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Heart failure and right ventricular pacing – how to avoid the need for cardiac resynchronization therapy

1. Introduction

Permanent artificial pacemaker implantation is a safe and effective treatment for bradycardia,[1] and is associated with extended longevity [2] and improved quality of life.[3] Approximately 350,000 people in the UK have a pacemaker, with over 40,000 new implants per year.

However, long term right ventricular (RV) pacing has been linked to adverse left ventricular (LV) remodeling,[4, 5] such that the most common long-term complication of standard pacemaker therapy is pacemaker-associated chronic heart failure (CHF) due to left ventricular systolic dysfunction (LVSD) [6, 7, 8]. Whilst up to 2-3% of the general population have CHF, the condition is much more common in pacemaker patients with a prevalence up to 50% [7, 9] and 12% of people admitted with acute decompensated heart failure (HF) (4% with a de novo admission for heart failure) have a pacemaker [10].

2. The deleterious effects of RV pacing:

Rapid RV apical pacing has been used as an animal model for dilated cardiomyopathy for decades [11] and whilst the abnormal contraction pattern and reduced contractility induced by acute RV pacing had been appreciated,[12, 13] it was thought to be of little clinical consequence. It was assumed that pacing-induced cardiomyopathy was the consequence of the rate rather than the site.

This changed as a result of observational, cross-sectional studies demonstrating a higher than expected prevalence of LVSD in people with RV pacemakers, especially those with high amounts of RV pacing [14, 15] and subsequently, the potential for RV pacing to adversely affect clinical outcomes was driven by two influential studies, originally designed to evidence the benefits of physiological DDD pacing compared to VVI stimulation in different settings. The Dual-Chamber and VVI Implantable Defibrillator (DAVID) trial aimed to assess the efficacy of preventing bradycardia on the incidence of bradycardic-induced ventricular tachyarrhythmia in 506 enrolled participants with heart failure due to severe LVSD. Subjects receiving a primary prevention defibrillator were allocated either to dual chamber pacing with a base rate of 70bts/min and rate response active (DDDR 70) or to simple back up ventricular pacing with a base rate of 40bts/min (VVI 40). In direct contrast to its aim, DAVID showed that more patients died or developed heart failure in the DDDR 70 group than in those allocated VVI 40 at 1 year (HR 1.61; 95% confidence interval 1.06-2.44) [14]. Subgroup analysis revealed that this was attributable to high levels of right ventricular (RV)pacing inherent in those programmed DDDR. All patients in DAVID had severe LVSD at baseline, so although the results demonstrated a clear adverse effect of RV pacing on HF, the study was unable to determine the effect of RV pacing on cardiac function as no serial assessment was performed.

The Mode Selection Trial (MOST) designed to assess the need for dual versus single chamber pacing, allocated 2010 people receiving pacemakers for sinus node disease to either VVIR or DDDR mode for a mean follow-up of 3 years [16]. The study was neutral for its primary endpoint of preventing atrial fibrillation through atrial pacing, but demonstrated at post-hoc analysis that patients with sinus node dysfunction exposed to high quantities of RV pacing were also at increased risk of HF hospitalization and atrial fibrillation in the presence of

unnecessary RV pacing [17]. Both studies focused on clinical endpoints and neither performed serial echocardiography.

More recent observational studies have clarified that the percentage of beats delivered through RV pacing is directly related to the degree of Left ventricular systolic dysfunction (LVSD), with the poorest LVEF seen in patients with a high percentage of RV pacing, [18] and that RV pacing burden has a linear relationship to risk of HF and cardiovascular death in large non-selected anti-bradycardia pacing cohorts [19]. This relationship has been shown to be exaggerated by the presence of existing cardiovascular disease (Figure 1) [20]. We have previously shown that patients requiring ≥40% of their ventricular rhythm from the pacemaker, who also had pre-existing cardiovascular disease had the highest prevalence of reduced LVEF, whereas those paced <40% with no cardiovascular morbidity had a very low rate of LVSD (Figure 1) [20]. This supports the clinical data from DAVID and MOST where there also seemed to be a threshold around 40% which was associated with an increase in adverse outcomes [14].

