

The Deleterious Consequences of Right Ventricular Apical Pacing: Time to Seek Alternate Site Pacing

ANTONIS S. MANOLIS

From the First Department of Cardiology, Evagelismos General Hospital of Athens, Athens, Greece

Background: The purpose of this article is to critically review the data accumulated to date from studies evaluating the hemodynamic and clinical effects of right ventricular apical pacing during conventional permanent cardiac pacing. The data from studies comparing the effects of right ventricular apical pacing and alternate site ventricular pacing are also reviewed.

Methods: We conducted a MEDLINE and journal search of English-language reports published in the last decade and searched relevant papers.

Results: Although intraventricular conduction delay in the form of left bundle branch block (LBBB) has traditionally been viewed as an electrophysiologic abnormality, it has now become abundantly clear that it has profound hemodynamic effects due to ventricular dyssynchrony, especially in patients with heart failure. These deleterious effects can be significantly ameliorated by cardiac resynchronization therapy effected by biventricular or left ventricular pacing. However, not only is spontaneous LBBB harmful, but the iatrogenic variety produced by right ventricular apical pacing in patients with permanent pacemakers may be equally deleterious. In this review new evidence from recent studies is presented, which strongly suggests a harmful effect of our long-standing practice of producing an iatrogenic LBBB by conventional right ventricular apical pacing in patients receiving permanent pacemakers. This emerging strong new evidence about the adverse hemodynamic and clinical effects of right ventricular apical pacing would dictate a reassessment of our traditional approach to permanent cardiac pacing and direct our attention to alternate sites of pacing, such as the left ventricle and/or the right ventricular outflow tract or septum, if not for all patients, at least for those with left ventricular dysfunction. Indeed, current convincing data on alternate site ventricular pacing are encouraging and this approach should be actively pursued and further investigated in future studies.

Conclusions: Not only is spontaneous permanent LBBB harmful to our patients, but the iatrogenic variety produced by right ventricular apical pacing during conventional permanent pacing may also be deleterious to some patients. The compelling evidence presented herein cannot be ignored; it may dictate a change of attitude toward right ventricular apical pacing directing our attention to alternate sites of ventricular pacing and avoidance of the right ventricular apex. (*PACE* 2006; 29:298–315)

left bundle branch block, conduction delay, right ventricular apex, cardiac pacing, heart failure, left ventricular dysfunction, cardiac resynchronization therapy

Introduction

Over the last decade, several studies have demonstrated the deleterious consequences of intraventricular conduction delay, particularly those produced by left bundle branch block (LBBB).^{1–10} In the presence of LBBB, ventricular dyssynchrony can lead to hemodynamic deterioration due to a resultant diminution of stroke volume and cardiac output. This further leads to clinical worsening in patients with left ventricular dysfunction

and heart failure, which often remains refractory to medical therapy. It is estimated that approximately 20–30% of patients with congestive heart failure are afflicted by ventricular dyssynchrony,^{1,9} defined as an abnormality in electromechanical coupling seen in association with intraventricular delay and QRS prolongation (>120 ms), most notably in the form of permanent LBBB.

Cardiac resynchronization therapy applied via biventricular or left ventricular pacing techniques has been heralded as a novel mode of non-pharmacological nonsurgical therapy in patients with moderate-to-advanced heart failure refractory to optimized medical therapy.^{11–21} Cardiac resynchronization therapy offers substantial clinical improvement to these patients according to the results of several recently published randomized

Address for reprints: Antonis S. Manolis, M.D., 41 Kourempana Street, Agios Dimitrios 173 43, Athens, Greece. Fax: 011-30-210-971 3244; e-mail: asm@otenet.gr

Received May 6, 2004; revised July 19, 2005; accepted July 20, 2005.

Table I.**Deleterious Effects of Right Ventricular Apical Pacing**

- Iatrogenically accentuated intraventricular conduction delay
- Left ventricular electrical and mechanical dyssynchrony
- Left ventricular remodeling
- Abnormalities in myocardial histopathology
- Left ventricular dysfunction (both systolic and diastolic)
- Congestive heart failure
- Myocardial perfusion defects and regional wall motion abnormalities
- Functional mitral regurgitation
- Increased risk of atrial fibrillation (in patients with sinus node dysfunction and normal baseline QRS duration)
- Left atrial enlargement
- Promotion of ventricular arrhythmias
- Activation of sympathetic nervous system

studies. There is also strong indication according to a recent meta-analysis, an efficacy review, and two randomized trials that cardiac resynchronization may also prolong survival, especially when combined with defibrillation back-up.^{22–25}

In concert with the above data regarding the adverse hemodynamic and clinical effects of the spontaneous LBBB, newer data are emerging, which convincingly indicate that the iatrogenic variety of LBBB, produced by conventional right ventricular apical pacing technique employed in permanent cardiac pacing, may be equally harmful^{26–32} (Table I). In the present review, data from recent studies will be presented, which suggest that, at least for certain patients, if not for all, we have to reconsider our standard approach to permanent cardiac pacemaker implantation of selecting the right ventricular apex as our preferred site for ventricular pacing. The evidence of a deleterious effect of right ventricular apical pacing on both otherwise healthy individuals and heart failure patients is such that we cannot afford being complacent with such a routine practice any longer.

Clinical Studies of Right Ventricular Apical Pacing

A longitudinal controlled study of the long-term effects of right ventricular apical pacing included 24 young patients (mean age of 19.5 years) who received conventional permanent pacemakers²⁸ (Table II). The study group was followed for a mean of 9.5 years. The duration of right ventricular apical pacing ranged from 0.7 to 18.9 years (median 10). Right ventricular apical pacing led to

irreversible left ventricular dysfunction. Both left ventricular systolic and diastolic function indexes were impaired, when compared with the indexes of 33 age- and basal surface area-matched healthy control individuals. Paced QRS interval and age were found to significantly influence global left ventricular contraction in these patients. In another study by the same investigators, myocardial biopsies were performed on 14 patients with congenital complete heart block and otherwise normal cardiac anatomy, with 8 biopsies obtained before and another 8 biopsies obtained after 3–12 years (median 5.5) of chronic right ventricular apical pacing.²⁹ Altered cardiac histology produced by chronic right ventricular apical pacing was demonstrated in these young patients, potentially explaining the diminished left ventricular function observed clinically. In 23 patients with congenital complete heart block, aged 24 ± 3 years, who had received a DDD transvenous pacemaker, echocardiography and exercise testing were performed before pacemaker implantation and after at least 5 years of pacing.³⁰ After a mean of 10-year cardiac pacing, these patients, in comparison with 30 matched healthy control individuals, had significantly higher values of intraventricular dyssynchrony, left ventricular remodeling, dilatation, and hypertrophy, with lower cardiac output and exercise performance.

In 12 patients with complete atrioventricular block without significant coronary artery disease, receiving dual-chamber permanent pacemakers with right ventricular apical pacing, regional myocardial perfusion and wall motion abnormalities were demonstrated near the sites of ventricular stimulation at 6 months after implantation, and these abnormalities increased with the duration of pacing at 18 months of follow-up.³¹ These functional abnormalities during right ventricular apical pacing were associated with impairment of left ventricular diastolic function and progressive deterioration of regional left ventricular ejection fraction over time in regions remote from the sites of electrical stimulation, which resulted in a significant reduction in global left ventricular function. Interestingly, right ventricular outflow tract pacing in another 12 patients in this randomized study prevented these deleterious effects of right ventricular apical pacing.³¹ In 13 patients with left ventricular dysfunction undergoing comparative evaluation of the acute effects of right ventricular, left ventricular, and biventricular pacing on muscle sympathetic nerve activity with the use of microneurography, right ventricular apical pacing had the highest sympathetic nerve activity.³²

In an interesting report of a case with atrioventricular junction ablation for uncontrolled atrial fibrillation, implantation of a permanent VVIR

Table II.
Clinical Studies of the Adverse Effects of Right Ventricular (RV) Apical Pacing

Trial	No. of Patients	Mean Age (y)	Mean FU (y)	LA Diameter	LV Function	CHF	AF
Tantengco et al. ²⁸	24	19.5	9.5	NA	↓	2 pts	NA
Karpawich et al. ²⁹	14	15.5	5.5	NA	Altered Histology	NA	NA
Thambo et al. ³⁰	23	24	10	NA	↓/DS	NA	NA
Tse et al. ³¹	12	72	1.5	NA	↓/MPD	NA	NA
Hamdan et al. ³²	13	66	NA*	NA	↓/↑SNA	NA	NA
DAVID ³⁶	506	64	1	NA	NA	↑	NA
MADIT II ^{37,38} Substudy	567	64	1.7	NA	NA	↑	NA
Wonisch et al. ³⁹	17	59	0.25	NA	NA	**	NA
Thackray et al. ⁴⁰	307	72	5.2	NA	NA	↑	↑
MOST ⁴¹	1,339	74	6	NA	NA	↑	↑
Nielsen et al. ⁴³	177	74	2.9	↑	↓	NA	↑
O'Keefe et al. ⁴⁴	59	69	1.5	NA	↓	NA	NA

AF = atrial fibrillation; CHF = congestive heart failure; DS = dyssynchrony; FU = follow-up; LA = left atrium; LBBB = left bundle branch block; LV = left ventricular; MPD = myocardial perfusion defects; NA = not available/ not assessed; SNA = sympathetic nerve activity.

