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1 Heart failure and right ventricular pacing – how to avoid the need for cardiac resynchronization  
2 therapy  
3

#### 4 **1. Introduction**

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

9

10 However, long term right ventricular (RV) pacing has been linked to adverse left ventricular  
11 (LV) remodeling,[4, 5] such that the most common long-term complication of standard  
12 pacemaker therapy is pacemaker-associated chronic heart failure (CHF) due to left ventricular  
13 systolic dysfunction (LVSD) [6, 7, 8]. Whilst up to 2-3% of the general population have CHF,  
14 the condition is much more common in pacemaker patients with a prevalence up to 50% [7,  
15 9] and 12% of people admitted with acute decompensated heart failure (HF) (4% with a de  
16 novo admission for heart failure) have a pacemaker [10].

17

#### 18 **2. The deleterious effects of RV pacing:**

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

24

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

42

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

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

51

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

64

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

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

73

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

80

#### 81 **4. Mechanisms of the adverse remodeling effects of right ventricular pacing**

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

88

89 In fact, QRS morphology, hemodynamic measures, and the electrical activation–peak  
90 contraction relationship vary greatly between pacing sites; RV septum, apex and LV septum  
91 [24], but even among individual patients [26, 27]. Inter-individual differences in QRS  
92 morphology have been attributed to localized changes in myocardial tissue, such as ischemia,  
93 affecting viability, contractility and relaxation properties [26, 27, 28]. Nevertheless a general  
94 widening of the QRS complex on ECG, lower overall stroke volume, worse mitral regurgitation  
95 are common features in RV paced patients[23].

96

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

105

## 106 **5. Potential Benefits of Synchronous RV pacing**

107 There is some evidence to support selected beneficial effects of RV pacing in context of  
108 maintaining a physiological atrioventricular (AV) interval as first-degree AV block may worsen  
109 heart failure [39]. A sub-analysis of the DAVID trial identified that those patients with less  
110 than 40% RV pacing when randomized to DDDR 70ppm, most of which were programmed  
111 with an AV delay of 170 or 150ms, actually had a trend towards better outcomes than the VVI  
112 40ppm arm [40]. Prolonged AV interval can promote rhythm disturbances, create non-  
113 physiological ventricular filling times, cause mitral regurgitation and pacemaker syndrome  
114 [41, 42].

115

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

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

127

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

132

133

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

### 135 6.1 Medical therapy

136 Despite the appreciation that RV pacing can induce or worsen LV function, and that patients  
137 who need their pacemaker the most are at highest risk of deteriorating heart function and  
138 heart failure events [14, 19, 20], there are no published studies exploring medical therapies  
139 to prevent deterioration of cardiac function. Patients with pacemakers were excluded from  
140 early heart failure studies of angiotensin converting enzyme inhibitors and beta-blockers [46,  
141 47] and form a small proportion of subjects enrolled into more recent studies [48]. Therefore,  
142 whether neurohormonal blockade is of benefit in preventing or slowing RV pacing associated  
143 LVSD is unknown. To our knowledge, no trials are currently underway to investigate this  
144 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-

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

198

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

205

#### 206 6.4 Alternative pacing sites

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

213

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

219

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

229

230 Recently, the use of HIS bundle pacing (HBP) which utilizes more of the intrinsic conduction  
231 pathways and might therefore generate an improved contraction profile, has grown.

232 However, studies are mostly observational with a variable success rate of implantation  
233 quoted acutely from 73-85%[68, 69]. To date though, these studies [70, 71] have included  
234 observational cohorts, or small samples with a large variation in patient co-morbidities and  
235 device types. Randomized trials are currently being undertaken including the BHF-supported  
236 HOPE-HF study. This will randomly allocate 160 subjects with heart failure due to left  
237 ventricular systolic dysfunction (LVEF<40%) without left bundle branch block but a PR

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

243

## 244 **7. Cardiac Resynchronization Therapy**

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

249

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

255

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

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

267

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

274

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

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

286

## 287 **9. Conclusions**

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

295

## 296 **10. Expert commentary**

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

306

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

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

314

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

321

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

330

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

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

339

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

344

#### 345 **11. Five year review**

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

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

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

371

## 372 **12. Key Issues**

373 There are a number of outstanding questions currently being investigated:

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

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

382

383

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