3. Right ventricular pacing and left ventricular dysfunction: causation or association

Whilst it is generally accepted that RV pacing is *associated* with LVSD and HF hospitalization, there remains considerable lack of clarity around causality. Patients with more severe heart disease, often have more severe conduction issue disease and therefore require more ventricular pacing. For example whilst complete heart block [8, 20, 21] or high RV pacing percentage [14, 15] are key predictors of adverse outcome in patients with pacemakers whilst cardiac dysfunction at baseline, age, coronary artery disease, diabetes [20], paced QRS [22] and atrial fibrillation [17] are also closely related.

Nielsen and colleagues have shown a drop in LVEF of approximately 5% subsequent to the introduction of RV pacing up to an average 2.9 years post implant [18]. However, there are very few observational studies describing outcomes or measures of cardiac function over time in unselected pacemaker patients large enough to allow correction for the relationship between each of these clinical features and also to describe the rate of progression of left ventricular remodeling in different clinical situations.

4. Mechanisms of the adverse remodeling effects of right ventricular pacing

Acute right ventricular apical pacing leads to both an altered pattern of electrical stimulation and myocardial contraction of the left and right ventricles compared to intrinsic activation, similar to the dyssynchrony seen with left bundle branch block, [23, 24]. The electrical wave produced from RV pacing does not propagate through the conduction system but the myocardium itself, therefore it is usually slower and heterogeneous in its activation of the myocardium [25].

In fact, QRS morphology, hemodynamic measures, and the electrical activation–peak contraction relationship vary greatly between pacing sites; RV septum, apex and LV septum [24], but even among individual patients [26, 27]. Inter-individual differences in QRS morphology have been attributed to localized changes in myocardial tissue, such as ischemia, effecting viability, contractility and relaxation properties [26, 27, 28]. Nevertheless a general widening of the QRS complex on ECG, lower overall stroke volume, worse mitral regurgitation are common features in RV paced patients [23].

The aetiology of pacing associated LV dysfunction is likely to be an interaction of multiple factors in a patient at higher risk due to genetics and past history. Longer term RV pacing has also been associated with abnormal myocardial perfusion [29, 30, 31] which has been hypothesized to subsequently lead to a redistribution of work and blood flow to late activated regions [32]. Also elevated catecholamine activity [4], myocardial structural [29, 33], histopathological[34], and genetic abnormalities [35] and neurohormonal alterations [36], have been shown, all of which are likely to contribute in a cyclical process to adverse remodeling, advocating persistent reductions in LV systolic and diastolic performance [37, 38].

5. Potential Benefits of Synchronous RV pacing

There is some evidence to support selected beneficial effects of RV pacing in context of maintaining a physiological atrioventricular (AV) interval as first-degree AV block may worsen heart failure [39]. A sub-analysis of the DAVID trial identified that those patients with less than 40% RV pacing when randomized to DDDR 70ppm, most of which were programmed with an AV delay of 170 or 150ms, actually had a trend towards better outcomes than the VVI 40ppm arm [40]. Prolonged AV interval can promote rhythm disturbances, create non-physiological ventricular filling times, cause mitral regurgitation and pacemaker syndrome [41, 42].

Interestingly, multiple trials on the efficacy of more modern RV pacing avoidance algorithms have demonstrated a lack of non-inferiority in relation to adverse cardiovascular events. In fact, the Managed Ventricular Pacing (MVP) trial showed in a subgroup of 1030 patients implanted with internal cardioverter defibrillator (ICD) devices with > 230ms PR interval at baseline, worse hospitalization and death rates [43]. Additionally, a PR interval >230ms was

shown to create a 3.4 fold increased risk for the development of persistent atrial fibrillation in an alternate trial [44]. The MOST trial established in a subanalysis that first degree AV block was associated with increased risk of composite death, stroke and HF hospitalization independent of pacing mode or RV pacing burden [15] and importantly the DAVID trial subanalysis identified that patients with prolonged PR interval at baseline did not significantly worsen in the presence of RV pacing [14].