* Acute study.

** Permanent RV pacing significantly reduced exercise capacity and submaximal cardiorespiratory parameters.

pacemaker was followed by refractory heart failure and severe mitral regurgitation produced by right ventricular apical pacing.³³ It was only left ventricular pacing, as compared to right ventricular apical, right ventricular septal, or biventricular pacing, which dramatically reduced the valvular regurgitation and improved the patient's heart failure, both acutely and over a 21-month follow-up. In another case of a patient with normal left ventricular function receiving a conventional DDD pacemaker for complete heart block, acute congestive heart failure developed several hours after pacemaker implantation, with echocardiography now showing new regional wall motion abnormalities, while coronary angiography did not show any significant coronary artery stenoses.³⁴ In a patient with tachycardiomyopathy due to chronic atrial fibrillation with uncontrolled ventricular rates, His bundle ablation was performed and a VVIR pacemaker was implanted.³⁵ Although the heart rate was now controlled, unexpectedly within a year after right ventricular pacing, mitral regurgitation worsened significantly and the left ventricular ejection fraction decreased from 35% to 29%. It was only after upgrading the pacing system to biventricular VVIR modality that the patient's condition improved. After 6 months of biventricular pacing, the left ventricular end-diastolic diameter diminished from 69 to 62 mm, the ejection fraction increased to 34%, and mitral regurgitation improved from severe to moderate, while pulmonary arterial pressure normalized

(from 40 to 22 mmHg). The patient's exercise tolerance increased, while New York Heart Association (NYHA) functional class improved from III to II.³⁵

The DAVID trial provided important evidence about the harmful effect that right ventricular pacing might be conferring to patients with implantable cardioverter defibrillators.³⁶ Patients (n = 256) with their defibrillator device programmed to standby VVI mode at 40 beats/min fared much better compared with those (n = 250) who had the device programmed to DDDR pacing at 70 bpm. Over one year, the hazard ratios for the DDDR pacing group compared with the VVI group were 1.61 for heart failure hospitalization or death, 1.54 for heart failure hospitalization, and 1.61 for death. Thus, this study gave the important message that programming of pacing functions in dual-chamber defibrillators should be optimized for individual patients. Right ventricular apical pacing in patients with left ventricular dysfunction, as those in this study who all had an ejection fraction $\leq 40\%$, and with no bradycardia indication for pacing can be harmful, justifying a preference for backup ventricular pacing in this patient population.

In addition, a MADIT II substudy reported during the NASPE meeting in May 2003,³⁷ and just recently published in full,³⁸ raised similar concerns about right ventricular apical pacing. During a 20-month follow-up, patients (n = 369) having high cumulative right ventricular pacing (>50%), had a higher incidence of new or worsened heart

failure (30% vs 17%, $P = 0.002$; hazard ratio 1.9) and heart failure or death (50% vs 20%, $P = 0.004$; hazard ratio 1.8) compared to patients ($n = 198$) with infrequent right ventricular pacing. In addition, patients in the high-frequency pacing group had significantly more episodes of ventricular tachycardia events requiring shock or anti-tachycardia pacing by the defibrillator than did patients in the low-frequency pacing group (hazard ratio 1.5, $P = 0.025$). In a recent study of 17 patients with chronic heart failure and a dual-chamber implantable cardioverter defibrillator, who were randomized either to back-up pacing or permanent right ventricular pacing for 3 months, with a crossover design, the impact of pacing was assessed on exercise capacity and related cardiorespiratory parameters.³⁹ Permanent right ventricular pacing significantly reduced maximal and sub-maximal measures of exercise. The authors concluded that for patients with chronic heart failure and adequate atrioventricular conduction, every effort should be made to minimize permanent right ventricular pacing.

More data on the adverse effect of right ventricular apical pacing have just become available via a recent study assessing the prevalence of congestive heart failure or left ventricular dysfunction among 307 chronically paced patients (about half of them with dual-chamber devices).⁴⁰ A large percentage (54%) of patients had symptoms of heart failure, with a slightly higher prevalence in those with single-chamber pacemakers (57%) compared to a dual-chamber device (50%). Low left ventricular ejection fraction ($<40\%$) was detected in 94 (31%) patients, of whom 83 (27%) had symptoms of heart failure. However, another 83 patients (27%) had symptoms of heart failure but an ejection fraction $>40\%$. With increasing years of pacing, an increasing prevalence of both heart failure due to left ventricular systolic dysfunction and of atrial fibrillation was documented. The prevalence of heart failure increased from 24% to 38% and that of atrial fibrillation from 26% to 45% after pacing for 10 or more years. Although the etiology of congestive heart failure in this population may be multifactorial, a good percentage is probably pacing-induced. If one considers that dual-chamber pacing may obviate these adverse effects of right ventricular pacing, a subanalysis of the MOST trial contradicts this belief.⁴¹ Of the 1,339 patients with sinus node dysfunction and baseline QRS < 120 ms, 707 (53%) were randomly assigned to DDDR and 632 (47%) to VVIR pacing. The overall rate of heart failure hospitalization was similar (10% DDDR, 9% VVIR). Despite maintenance of atrioventricular synchrony, ventricular pacing in the DDDR mode $>40\%$ of the time conferred a 2.6-fold increased risk of heart failure hospital-

ization compared with less pacing among similar patients with normal baseline QRS duration.⁴¹ Thus, ventricular desynchronization imposed by right ventricular pacing even when atrioventricular synchrony is maintained increases the risk of heart failure hospitalization, in addition to the risk of atrial fibrillation, in sinus node dysfunction with normal baseline QRS duration. In a follow-up analysis in the same group of patients, paced QRS duration was a significant, independent predictor of heart failure hospitalization.⁴² Patients with a wider-paced QRS had a higher risk of heart failure hospitalization, with a 17% relative risk increase for every 10-ms increase in paced QRS duration.⁴² These were all patients with sinus node dysfunction, but with preserved left ventricular function prior to pacing (mean left ventricular ejection fraction of 55%).

In another randomized trial, 177 patients with sinus node dysfunction and normal atrioventricular conduction, aged 74 ± 9 years, were randomized to three modes of pacing: AAIR ($n = 54$), DDDR with short atrioventricular delay ($n = 60$), or DDDR with a fixed long atrioventricular delay ($n = 63$).⁴³ Before pacemaker implantation and during follow-up, M-mode echocardiography was performed to measure left atrial and left ventricular diameters and fractional shortening. Over a mean follow-up of 2.9 ± 1.1 years, patients in the two DDDR groups having conventional right ventricular apical pacing, in addition to an increase in the left atrial and left ventricular end-systolic diameters ($P < 0.05$) and more common atrial fibrillation ($P = 0.03$), those with a high (90%) proportion of right ventricular pacing (DDDR pacing with short atrioventricular delay) had a significantly decreased left ventricular fractional shortening, compared to patients with AAIR pacing ($P < 0.01$). Mortality, thromboembolism, and congestive heart failure did not differ significantly among groups in this study. This study suggests that atrial pacing is preferred over right ventricular apical pacing in patients with sick sinus syndrome and normal atrioventricular conduction, as it avoids the adverse effects of right ventricular apical pacing, which include both the promotion of atrial fibrillation probably by causing left atrial dilation and the reduction of left ventricular function.

Finally, in a most recent retrospective analysis of a large database, 1,128 patients with moderate left ventricular dysfunction (ejection fraction 25–40%) were identified and in the subgroup of 59 patients having a decreased ejection fraction at 18 months later, the strongest independent predictor of such a decrease (of ≥ 7 points; from $35 \pm 4\%$ to $25 \pm 5\%$) was the presence of a permanent right ventricular apical pacemaker (odds ratio 6.6, $P = 0.002$).⁴⁴ Nevertheless, in a study by Ueng et al.,

50 patients with chronic lone atrial fibrillation who underwent atrioventricular nodal ablation and implantation of a conventional permanent single-chamber pacemaker fared well with right ventricular apical pacing at one year.⁴⁵ However, it is not clear whether the adverse pacing effects were superseded and the results were influenced by the fact that the pacemaker eliminated the adverse effect that had been posed by the longstanding irregular rhythm and uncontrolled ventricular rate. As the authors themselves state “because pacing from the right ventricular apex produced its own adverse hemodynamic effects, the beneficial effect of rhythm regularization might have been counteracted in part by the deleterious effect of asynergic ventricular contraction caused by right ventricular apex pacing. It is uncertain whether these results are improved further by pacing at an alternative site.”⁴⁵

Alternate Sites of Ventricular Pacing

In view of these harmful effects of right ventricular apical pacing, alternate sites of ventricular stimulation would be desirable (Figs. 1–3). Alternate site pacing may involve other right ventricular sites (outflow or septal sites) or left ventricular sites in either unifocal or bifocal or biventricular modes^{46–64} (Tables III–V). There is already ample evidence currently in the literature that cardiac resynchronization therapy effected by left ventricular pacing (Fig. 1), mainly as part of biventricular pacing but also as a stand-alone pacing site, is beneficial, particularly in patients with moderate-to-severe left ventricular dysfunction and refrac-

tory heart failure.^{11–25} Older attempts at applying electrical pacing techniques with conventional dual-chamber pacemakers restoring or optimizing atrioventricular synchrony to manage heart failure in patients with dilated cardiomyopathy, did not succeed in improving symptoms and prognosis,¹⁴ most likely because at that time attention had not been paid to the adverse effects of electrical and mechanical dyssynchrony produced by a preexisting LBBB or iatrogenically accentuated intraventricular conduction delay conferred by right ventricular apical pacing.

