no increase in AF risk or a change in LV fractional shortening, when compared with the AAIR group. No difference in occurrence of HF or mortality was observed between the 3 study groups. Three more RCTs compared DDD with VVI pacing in SSS and AV block [23,25], and AV block alone [28]. Atrial-based pacing (DDD) failed again to demonstrate a reduction in mortality or stroke, with only minor benefits in quality of life and modest or no effects on HF progression and AF rate. A meta-analysis of the five discussed RCTs found that atrial-based pacing (AAI or DDD) does not improve HF status or cardiovascular death but significantly reduced AF incidence [29].

The failure to convincingly demonstrate superiority in terms of mortality and HF with DDD over VVI pacing likely represents the balance between the benefits of preserving AV synchrony and the detrimental effects of RV pacing. The positive results from the Danish trial [22] in favor of AAI pacing, where AV synchrony was preserved but RVA pacing avoided, further supports this observation. Nevertheless, the previously discussed study results are mainly indirect interpretations of studies not primarily designed to evaluate this, making the evaluation of the clinical impact of RVA pacing in patients without HF at baseline difficult. In contrast to the previous RCTs, the recent Danish Multicenter Randomized Trial on Single Lead Atrial Pacing versus Dual-Chamber Pacing in Sick Sinus Syndrome (DANPACE) [27] which included 1415 patients, 90% with normal LV function, found no difference in mortality, HF, or AF