Unfortunately the balance between avoiding potentially detrimental RV pacing and achieving an optimal AV interval is not clearly understood, has not been investigated substantially as a primary endpoint, and has not been included in a meta-analysis [45] therefore currently suggestions for clinical practice are limited.

6. Prevention and treatment of pacemaker-related left ventricular systolic dysfunction

6.1 Medical therapy

Despite the appreciation that RV pacing can induce or worsen LV function, and that patients who need their pacemaker the most are at highest risk of deteriorating heart function and heart failure events [14, 19, 20], there are no published studies exploring medical therapies to prevent deterioration of cardiac function. Patients with pacemakers were excluded from early heart failure studies of angiotensin converting enzyme inhibitors and beta-blockers [46, 47] and form a small proportion of subjects enrolled into more recent studies [48]. Therefore, whether neurohormonal blockade is of benefit in preventing or slowing RV pacing associated LVSD is unknown. To our knowledge, no trials are currently underway to investigate this possibility.

145

146 6.2 Device approaches

147 Device-based approaches, or novel pacemaker algorithms to prevent or reduce pacing-
148 associated LVSD have taken several directions but none have yet demonstrated benefits on
149 patient-orientated end-points such as HF hospitalization or death [43, 49, 50, 51]. Results
150 have been promising in terms of short-term efficacy of ventricular pacing reduction and safety
151 and are further discussed in this review, yet no long-term trials utilising clinical endpoints
152 including patients with high grade AV block have been undertaken [52].

153

154 6.3 Withdrawal of RV pacing

155 Ideally, RV pacing should be delivered only when necessary to maintain quality of life. In
156 recent years pacemaker manufacturers have developed software algorithms that when
157 activated, can reduce RV pacing [49, 53, 54]. These work principally by extending the time
158 between a sensed or paced atrial signal and the delivery of an RV pulse. This prolongation of
159 the AV delay reliably reduces RV pacing and although more complex algorithms can deliver
160 physiological AV delays in the context of intermittent heart block,[32] there are some
161 disadvantages such as reduced ventricular preload and induced mitral regurgitation [55]
162 which are associated with increased mortality and worse symptoms in patients with dilated
163 cardiomyopathy [56].

164 In fact, the trial designed to assess the efficacy of the managed ventricular pace algorithm
165 failed to show inferiority of atrial pacing at 60 beats/min compared to ventricular backup
166 pacing at 40 beats/min in terms of all cause-mortality and HF events at 30 months (80.3%
167 vs. 77.7%; HR:1.14: upper 95% CI bound 1.59) in 1030 patients. There was an unexpectedly

168 low event rate overall, however the study highlighted the fundamental trade-off between
169 avoiding RV pacing and increased burden of lifelong increase AV intervals. Interestingly
170 there was no difference in cumulative RV pacing percentage (MVP-60 vs. VVI-40: 0.8 vs. 0.7
171 at 6 months and 1.6 vs. 1.8 at 24 months), which may be explained by the patient cohort
172 which did not include patients with symptomatic bradycardia.

173 We have previously described that in an unselected cohort of in 66 patients with a long-
174 term pacemaker (8-12 years) a pre-specified protocol (Figure 2) [9] including reducing the
175 day-time base rate to 50 beats per minute, with a nocturnal, sleep or hysteresis rate to 40
176 beats per minute, deactivating rate-adaptive pacing, extending the AV delays or activating
177 an algorithm to reduce unnecessary RV pacing, led to a reduction in mean RV pacing
178 percentage by 49 (95% CI: 41-57)%, ($p<0.001$) [57]. This was associated with an
179 improvement in LVEF of 6 (95% CI: 4-8)% ($p<0.001$) with no adverse effect on quality of life
180 as measured using the validated EQ-5D questionnaire designed by the EuroQol group in
181 order to standardize the measures. Since beneficial remodeling is a powerful prognostic tool
182 [58] our data confirm the potential that a pragmatic yet rigorously applied programming
183 protocol could have on patient-orientated outcomes. Furthermore, our data also support
184 the concept that RV pacing is not merely a bystander in people with worse and deteriorating
185 heart function but is also a contributor. A larger randomized, placebo-controlled study of
186 personalized pacing programming is underway to confirm these results on patient-
187 orientated endpoints and pacemaker battery longevity (NCT: 01819662).