In the case report of severe mitral regurgitation mentioned above, which was produced by right ventricular apical pacing, left ventricular pacing was more effective than biventricular pacing or right ventricular septal pacing in reducing mitral regurgitation.³³ There are currently a few other studies comparing the effects of conventional right ventricular apical pacing with those of left ventricular or biventricular pacing techniques on the left ventricular function and clinical status of patients^{32,46,60–68} (Table III). However, the techniques for effecting left ventricular pacing are generally demanding and tedious. Although epicardial lead placement has been performed via limited surgical approaches and more recently via robotic-enhanced thoracoscopic implantation,⁶⁹ usually more practical transvenous techniques with the insertion of the left ventricular lead via the coronary sinus branches have been employed in most studies^{11–21,70} (Fig. 1). A transeptal approach to endocardial left ventricular pacing has also been suggested but it is technically difficult and there

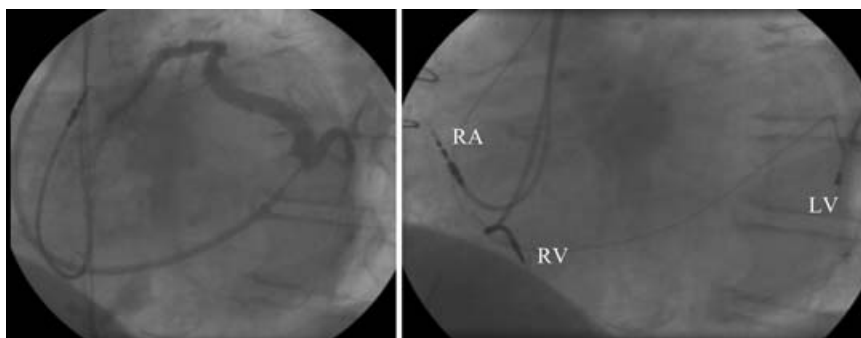


Figure 1. Alternate site pacing includes left ventricular pacing as a stand-alone pacing site or most commonly as part of biventricular pacing. The most critical part of left ventricular or biventricular pacing relates to the placement of the left ventricular (LV) lead. This is now accomplished with a transvenous technique by inserting the pacing lead (right panel) into a coronary sinus tributary, to capture and resynchronize the left ventricle. The target venous branch can be identified via a coronary venous angiogram (left panel), which precedes and guides the lead insertion. Guiding catheter sheaths and over-the-wire systems similar to those used during coronary angioplasty are currently used, which together with coronary sinus angiography greatly facilitate the procedure. RA = right atrial (lead); RV = right ventricular (lead).

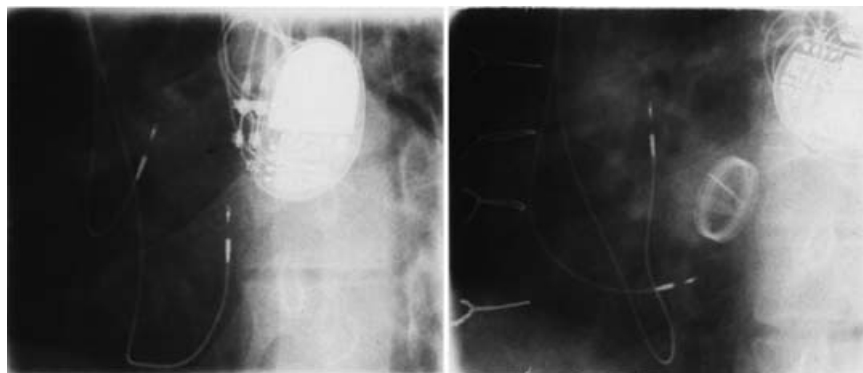


Figure 2. The conventional positions for lead placement during permanent cardiac pacing include the right atrial appendage and right ventricular apex. However, these traditional pacing sites may produce or promote atrial and ventricular dyssynchrony with its attendant harmful effects, at least in patients with atrial fibrillation or left ventricular dysfunction respectively. Alternate or multisite atrial and/or ventricular pacing may facilitate atrial and/or ventricular resynchronization. A new steerable system allows the placement of very thin active fixation leads into alternate right atrial and right ventricular (RV) sites, e.g., interatrial septum and RV outflow tract (left panel), or coronary sinus os and RV outflow tract (right panel) (in both panels left anterior oblique fluoroscopic views are displayed). The leads have no lumen for stylet insertion, are steroid-eluting, and yield very low pacing thresholds, both acutely and at 3-month follow-up measurements.⁷⁶

is need for permanent anticoagulation to avoid thromboembolism.⁷¹ Experimentally, in animals, left ventricular septal pacing has been effected via a transvenous approach from the right side of the interventricular septum with the use of a special lead and guiding sheath.⁷² Permanent His bundle pacing has also been suggested and animal data indicate that this may be feasible and it might be an option in the future.⁷³⁻⁷⁵

Right Ventricular Outflow Tract

In search of alternate right ventricular sites of pacing, the right ventricular outflow tract has been more extensively studied^{47,49-52,54-57,59} (Table III, Figs. 2 and 3). A pooled analysis of nine prospective studies evaluating the hemodynamic effects of right ventricular outflow-tract pacing in 217 patients indicated a modest but significant hemodynamic benefit compared with right

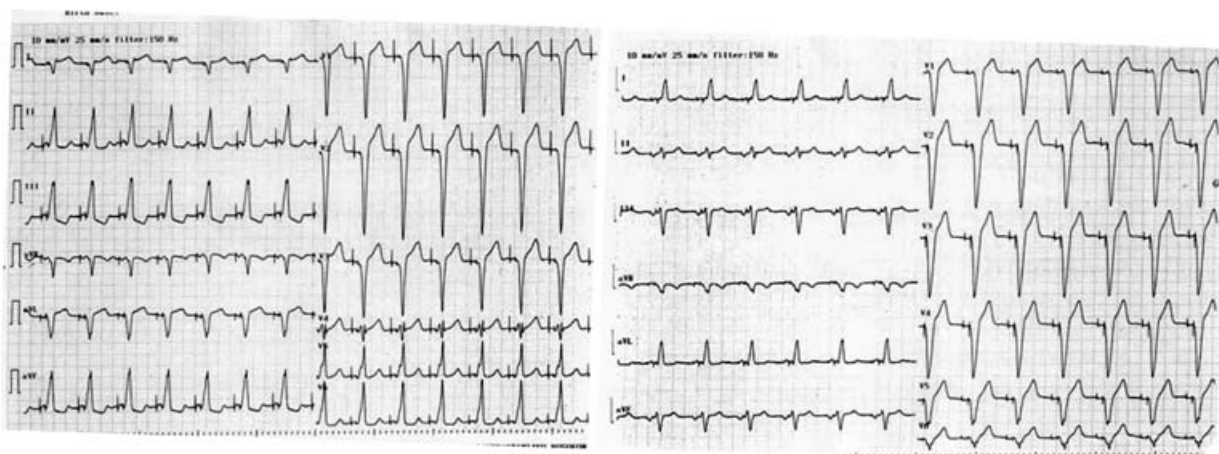


Figure 3. Twelve-lead electrocardiograms indicate the specific alternate site of atrial and ventricular pacing. The electrocardiogram on the left is recorded from a patient who had the atrial lead placed in the interatrial septum and the ventricular lead at the high anterior right ventricular outflow tract, while the electrocardiogram on the right was recorded from a patient who had the leads placed in the coronary sinus os and the low septal right ventricular outflow tract.

Table III.

Studies Comparing Hemodynamic and/or Clinical Effects of Right Ventricular (RV) Apical Pacing and Alternate Site Pacing in the RV Outflow Tract (RVOT) or RV Septal (RVS) or Left Ventricular (LV) or Biventricular (Biv) Site

Study	No. of Patients	Mean Age (y)	Hemodynamic/ Clinical Variables	Improved Results	
				Acute	Chronic
Cowell et al. ⁴⁸	15	59	CO (Cath)	RVS	NA
Giudici et al. ⁴⁹	89	68	CO (Echo)	RVOT	NA*
Buckingham et al. ⁵⁰	11	48	CO (Echo)	RVOT	NA
Karpawich and Mital. ⁵¹	22	10	LVEDP (Cath)	RVS	NA
Blanc et al. ⁴⁶	23	66	PWP (Cath)	LV/Biv	NA
De Cock et al. ⁵²	17	58	CO (Echo)	RVOT	NA
Mera et al. ⁵³	12	68	FS/EF (Echo/RNV)	NA	RVS
Buckingham et al. ⁵⁴	14	55	12 (Echo/Cath)	RVOT/BF	NA
Victor et al. ⁵⁵	16	69	4 (Echo/RNV)	NA	None
Schwaab et al. ⁵⁶	14	71	EF (RNV)	RVS	NA
Kolettis et al. ⁵⁷	20	62	CO (Echo)	RVOT	NA
Bourke et al. ⁵⁹	20	64	8 (RNV)	NA	RVOT
Tse et al. ³¹	24	75	WMA/EF (RNS/RNV)	NA	RVOT
Hamdan et al. ³²	13	66	BP/CVP/SNA	LV/Biv	NA
Kass et al. ⁶⁰	18	66	10 (Cath)	LV/Biv	NA
Yu et al. ⁶¹	33	66	14 (Echo)	Biv	NA
Leclercq et al. ⁶²	37	63	6 (Clinical)	NA	Biv
Leon et al. ⁶³	20	70	6 (Echo/Clinical)	NA	Biv
Leclercq et al. ⁶⁴	56	73	5 (Clinical)	NA	Biv
ROVA ^{65**}	103	69.5	6 (Clinical/Echo)	ND	ND
OPSITE ^{66**}	56	70	QOL/exercise capacity	Biv/LV	NA
PAVE ^{67,68**}	252	NA	4 (Clinical)	NA	Biv

BF = bifocal; BP = arterial blood pressure; Cath = cardiac catheterization; CO = cardiac output; CVP = central venous pressure; Echo = echocardiography; EF = (left ventricular) ejection fraction; FS = (left ventricular) fractional shortening; LVEDP = left ventricular end-diastolic pressure; NA = not available/not assessed; ND = no difference; PWP = pulmonary wedge pressure; RNS = radionuclide scintigraphy; RNV = radionuclide ventriculography; SNA = sympathetic neural activity (measured by microneurography); WMA = wall motion abnormalities.