188

189 None of the randomized studies of pacing avoidance algorithms were individually or in meta-
190 analysis large enough or had long enough follow-up to demonstrate benefits on patient-

orientated endpoints such as HF hospitalizations or survival [45]. Moreover, many included patients with unavoidable RV pacing due to third degree AV block, and allowed cross-over to cardiac resynchronization therapy (CRT) [59]. Evidence demonstrating the benefits of a pragmatic approach to optimized programming to avoid RV pacing is therefore lacking and this is reflected in the guidelines for pacemaker implantation which make limited reference to the potential importance of personalization of programming for patient care and device longevity.

Pacemaker therapy though, does not fulfil a one-size-fits-all paradigm, more that particular subgroups of patients are at increased risk of developing or worsening heart failure after the introduction of RV pacing. It has been identified the risk is especially high in people requiring a high proportion of ventricular pacing, those with diabetes mellitus, previous myocardial infarction and raised creatinine [20, 60], although more trials are required to permit more appropriate risk stratification of pacemaker patients.

6.4 Alternative pacing sites

It has been proposed that the adverse effects of RV pacing could be limited by choosing an alternative pacing site in the right ventricle. This led to the development of septal pacing which although promising in observational studies, did not avoid the hemodynamic effect of RV pacing [61], prevent adverse LV remodeling [62, 63, 64, 65] or heart failure events [66] in randomized, controlled studies. These studies are further limited by not employing optimal RV pacing avoidance programming in either arm [9].

Although one meta-analysis of randomized trials concluded that RV non-apical pacing exhibited favorable effects in improving LVEF and interventricular synchrony after 6 month follow-up period [67] this included all non-apical pacing sites in the intervention arm (His bundle, RV septum, RV outflow tract) hence the findings are less translational into clinical practice.

One first-in-man study assessed the efficacy of LV septal pacing in 10 patients indicated for bradycardia pacing due to sinus node dysfunction by driving a pacing lead through the interventricular septum [24]. Acute invasive hemodynamic measures were taken during periods of RV apical, RV septal and LV septal pacing, showing that RV apical and septal pacing reduced LV dP/dtmax compared to a baseline of atrial only pacing (-7.1±4.1% and -6.9±4.3% respectively), whereas LV septal pacing maintained dP/dtmax (1.0±4.3%; p=0.001 versus RV apical and septal) [24]. Nevertheless, all pacing sites induced a bundle branch block-like morphology and without longer term follow-up, functional implications as well as data on the magnitude of potential risks are unknown.

Recently, the use of HIS bundle pacing (HBP) which utilizes more of the intrinsic conduction pathways and might therefore generate an improved contraction profile, has grown. However, studies are mostly observational with a variable success rate of implantation quoted acutely from 73-85%[68, 69]. To date though, these studies [70, 71] have included observational cohorts, or small samples with a large variation in patient co-morbidities and device types. Randomized trials are currently being undertaken including the BHF-supported HOPE-HF study. This will randomly allocate 160 subjects with heart failure due to left ventricular systolic dysfunction (LVEF<40%) without left bundle branch block but a PR

interval ≥200ms to either AV optimized pacing through a ventricular lead placed to achieve HIS-bundle capture or back up rate support through a ventricular lead placed also in the RV apex or a lateral coronary sinus branch vessel in a 6-month cross-over design with the primary endpoint of peak oxygen consumption assessed at baseline, 6 months and 12 months after the implant [NCT number: 02671903).