* Only 5 patients were evaluated at 6 months and demonstrated a similar improvement in cardiac output with RV outflow tract pacing compared with RV apical pacing.

** Randomized studies; ROVA compared quality of life between RV apical and RV outflow tract pacing only after 3 months of pacing in patients with heart failure and chronic atrial fibrillation; OPSITE: randomized, single-blind, 3-month crossover comparison between RV and LV pacing and between RV and Biv pacing in patients with atrial fibrillation and heart failure undergoing AV node ablation; PAVE: randomized study evaluating Biv vs RV pacing in atrial fibrillation patients receiving ablate and pace therapy.

ventricular apical pacing (odds ratio of 0.34).⁴⁷ Among these studies, most of them reported acute hemodynamic effects, while only two studies reported long-term hemodynamic effects, with one indicating no difference between the two sites after 3 months of pacing⁵⁵ and the other reporting a significant increase in left ventricular fractional shortening following 2 months of right ventricular outflow tract pacing.⁵³ The largest study included in this analysis compared the acute hemodynamic effects of right ventricular apical and outflow tract pacing in 89 patients.⁴⁹ Cardiac output was improved at the time of implant in 85 of 89 patients by pacing the outflow tract from 6.6 ± 2.4 L/min

at the apex to 7.8 ± 2.9 L/min at the outflow tract, a 19% increase, while cardiac index improved by 21% ($P < 0.0001$). Patients with a low baseline cardiac index had a greater relative improvement with right ventricular outflow tract pacing. In a very small subgroup ($n = 5$) of these patients, reevaluation at 6 months later demonstrated a similar improvement in cardiac output with outflow tract pacing compared with apical pacing.

Apart from the pooled analysis, there are additional studies, which compare right ventricular apical with alternate site pacing (Table III). In a small study involving 13 patients with heart failure who received permanent atrioventricular

Table IV.

Other Studies of Alternate Site Pacing

Study	No. of Patients	Target Population	Pacing Site	Studied Variables	Improvement
Turner et al. ⁸⁹	10	HF	LV	Hemodynamic	Yes
Vanagt et al. ⁹¹	8	Children during cardiac surgery	LV apex	Hemodynamic	Yes*
Touiza et al. ⁹²	18	HF/LBBB	LV	Clinical/echo	Yes
Blanc et al. ⁹³	22	HF/LBBB	LV	Clinical/echo	Yes
Auricchio et al. ⁹⁴	57	HF/LBBB	LV	Clinical	Yes
Garrigue et al. ⁹⁵	13	HF/AF/LBBB	LV/Biv	Clinical/pm sensor	Yes
Vlay ⁸⁴	22	HF/LBBB	Bifocal RV (RVA+RVOT)	Clinical/echo	Yes
Pachon et al. ⁸⁵	39	HF/LBBB	Bifocal RV (RVA+RVS)	Clinical/echo/nuclear	Yes**
O'Donnell et al. ⁸⁶	6	HF/LBBB	Bifocal RV (RVA+RVOT)	Clinical/echo	Yes***
ROVA ⁶⁵	50	HF/AF	Bifocal RV (RVA+RVOT)	Clinical/echo	NS****
Deshmukh and Romanyshyn ⁷⁵	39	HF/AF	HB	Clinical/echo	Yes
Zamparelli and Martiniello ⁸⁷	25	HF/LBBB	Bifocal RV (RVA+RVS)	Clinical/echo	Yes
Aonuma et al. ⁹⁶	13	HF	Trifocal (RVA+LV+RVOT)	(Acute) hemodynamic/clinical	Yes

BF = bifocal; BP = arterial blood pressure; Cath = cardiac catheterization; CO = cardiac output; CVP = central venous pressure; Echo = echocardiography; EF = (left ventricular) ejection fraction; FS = (left ventricular) fractional shortening; HB = His bundle; HF = heart failure; LBBB = left bundle branch block; LV = left ventricle; NS = no significant (differences); pm = pacemaker; RV = right ventricle; RVA = right ventricular apex; RVOT = right ventricular outflow tract; RVS = right ventricular septum.

* Comparison made with RV apical pacing (parameters were maintained at sinus rhythm level with left ventricular apex pacing).

** Comparison made with RV apical and RV septal pacing.

*** Comparison made with biventricular pacing.

**** Comparison was made with RV apical and RVOT pacing; at 3 months, physical functioning score was worse than during RV apical pacing and mental health scores were worse than during RVOT pacing. NYHA class during dual-site RV pacing was slightly better than during RVOT ($P = 0.03$), but not different than RV apical pacing; there were no other significant differences in other studied parameters.

pacemakers with the ventricular lead placed at the right ventricular septum, there was no change in the hemodynamic parameters as measured acutely during intrinsic rhythm and after 15 to 20 minutes of pacing over a wide range of atrioventricular delays.⁵⁸ A more recent study comparing right ventricular apical pacing with outflow tract pacing in 20 patients without cardiac failure, suggested that systolic left ventricular function is better preserved by outflow tract rather than apical site pacing at 23 weeks later, as assessed by radionuclide ventriculograms.⁵⁹ In another randomized study, 24 patients with complete atrioventricular block without coronary artery disease and with normal left ventricular function were randomly assigned to permanent right ventricular apical pacing ($n = 12$) and outflow tract pacing ($n = 12$).³¹ With right ventricular outflow tract pacing the duration of QRS complex was shorter compared to apical pacing. Most importantly, although at 6 months there was no difference between the two groups, at 18 months the incidence of myocardial perfusion defects by thallium scintigraphy (33% vs 83%) and

regional wall motion abnormalities by radionuclide ventriculography (33% vs 75%) were lower, and left ventricular ejection fraction was higher (56 ± 1 vs $47 \pm 3\%$) during right ventricular outflow tract pacing than right ventricular apical pacing ($P < 0.05$).

In the same direction, a new randomized multicenter study, currently in completion, examined the feasibility of a new steerable system of novel technology allowing the implantation of a very thin active fixation lead in alternate sites in the right atrium and right ventricular outflow tract. We participated in this multicenter study and in 30 patients, in whom alternate site pacing was evaluated with the new system, the success rate of implantation was 93% with excellent measurements obtained acutely and during short-term 1- and 3-month follow-up.⁷⁶ Patients were randomized to receive the new active fixation lead in either the interatrial septum/high anterior right ventricular outflow tract or coronary sinus os/low septal right ventricular outflow tract positions (Figs. 2 and 3). This novel pacing lead bears no lumen and thus

Table V.

Ongoing Studies of Alternate Site Pacing or Studies of Right Ventricular Pacing Reduction Strategies

Study	No. of Patients	Target Population	Type of Pacing	Clinical Variables
BRIGHT ⁸¹	NA	HF /class III LBBB/EF<35% QRS \geq 120 ms	bifocal RV (RVA+RVOT)	QOL/exercise EF/NYHA class
BIOPACE	250	ppm indication/any QRS/ any EF	RV vs CRT	NA
BLOCK-HF	1,200	ppm indication/ HF/class I-III/ EF<45%	RV vs CRT	NA
MVP trial ¹⁰⁴	149	ppm indication	MVP vs DDD/R	AF/HF
SAVE PACe ¹⁰⁵	1,100	SAND	Search AV extension & managed ventricular pacing	AF, HF, CVA
DANPACE	NA	SSS	AAIR vs DDDR	LA/FS/AF
AAIsafeR ¹⁰⁶	NA	SAND/pAVB	DDD(R) / AAI(R)	AF
INTRINSIC RV ¹⁰⁷	>1,200	ICD	DDDR with AV search hysteresis vs VVI	MR/HF

AF = atrial fibrillation; AV = atrioventricular; BF = bifocal; CRT = cardiac resynchronization therapy (biventricular pacing); CVA = cerebrovascular accident (stroke); Echo = echocardiography; EF = (left ventricular) ejection fraction; FS = (left ventricular) fractional shortening; HF = heart failure; ICD = implantable cardioverter defibrillator; LA = left atrium (diameter); MVP = managed ventricular pacing (mode switching between AAI/R and DDD/R); MR = mortality rate; NA = not available; NYHA = New York Heart Association; pAVB = paroxysmal atrioventricular block; ppm = permanent pacemaker; QOL = quality of life; RV = right ventric-le (-ular); RVA = right ventricular apex; RVOT = right ventricular outflow tract; SAND = sino-atrial node dysfunction; SSS = sick sinus syndrome.

no guiding stylet, but its insertion and endocardial positioning is facilitated by a steerable guiding catheter. Recently, right ventricular outflow tract pacing was employed alone or as a part of bifocal right ventricular pacing in 3 patients in whom left ventricular pacing was not possible due to difficulties in placing the electrode via the coronary sinus. A major clinical improvement was documented in all three patients.⁷⁷

The only randomized study comparing right ventricular outflow tract with apical pacing is the ROVA study.⁶⁵ This study assessed quality of life after 3 months of apical or outflow tract pacing and included 103 patients with heart failure, chronic atrial fibrillation, and left ventricular ejection fraction <40%. Although outflow tract pacing shortened the QRS duration, it did not consistently improve quality of life compared with right ventricular apical pacing at the short-term follow-up of 3 months.