7. Cardiac Resynchronization Therapy

In context of inconsistent results obtained from lead site manipulation and the growing epidemic of dyssynchrony in pacemaker patients, investigators contemplated the role of cardiac resynchronization therapy (CRT) as a first line treatment for patients considered high risk of cardiac dysfunction.

Yu and colleagues [72] found patients with a normal ejection fraction randomized to RV pacing or biventricular pacing had a significant difference in LVEF at 12 months. However, both patient groups still had a normal ejection fraction (54.8% vs 62.2%) so it was hypothesized that the deleterious effects of RV pacing likely occurred in subgroups of patients and over the longer term.

The Homburg pacing evaluation [73] and COMBAT [74] studies described similar findings in populations of patients with pre-existing LV dysfunction and remodeling prior to implant; building on the growing evidence that patients with pre-existing LV dysfunction are most at risk of further pacing-induced impairment. The BLOCK-HF study, which allocated 691 patients with heart block and a range of left ventricular dysfunction to CRT pacing or RV pacing, demonstrated reductions in heart failure hospitalization commonly in those with marked

LVSD. Furthermore, all patients received CRT hardware, limiting the use of pacing avoidance protocols and the ability to assess complication rates associated with more complex procedures [[75]. BIOPACE, which recruited 1810 patients with heart block and no significant LVSD to CRT or RV devices for up to 8 years has as yet only been presented in abstract form showing no benefit on clinical outcomes [76].

At present it is therefore premature to suggest all patients with high grade AV block should receive CRT. Careful consideration on device type and RV pacing site could be made for patients at initial device implant whom are likely to require a high rates of RV pacing, those with existing cardiac dysfunction or significant ischemic history, or broad QRS duration, although further investigations are needed to validate risk stratification factors in larger cohorts with modern device settings.

8. How do we explain the lack of benefit of alternative pacing options?

The principle issue facing implanters and their patients is that despite the adverse effects of RV pacing, many patients will not develop LVSD or HF as a consequence of long term RV pacing, whilst others will develop it rapidly and follow a fulminant course [20]. The benefit of more complex approaches is likely to be limited to a subgroup of patients that must be identified prior to the initial procedure. Despite considerable investment, the features predicting preventable future clinical deterioration due to incident pacing-related left ventricular dysfunction remain elusive although the presence of pre-existing cardiovascular co-morbidities increases the risk [5].Even the simplest clinical feature, complete heart block recorded indication is unreliable since at long term follow-up a large proportion will not require high amounts of RV pacing (Figure 3) [20].

9. Conclusions

Although there is increasing recognition of the probably causative relationship between RV pacing and LVSD, clinical heart failure is frequently overlooked in the pacemaker population but has major effects on mortality and morbidity. Device-based strategies to overcome pacing-induced cardiac dysfunction have largely failed to be adopted due to poor efficacy or difficulties in patient selection. Optimal medical therapy and programming should therefore be considered in every patient prior to the use of more complex approaches including upgrades to CRT.

10. Expert commentary

Despite significant progress, the optimal strategy for people requiring ventricular rate support is undetermined. The evidence weakness is that it is contradictory; most trials indicate RV pacing is detrimental and that a reduction in RV pacing improves LV function, yet there has been no resultant benefit to clinical patient outcomes. This is not entirely unexpected as there is almost always fundamental potential confounding within the pacemaker population who arguably have existing underlying cardiac disease predisposing them to heart failure. Additionally there is vast heterogeneity across pacemaker reprogramming interventions; between devices, manufacturers and individual patients, making comparisons between trials and the formation of a clinical strategy problematic.