An important issue with right ventricular outflow tract pacing still remaining unresolved relates to which site in the outflow tract would be preferable. Different ECG patterns are obtained with pacing from the various locations in the outflow tract, but whether any single site is preferred over an-

other, e.g., septal versus free wall sites, heretofore remains largely a moot point. From the studies of ECG patterns of right ventricular outflow tract tachycardia, it has been learnt that the surface ECG, either during spontaneous tachycardias or during pace-mapping, could localize and separate septal from free wall right ventricular outflow tract tachycardias, and tachycardias arising from the right ventricular inflow tract (just above the His bundle) either from the septal or the free wall side.^{78,79} In analogy, the surface ECG could be a useful tool in discerning these alternate pacing sites. With alternate site and biventricular pacing, the surface ECG patterns are becoming extremely important, not only to help select appropriate pacing sites, but even more importantly, to assist ECG evaluation of device and lead function and facilitate troubleshooting during follow-up.⁸⁰

A critical issue with right ventricular outflow tract pacing relates to lead and pace/sense threshold stability over the long-term follow-up. In the study by Victor et al. in 16 patients having permanent right ventricular pacing leads both at the apex and outflow tract, there was no lead dislodgement over a 10-month mean follow-up, while the chronic pacing thresholds were comparable

between the two sites.⁵⁵ According to an interim analysis of the BRIGHT study, testing right ventricular bifocal (apex and outflow) pacing, lead and pacing threshold stability was comparable at both right ventricular sites.⁸¹ In general, the rate of lead dislodgement of permanent active fixation leads in the outflow tract has ranged between 0% and 5%, averaging <1%.⁸¹ Lead stability in the outflow tract has even been confirmed for the heavier and bulkier defibrillating leads, as long as these are active fixation leads.^{82,83}

His Bundle or Right Ventricular Septal Pacing or Bifocal Right Ventricular Pacing

Among the various hypotheses about the mechanisms that may explain the harmful effect of right ventricular apical pacing on left ventricular function, the most plausible hypothesis relates to the ventricular dyssynchrony produced by the altered ventricular depolarization vector incurred by pacing from the right ventricular apex. Thus, restoration of a more physiological depolarization, such as that produced by direct His bundle pacing, might reduce or prevent ventricular dyssynchrony and its consequent ventricular dysfunction. Although interest in His bundle pacing has been known for quite some time, due to technical difficulties in applying such pacing relating to lead positioning, reliable capture, and long-term stability, there is a dearth of clinical data regarding this pacing approach^{73–75} (Table IV). Furthermore, the need for an intact bundle branch conduction system may be a limiting factor in obtaining benefit from His bundle pacing. A significant improvement in left ventricular performance was reported in 12 patients with a narrow QRS, chronic atrial fibrillation, and reduced ejection fraction (<40%), when permanent direct His bundle pacing could be effected.⁷⁴ Subsequently, the same investigators were successful in applying this pacing technique in 39 of 54 patients with cardiomyopathy, low ejection fraction (mean 23%), persistent atrial fibrillation, and normal QRS (<120 ms). After a mean follow-up of 42 months, 29 patients were alive with improved symptoms and ejection fraction (mean 33%).⁷⁵ However, it is not clear whether this improvement could be ascribed more to rate control and rhythm regularity provided by pacing, than to pacing site. Another approach closely related to His bundle pacing is right ventricular septal pacing.

In an acute study of 14 patients receiving a dual-chamber pacemaker for complete heart block, the septum was mapped to provide the narrowest QRS.⁵⁶ The reduction of QRS duration obtained with right ventricular septal pacing correlated with homogenization of left ventricular contrac-

tion and improved systolic performance, albeit with minor differences in ejection fraction. In 12 patients with atrial fibrillation undergoing His bundle ablation, right ventricular septal pacing was compared with apical pacing in a randomized crossover design. Septal pacing resulted in a narrower QRS and better systolic performance with greater fractional shortening and higher resting ejection fraction.⁵³

Bifocal right ventricular (apical and outflow tract) pacing has been proposed for patients with heart failure where the coronary sinus approach to effect biventricular pacing turns out to be unsuccessful due to various reasons, such as failure to cannulate the os or to advance the lead, absence of a suitable venous tributary to place the lead, phrenic nerve stimulation, or failure to pace or sense due to scarred tissue. The long-term (over a 22-month period) clinical response of 22 patients undergoing this approach has been favorable with ensuing clinical improvement⁸⁴ (Table IV). Similar results were reported for 39 patients having NYHA class III symptoms of heart failure requiring permanent cardiac pacing for atrioventricular block.⁸⁵ In a subset of 50 patients with NYHA class II-III symptoms in the ROVA study, there was partial improvement reported with right ventricular bifocal pacing.⁶⁵ The clinical improvement conferred by biventricular pacing in 44 patients was matched by a system of bifocal right ventricular pacing in a small group of 6 patients.⁸⁶ More data about the usefulness of bifocal right ventricular pacing will be provided by the ongoing, randomized, single-blind, crossover study (BRIGHT), which is recruiting patients with NYHA class III heart failure, a left ventricular ejection fraction <35%, LBBB, and QRS complex ≥ 120 ms⁸¹ (Table V).

A modified approach to bifocal pacing, performed at the right ventricular apex and at the roof of the interventricular septum, was applied in 25 patients with heart failure, dilated cardiomyopathy, LBBB, and mitral regurgitation.⁸⁷ At 18 months of follow-up, bifocal right ventricular pacing significantly shortened the QRS duration, reduced mitral regurgitation, improved hemodynamics and quality of life in heart failure patients, by producing ventricular resynchronization by shortening both inter- and intraventricular conduction delays.

Biventricular or Left Ventricular Pacing

A few studies have compared right ventricular apical pacing with left ventricular or biventricular pacing, which has now become the standard method to apply cardiac resynchronization therapy in patients with refractory heart failure (Table III). Of these, four studies examined the

acute effects of right ventricular and biventricular or left ventricular pacing.^{32,46,60-61} In 27 patients with severe refractory heart failure and either first-degree atrioventricular block and/or intraventricular conduction delay, both left ventricular pacing alone and biventricular pacing resulted in significant acute improvement of hemodynamic parameters compared with measurements at baseline and during right ventricular pacing alone.⁴⁶ In 33 patients with heart failure receiving cardiac resynchronization therapy, acute hemodynamic changes were assessed with tissue Doppler imaging, which was performed after the implant procedure when the pacemaker device was randomized to biventricular, right ventricular apical, and no pacing modes.⁶¹ Only biventricular, but not right ventricular pacing, improved systolic function, reduced mitral regurgitation and left ventricular size, and corrected systolic asynchrony. The third study has been mentioned earlier and involved measurement of both hemodynamic parameters and sympathetic nerve activity in 13 patients with a mean left ventricular ejection fraction of 28%.³² Measurements were made during 3 minutes of atrioventricular pacing in the right ventricular, left ventricular, and biventricular pacing modes. The study showed that left ventricular-based pacing resulted in improved hemodynamics and a decrease in sympathetic nerve activity compared with right ventricular pacing in patients with left ventricular dysfunction regardless of the QRS complex duration. Another acute study involved 18 heart failure patients with conduction delay getting catheterized.⁶⁰ Left ventricular pacing via a coronary sinus catheter enhanced systolic pressures and improved left ventricular systolic function slightly more than biventricular pacing, but to a significantly greater degree than right ventricular apical or septal pacing.

Another three studies have compared the chronic effects of biventricular and right-univentricular pacing in patients with heart failure and/or chronic atrial fibrillation⁶²⁻⁶⁴ (Table III). In 20 such patients having chronic right ventricular pacing, of at least 6 months' duration, after atrioventricular junction ablation performed for permanent atrial fibrillation, the pacemakers were upgraded to biventricular pacing systems.⁶³ Evaluation was completed before and at 3 to 6 months after the upgrading procedure. The NYHA functional classification improved by 29%, the left ventricular ejection fraction increased by 44%, the left ventricular diastolic diameter decreased by 6.5%, and the end-systolic diameter decreased by 8.5% (all $P < 0.01$). The number of hospitalizations decreased by 81% and the quality of life improved by 33% after biventricular pacing compared with right ventricular pacing alone. A single-blind, randomized,

controlled, crossover study compared the clinical parameters of 59 patients with heart failure and chronic atrial fibrillation, as monitored during 3-month treatment periods of conventional right ventricular versus biventricular pacing.⁶² Due to a high drop-out rate, only 37 patients completed both crossover phases. In the patients with effective therapy, the mean 6-minute walked distance increased by 9% with biventricular pacing, the peak oxygen uptake increased by 13%, and hospitalizations decreased by 70%, while 85% of the patients preferred the biventricular pacing period (all $P \leq 0.05$). In another recent study, 56 patients with advanced heart failure, left ventricular dysfunction with a mean left ventricular ejection fraction of 25%, and left ventricular dyssynchrony, were randomized to either right ventricular pacing or biventricular pacing for 3 months, and 44 of these patients were then crossed over for an additional 3 months.⁶⁴ Of the 44 patients who crossed over to the other pacing mode, 21 were in sinus rhythm and 23 were in permanent atrial fibrillation. Overall, patients treated with biventricular pacing had significantly greater improvement in QRS duration, 6-minute walk test, and quality-of-life scores compared to right ventricular pacing therapy. During the initial crossover period, significantly more patients treated with right ventricular pacing required rehospitalization than did patients treated with biventricular pacing (81% vs 19%, respectively).

In patients undergoing atrioventricular nodal ablation for chronic atrial fibrillation, the PAVE trial evaluated the benefits of biventricular pacing over right ventricular apical pacing.⁶⁷ In this study (peer review publication pending), a total of 252 patients were randomized in a 2:1 fashion to either ablation plus biventricular pacing ($n = 146$) or ablation plus right ventricular pacing ($n = 106$). The primary endpoint was exercise capacity as measured by the 6-minute hall walk test, with secondary endpoints of functional capacity as measured by peak VO_2 , exercise duration, and quality-of-life score. Device implantation was unsuccessful in 21 patients in the biventricular group vs 0 patients in the right ventricular pacing group. Death occurred in 6 and 10 patients, respectively, finally leaving for analysis 82 patients in the biventricular group and 102 patients in the right ventricular group. From baseline to 3 months, both groups showed an improvement in hall walk exercise capacity, but after 3 months, only patients in the biventricular group maintained their functional capacity. The latter group also experienced significant improvement in peak VO_2 and exercise duration between 6 weeks and 6 months. Left ventricular ejection fraction remained stable (at 46%) in patients with biventricular pacing, while it

significantly declined in the right ventricular pacing group over 6 months (from 45% to 41%).

Subanalysis of the PAVE study results indicated that the benefit of biventricular pacing was mainly noted in patients with baseline left ventricular systolic dysfunction (ejection fraction <45%) or patients with NYHA class II or III heart failure.⁶⁸ Patients in NYHA class I or normal left ventricular function did not have a similar benefit with biventricular pacing. There was, however, a worrisome trend toward worsened functional status at 6 months in those patients with normal left ventricular function randomized to right ventricular apical pacing. Furthermore, patients randomized to biventricular pacing demonstrated preservation or improvement in ejection fraction, whereas right ventricular pacing patients showed a modest decrease in ejection fraction. Quality of life was improved in all patients regardless of baseline functional status, ejection fraction, or randomization. Thus, in patients with chronic atrial fibrillation undergoing atrioventricular nodal ablation, there is now compelling evidence that biventricular pacing can be of benefit, particularly in patients with either poor baseline ejection fraction or poor clinical functional status. In patients with preserved left ventricular function, there remains concern about the possible adverse effects of the long-term mechanical dyssynchrony caused by right ventricular apical pacing. Of course, we are in dire need of further studies, as there remain important questions relating to whether this dyssynchrony is produced by adverse remodeling, which might be reversible or preventable by biventricular pacing, what the time course of this phenomenon might be, and why some patients with chronic right ventricular apical pacing appear to do well over the long term without a decrease in right ventricular function.^{45,68}

Exclusive Left Ventricular Pacing

As alluded to earlier, right ventricular apical pacing may not be necessary even for patients receiving biventricular pacing. Preliminary data have indicated that there were no significant differences between single-site left ventricular pacing and biventricular pacing for cardiac resynchronization therapy, suggesting that right ventricular pacing may be redundant and left ventricular pacing alone might suffice.¹⁶ Acute hemodynamic measurements in 27 patients with heart failure having an epicardial left ventricular lead indicated that left ventricular pacing alone was superior to right ventricular pacing, but also to biventricular pacing as well.⁸⁸ In another acute hemodynamic study in 18 heart failure patients with conduction delay getting catheterized,

left ventricular pacing yielded the best hemodynamic response compared to both right ventricular pacing and biventricular pacing.⁶⁰ Similar acute hemodynamic benefit could be derived from temporary left ventricular pacing in 10 patients with heart failure and pulmonary wedge pressure >15 mmHg, compared with 10 heart failure patients but with normal wedge pressure.⁸⁹ Experiments in dogs investigating the hemodynamic effects of pacing at various right and left ventricular sites indicated that the left ventricular pump function was maintained best when pacing at the left ventricular septum or apex, possibly because pacing from these sites, where the impulses exit the Purkinje system, created a physiological propagation of electrical conduction.⁹⁰ In another study involving 11 healthy dogs and 8 children, left ventricular apical pacing, rather than right ventricular apical pacing, was associated with superior hemodynamic performance and designated as the optimal site for pediatric pacing.⁹¹ The results of a 6-month follow-up of permanent left ventricular pacing have been reported in 18 patients and compared with those in 15 patients receiving biventricular pacing.⁹² The two pacing modes (left ventricular and biventricular) were associated with almost equivalent improvement of symptoms and parameters of left ventricular performance. Similarly, at 12 months, 22 patients with severe heart failure and LBBB, receiving left univentricular pacing, had significant benefit in exercise tolerance and left ventricular function.⁹³ The clinical efficacy of single-site left ventricular pacing was assessed in 86 patients with heart failure.⁹⁴ Left ventricular pacing significantly improved exercise tolerance and quality of life, particularly in those patients with a QRS interval over 150 ms. However, in a study of 13 patients with chronic atrial fibrillation and severe heart failure who had His bundle ablation, chronic biventricular pacing provided better hemodynamic performance than left ventricular pacing.⁹⁵ The authors ascribed the inferior performance of left ventricular pacing to the interventricular dyssynchronization induced by left ventricular pacing. Studies have been planned to test the relative merits of left ventricular pacing alone versus biventricular pacing (BELIEVE, OPSITE).¹⁶ Indeed, OPSITE, a prospective randomized trial, compared, in a single-blind, 3-month cross-over design, right ventricular and left ventricular pacing (phase 1) and right ventricular and biventricular pacing (phase 2).⁶⁶ The study was performed in 56 patients affected by severely symptomatic permanent atrial fibrillation, uncontrolled ventricular rate, or heart failure. Primary endpoints were quality of life and exercise capacity, which were modestly improved mainly by biventricular, rather than left ventricular, pacing.

Triventricular Pacing

In heart failure patients not responding to biventricular pacing, a novel approach has been proposed: that of pacing from the right ventricular apex and outflow tract in conjunction with lateral left ventricular pacing. In a recent preliminary report of 13 patients receiving this type of triventricular pacing, the QRS duration shortened considerably and all the hemodynamic parameters significantly improved.⁹⁶

Resynchronization

It appears that mechanical resynchronization may actually be more important than electrical resynchronization,⁹⁷ whatever the means used to achieve this mechanical synchrony, be it left ventricular pacing alone, the classical biventricular pacing, nonapical right ventricular pacing, bifocal right ventricular pacing, or trifocal ventricular pacing. It is thus possible in the future that we could altogether abandon right ventricular apical pacing, at least as stand-alone pacing, as being obsolete or potentially deleterious for all groups of patients, with or without left ventricular dysfunction or structural heart disease. This notwithstanding, we will certainly need more data from future studies in order to implement such a course, as there is still evidence that some patients tolerate right ventricular apical pacing well,⁴⁵ while others do so poorly, as has amply been shown in this review.

From the studies on cardiac resynchronization therapy there is now evidence that biventricular pacing may lead to reversal of some of the chronic deleterious effects of ventricular dyssynchrony.⁹⁸⁻¹⁰⁰ Studies using Doppler echocardiograms and tissue Doppler imaging techniques have shown that cardiac resynchronization significantly improved left ventricular function and reversed left ventricular remodeling during long-term follow-up.^{35,98-100} Whether this can be achieved with other alternate site pacing methods remains to be elucidated in future studies.