Substantial data now exist to show in patients with pre-existing LV dysfunction, the risk of worsening function after RV pacing induction is exaggerated. Whether RV pacing is harmful to patients with preserved or mild LV dysfunction, how pacemaker-induced cardiac

dysfunction progresses, and how widely is it reversible, remain ambiguous but are ultimately key to understanding the conflicting results. In light of the numerous uncertainties and limited guidance to stratify patients, the appropriateness of programmed pacemaker parameters has begun to dominate the research field.

Research demonstrating the beneficial impact of pacemaker reprogramming on cardiac function is responsible for forming the foundations for reprogramming to be recognized as a medical intervention, and as such should be personalized for each individual patient, moving away from a one-size-fits-all approach. Currently, nominal pacemaker parameters are often utilized in clinical practice, but are substantially inadequate, highlighted by the findings that even a pacing indication of complete heart block does not predict high volumes of RV pacing.

The benefits of precision and personalized treatment approaches remain under-investigated due to a number of challenges. One of the biggest challenges is that many pacing studies have poorly documented programming data and with an absence of head-to-head trials, no direct comparisons are achievable across algorithms. There has also been no demonstration of a reduction in all-cause mortality from RV pacing avoidance and reprogramming, no evaluation of the efficacy of avoiding deteriorating LV function in a randomized fashion, and no assessment of the impact on battery longevity, hypotheses currently being tested in a studies of ours.

More scientific efforts should be made to achieve greater understanding about the development of pacing-induced LV remodeling and dysfunction with the key aim of identifying subgroups of patients where RV pacing is likely to be harmful prior to implant. This

is especially desirable in device therapy, since a decision must be made at baseline about which device will suit the patient for the next 10-20 years and the implantation of any cardiac device remains an invasive, possibly complex procedure with significant associated cost. More of these studies should be independently funded to minimize the presently heavy influence in research from industry.

Evidence then needs to be fed into up-to-date guidelines on device therapy and patient management. At present there is only very limited advice on pacemaker programming regardless of the increased focus of reprogramming interventions in the literature. Every effort should be made to ensure maximal benefit for the patient and society.

11. Five year review

The field of cardiac pacing is continually evolving due to the fast paced innovative nature of device technology. There are a number of areas that have become focal points for progress and are likely to direct cardiac pacing advancements; magnetic resonance imaging (MRI) of device patients, battery technology, leadless pacing and His bundle pacing.

- MRI compatible devices have already started to influence the pacing research landscape. With advanced imaging techniques available, researchers will be able to investigate cardiac size and function in a variety of methods with enhanced specificity and sensitivity than provided by other non-invasive techniques. These data will allow a more detailed assessment of the effects of RV pacing and will inevitably improve the body of research attempting to identify patients at high risk of cardiac dysfunction and heart failure prior to implant.

- The research invested currently into battery technology advancements is overwhelming. Engineers worldwide are attempting to develop life-long energy stores which fulfill the requirements of a cardiac pacemaker utilizing both chemical and mechanical methods. Within 5 years we will see huge contributions to this field of research and likely the initial stages of impactful clinical trials.
- Leadless pacing, although marketed as one of the most recent significant advancements in pacing, is largely restricted in use due to the single chamber nature of the devices. Once devices have the capability of dual chamber pacing, and their cost aligns more with a standard system, there is likely to be broadened application.
- His bundle pacing is theoretically an elegant solution to prevent cardiac dysfunction caused by RV pacing. Stimulation via the normal conduction system avoids RV dyssynchrony and has the potential to negate RV avoidance algorithms and promote physiological AV delays during pacing. Early research findings are encouraging but more trials into its efficacy and feasibility in widespread practice are required.

12. Key Issues

There are a number of outstanding questions currently being investigated:

- Is pacing-induced left ventricular dysfunction progressive and reversible through device reprogramming?
- Can pacing patient outcomes be improved through the use of optimal medical management and personalized pacing programming guided by non-invasive imaging and clinical characteristics?

- Can patients who are at higher risk of worsening cardiac function after pacemaker implantation, who may benefit from more advanced device therapy or adjunct medical therapy, be identified prior to device implantation?

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