Clinical Implications

The adverse hemodynamic effects of *spontaneous LBBB* may be profound.¹⁻¹⁰ There is asynchronous myocardial activation that may trigger ventricular remodeling. This ventricular desynchronization can lead to both systolic and diastolic left ventricular dysfunction and the development or worsening of heart failure symptoms. In the presence of LBBB, reversible myocardial perfusion defects have been demonstrated on radionuclide scintigraphy in the absence of significant coronary artery disease. Some patients with intermittent LBBB may develop angina concur-

rently with the onset of LBBB; whether this is due to the development of myocardial ischemia or ventricular asynergy is not clear. In patients with dilated cardiomyopathy, LBBB is accompanied by progressive left ventricular dilation and mitral regurgitation and shortening of left ventricular filling time.⁴ Whether LBBB is the cause or a consequence of left ventricular dilation is not always clear. Patients with dilated cardiomyopathy with LBBB compared with those without LBBB, are more likely to have nonischemic etiology, profound left ventricular dilation, lower left ventricular ejection fraction, increased symptomatology, and reduced survival.⁸ The presence of LBBB generally conveys poor prognosis.^{1,2,9,10} Restoring left ventricular synchrony with cardiac resynchronization therapy has been demonstrated to have a significant impact on patients' symptomatology and clinical course, and most probably on their survival.²¹⁻²⁵

Although the deleterious effects of spontaneous LBBB have been well described, it is only recently that we have started becoming aware of similar harm caused by the *iatrogenic LBBB*, which is produced by right ventricular apical pacing in patients with conventional permanent pacemakers. The harm incurred by such type of pacing may more specifically relate to the *abnormal axis* conferred by apical pacing rather the LBBB per se. It appears critically important in understanding the difference between a normal axis of depolarization one sees with right ventricular outflow tract pacing and the reversal of the normal axis of depolarization and anisotropic conduction one gets with right ventricular apical pacing. This may explain in part the evidence that right ventricular outflow tract or His bundle or septal pacing may be more advantageous than apical pacing. Indeed, there is evidence that the His-Purkinje fibers may be used for propagation during right ventricular outflow pacing resulting in narrower QRS compared with right ventricular apical pacing.¹⁰¹

Normal activation of the myocardium during sinus rhythm both in the septum and in the right and left ventricular free wall occurs mainly from apex to base and from endocardium to epicardium.¹⁰² The importance of normal electrical activation of the ventricle for optimal pump function has been known for years, but only recently did it generate broader interest. It has thus been recognized that in addition to atrioventricular synchrony, a proper sequence of activation is equally important. Several studies using single-chamber pacing and virtually all studies using atrioventricular sequential pacing showed a significant influence of the site of pacing on hemodynamic performance. While ventricular pacing at any site may have an adverse effect on pump

function, many studies showed that right ventricular apical pacing resulted in the most pronounced deleterious effect. Not only are the acute disturbances in pump function important, but the myocardial changes occurring during chronic ventricular pacing, as outlined above, may be more worrisome. The combination of reduced pump function and long-term maladaptive changes could account for higher morbidity and mortality in patients with chronic right ventricular apex pacing compared with atrial pacing. Therefore, investigators are exploring alternative sites for pacing.

His bundle pacing has been shown to result in the same QRS duration and pressure development as sinus rhythm and atrial pacing and better hemodynamics than right ventricular apex pacing. Right ventricular outflow tract or bifocal (apex and outflow tract) pacing may synchronize contraction and improve pump function, although QRS duration and configuration is still abnormal as compared to atrial pacing. Left ventricular pacing sites become increasingly useful, especially since newly developed leads and delivery systems facilitate this transcatheter venous approach. Left ventricular function is consistently better when pacing left ventricular sites than when pacing right ventricular sites.

Among all left ventricular pacing sites, the left ventricular apex generally results in the best maintenance of pump function at least in normal animal hearts.^{90,102} However, the better left ventricular function during left ventricular pacing is not associated with shorter QRS duration. With biventricular pacing, QRS duration is reduced but left ventricular function may not improve. However, multisite pacing (left ventricular apex in combination with the right ventricular apex and outflow tract or in combination with right ventricular apex, outflow tract, and left ventricular base) slightly increases cardiac output compared to left ventricular apex pacing alone. All these data concern animal hearts with an intact ventricular conduction system.¹⁰² It is important to note that, even though left ventricular pacing results in better pump function than right ventricular pacing, long-term left ventricular pacing, similar to chronic right ventricular pacing, may still cause structural abnormalities, which at 6 months may still be reversible.

The electrical impulse is conducted approximately four times slower in the normal myocardium than in the Purkinje system. Due to this delayed myocardial conduction, ventricular pacing often leads to lengthening of QRS duration as compared to sinus rhythm. Generally, QRS duration is less prolonged during right ventricular apex than during left ventricular lateral wall pacing. To

avoid the abnormal activation during ventricular pacing, pacing in or close to the rapid conduction system has been suggested. Indeed, several animal studies showed reduced QRS duration when pacing in the high ventricular septum as compared to right ventricular apex pacing. Shortest QRS durations and normal QRS configurations occur during pacing in the His bundle. An alternative to the technically difficult His-bundle pacing is to pace at multiple sites. Pacing at two or three sites, more or less opposite to each other, reduces QRS duration by no more than 20% as compared with single-site pacing. This limited reduction is probably explained by the fact that at each pacing site, the initial impulse conduction still occurs through the slow muscular conduction. Some studies reported a correlation between QRS duration and systolic left ventricular function, but such correlation was absent in other studies. A possible explanation for the inconsistent correlation between QRS duration and left ventricular function is that QRS duration is a measure of the duration of activation of both the right and left ventricle. This is further supported by the finding that left ventricular function correlates better with the duration of left ventricular endocardial activation than with QRS duration.

Abnormal electrical activation of the ventricles, induced by right ventricular apical pacing or conduction disturbances (LBBB), has strong implications for hemodynamic performance. During both LBBB and right ventricular apical pacing, the activation sequence deviates significantly from the physiological sequence and is associated with a significant decline in left ventricular function. Pacing at alternative sites, like right ventricular septum or outflow tract, left ventricle, or multiple sites, causes less pronounced decreases in left ventricular function in hearts with intact conduction system and improves left ventricular function in hearts with LBBB. However, pacing at various ventricular sites used until now, except the His bundle, results in a ventricular activation sequence different from sinus rhythm. Hence, the search for pacing site(s), leading to more physiological activation sequence and optimal pump function of the ventricles will continue.¹⁰²

Taking into account all the evidence presented herein about the harmful effects of the iatrogenic LBBB, we need to reconsider our approach to conventional right ventricular apical pacing. First, for those patients already having conventional pacing systems, particularly in the presence of left ventricular dysfunction or heart failure, pacemaker programming should be employed to minimize right ventricular pacing. This can be accomplished in patients with sinus node dysfunction but with normal atrioventricular conduction, by

establishing functional AAIR pacing with use of the DDDR mode with a long atrioventricular delay (≥ 250 ms). However, many a time this is not consistently feasible and it remains an inefficient way to reduce ventricular pacing in at least 17–32% of patients even when the longest fixed atrioventricular delay is programmed for.^{43,103} Manufacturers need to redesign their pacemakers to make such programming feasible or have the pacemakers search for atrioventricular conduction and withhold unnecessary ventricular pacing; automatic mode switching from AAIR to DDDR and vice versa would be desirable. Indeed, newly designed pacemaker models are emerging, which bear algorithms that drastically curtail the amount of ventricular pacing.^{104–107} As regards patients with permanent atrioventricular block, we need to act now and use alternate sites of pacing for those receiving new pacing systems. For those patients who already have an implanted conventional pacemaker, either a dual-chamber pacing system in the presence of sinus rhythm or a single-chamber system in cases of permanent atrial fibrillation, we should seriously consider upgrading them to biventricular systems if moderate or severe left ventricular dysfunction is present.^{35,63} This appears feasible and safe in the majority of patients.¹⁰⁸ In select cases, there is indication that even right ventricular outflow tract pacing alone or in combination with right ventricular apical pacing (bifocal pacing) may be hemodynamically more advantageous than right ventricular apical pacing^{77,84}; the technical means to effect such an approach are improving and may be more time- and cost-efficient than left ventricular pacing. Further studies are needed to assess the merits of such an approach. However, a better preventive approach to cardiac desynchronization than secondary prevention applied in patients with heart failure who already have manifest left ventricular dyssynchrony, is always primary prevention in selected or even in all patients requiring continuous ventricular pacing. This can only be effected with a priori use of alternate sites for ventricular pacing. However, which alternate site constitutes the optimal pacing site still remains elusive. Again, for patients with sinus node dysfunction or transient atrioventricular block, pacemakers with ventricular pacing

reduction algorithms might offer a tangible benefit to many patients.^{104–107}

Conclusion

A significant percentage of heart failure patients, ranging from 20% to 30% or higher, are afflicted by cardiac dyssynchrony as reflected by prolongation of the QRS complex, mostly in the form of LBBB. Those with refractory heart failure despite optimized medical treatment, estimated to represent about 10–15% of heart failure patients, are candidates for cardiac resynchronization therapy with biventricular or left ventricular pacing. Many studies have confirmed a significant hemodynamic and clinical improvement conferred by cardiac resynchronization in these patients. However, it is only recently that we have come to realize that not only spontaneous permanent LBBB is harmful to our patients, but the iatrogenic LBBB, produced by right ventricular apical pacing during conventional permanent pacing, is also deleterious to our patients. The evidence presented herein is compelling and it cannot be ignored; it may dictate a change of attitude toward right ventricular pacing directing our attention to alternate sites of pacing, such as the left ventricle and/or the right ventricular outflow tract. Technical advances have already raised the success rate of implantation of the left ventricular lead via the coronary sinus branches to >90% in heart failure patients, while newer technology is on the horizon facilitating the implantation of active fixation leads in selective sites at the right ventricular outflow tract. The recently emerging data from the DAVID trial, the MADIT II substudy, and several recent reports discussed in this review, are quite alarming and disconcerting about our long-standing practice of producing an iatrogenic LBBB in our patients, especially when we are considering heart failure patients, and when we have already become abundantly aware and fully cognizant of the harmful effects of the spontaneous LBBB! All these data have recently spawned investigation with a strong interest and new surge in seeking nonconventional approaches to cardiac pacing with methods and techniques that aim at avoiding unnecessary ventricular pacing and employing alternate site pacing.

References

- Baldasseroni S, Opasich C, Gorini M, et al. Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: A report from the Italian Network on Congestive Heart Failure. *Am Heart J* 2002; 143:398–405.
- Shamim W, Francis DP, Yousufuddin M, et al. Intraventricular conduction delay: A prognostic marker in chronic heart failure. *Int J Cardiol* 1999; 70:171–178.
- Grines CL, Bashore TM, Boudoulas H, et al. Functional abnormalities in isolated left bundle-branch block. The effect of interventricular asynchrony. *Circulation* 1989; 79:845–853.
- Xiao HB, Lee CH, Gibson DG. Effect of left bundle-branch block on diastolic function in dilated cardiomyopathy. *Br Heart J* 1991; 66:443–447.
- Xiao HB, Roy C, Fujimoto S, et al. Natural history of abnormal conduction and its relation to prognosis in patients with dilated cardiomyopathy. *Int J Cardiol* 1996; 53:163–170.
- Ozdemir K, Altunkeser BB, Danis G, et al. Effect of the isolated left bundle branch block on systolic and diastolic functions of left ventricle. *J Am Soc Echocardiogr* 2001; 14:1075–1079.
- Lee SJ, McCulloch C, Mangat I, Foster E, De Marco T, Saxon LA.

HARM FROM RIGHT VENTRICULAR APICAL PACING

- Isolated bundle branch block and left ventricular dysfunction. *J Card Fail* 2003; 9:87–92.
8. Littman L, Symanski JD. Hemodynamic implications of left bundle branch block. *J Electrocardiol* 2000; 33(Suppl.):115–121.
 9. Shenkman HJ, Pampati V, Khandelwal AK, et al. Congestive heart failure and QRS duration: Establishing prognosis study. *Chest* 2002; 122:528–534.
 10. Hesse B, Diaz LA, Snader CE, et al. Complete bundle branch block as an independent predictor of all-cause mortality: Report of 7,073 patients referred for nuclear exercise testing. *Am J Med* 2001; 110:253–259.
 11. Daubert JC, Ritter P, Le Breton H, et al. Permanent left ventricular pacing with transvenous leads inserted into the coronary veins. *Pacing Clin Electrophysiol* 1998; 21:239–245.
 12. Cazeau S, Leclercq C, Lavergne T, et al. for the MUSTIC Study Investigators. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001; 344:873–880.
 13. Abraham WT, Fisher WG, Smith AL, et al. for the MIRACLE study group. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002; 346:1845–1853.
 14. Gerber TC, Nishimura RA, Holmes DR, et al. Left ventricular and biventricular pacing in congestive heart failure. *Mayo Clin Proc* 2001; 76:803–812.
 15. Young JB, Abraham WT, Smith AL, et al. for the MIRACLE ICD Trial Investigators. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure. The MIRACLE ICD Trial. *JAMA* 2003; 289:2685–2694.
 16. Leclercq C, Kass DA. Retiming the failing heart: Principles and current clinical status of cardiac resynchronization. *J Am Coll Cardiol* 2002; 39:194–201.
 17. Linde C, Leclercq C, Rex S, et al. (MUSTIC Study Group). Long-term benefits of biventricular pacing in congestive heart failure: Results from the Multisite Stimulation In Cardiomyopathy (MUSTIC) Study. *J Am Coll Cardiol* 2002; 40:111–118.
 18. Linde C, Braunschweig F, Gadler F, Bailleul C, Daubert J-C. Long-term improvement in quality of life by biventricular pacing in patients with chronic heart failure: Results from the MUSTIC study. *Am J Cardiol* 2003; 91:1090–1095.
 19. Puererfellner H, Nesser HJ, Winter S, et al. for the EASYTRAK Clinical Investigation Study Group and the European EASYTRAK Registry. Transvenous left ventricular lead implantation with the EASYTRAK lead system: The European experience. *Am J Cardiol* 2000; 86:157K–164K.
 20. Alonso C, Leclercq C, Revault d'Allonnes F, et al. Six year experience of transvenous left ventricular lead implantation for permanent biventricular pacing in patients with advanced heart failure: Technical aspects. *Heart* 2001; 86:405–410.
 21. Manolis AS. Cardiac resynchronization therapy in congestive heart failure: Ready for prime time? *Heart Rhythm* 2004; 1:355–363.
 22. Bradley DJ, Bradley EA, Baughman KL, et al. Cardiac resynchronization and death from progressive heart failure. A meta-analysis of randomized controlled studies. *JAMA* 2003; 289:730–740.
 23. Bristow MR, Saxon LA, Boehmer J, et al., for the COMPANION Investigators. Cardiac resynchronization therapy with or without implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004; 350:2140–2150.
 24. McAllister FA, Ezekowitz JA, Wiebe N, et al. Systematic review: Cardiac resynchronization in patients with symptomatic heart failure. *Ann Intern Med* 2004; 141:381–390.
 25. Cleland JGF, Daubert J-C, Erdmann E, et al., for the CARE-HF Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005; 352:1539–1549.
 26. Tanabe A, Mohri T, Ohga M, et al. The effects of pacing-induced left bundle branch block on left ventricular systolic and diastolic performances. *Jpn Heart J* 1990; 31:309–317.
 27. Modena MG, Mattioli AV, Mattioli G. Right ventricular pacing and left ventricular filling pattern: An echo-Doppler study. *Chest* 1991; 100:744–747.
 28. Tantengco MVT, Thomas RL, Karpawich PP. Left ventricular dysfunction after long-term right ventricular apical pacing in the young. *J Am Coll Cardiol* 2001; 37:2093.
 29. Karpawich PP, Rabah R, Haas JE. Altered cardiac histology following apical right ventricular pacing in patients with congenital atrioventricular block. *Pacing Clin Electrophysiol* 1999; 22:1372–1377.
 30. Thambo J-B, Bordachar P, Garrigue S, et al. Detrimental ventricular remodeling in patients with congenital complete heart block and chronic right ventricular apical pacing. *Circulation* 2004; 110:3766–3772.
 31. Tse H-F, Yu C, Wong K-K, et al. Functional abnormalities with permanent right ventricular pacing. *J Am Coll Cardiol* 2002; 40:1451–1458.
 32. Hamdan MH, Zagrodzky JD, Joglar JA, et al. Biventricular pacing decreases sympathetic activity compared with right ventricular pacing in patients with depressed ejection fraction. *Circulation* 2000; 102:1027–1032.
 33. Nunez A, Alberca MT, Cosio FG, et al. Severe mitral regurgitation with right ventricular pacing, successfully treated with left ventricular pacing. *Pacing Clin Electrophysiol* 2002; 25:226–230.
 34. de Cock CC, van Campen LMC, Kamp O, Visser CA. Pacing-induced left ventricular dysfunction: Relationship with coronary perfusion. *Europace* 1999; 1:146–148.
 35. Erol-Yilmaz A, Tukkie R, Schrama TAM, Romkes HJ, Wilde AAM. Reversed remodeling of dilated left sided cardiomyopathy after upgrading from VVIR to VVIR biventricular pacing. *Europace* 2002; 4:445–449.
 36. The DAVID Trial Investigators. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: The dual chamber and VVI implantable defibrillator (DAVID) trial. *JAMA* 2002; 285:3115–3123.
 37. Moss AJ. Findings from MADIT II substudies. *Eur Heart J* 2003; 5(Suppl. I):134–138.
 38. Steinberg JS, Fischer A, Wang P, et al., for the MADIT II Investigators. The clinical implications of cumulative right ventricular pacing in the multicenter automatic defibrillator trial II. *J Cardiovasc Electrophysiol* 2005; 16:359–365.
 39. Wonisch M, Lercher P, Scherr D, et al. Influence of permanent right ventricular pacing on cardiorespiratory exercise parameters in chronic heart failure patients with implanted cardioverter defibrillators. *Chest* 2005; 127:787–793.
 40. Thackray SDR, Witte KKA, Nikitin NP, Clark AL, Kaye GC, Cleland JGF. The prevalence of heart failure and asymptomatic left ventricular dysfunction in a typical regional pacemaker population. *Eur Heart J* 2003; 24:1143–1152.
 41. Sweeney MO, Hellkamp AS, Ellenbogen KA, et al. for the MOST Investigators. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation* 2003; 107:2932–2937.
 42. Shukla HH, Hellkamp AS, James EA, et al., on behalf of the MOST Investigators. Heart failure hospitalization is more common in pacemaker patients with sinus node dysfunction and a prolonged paced QRS duration. *Heart Rhythm* 2005; 2:245–251.
 43. Nielsen JC, Kristensen L, Andersen HR, Mortensen PT, Pedersen OL, Pedersen AK. A randomized comparison of atrial and dual-chamber pacing in 177 consecutive patients with sick sinus syndrome. *J Am Coll Cardiol* 2003; 42:614–623.
 44. O'Keefe JH, Abuissa H, Jones PG, et al. Effect of chronic right ventricular apical pacing on left ventricular function. *Am J Cardiol* 2005; 95:771–773.
 45. Ueng K-C, Tsai T-P, Tsai C-F, et al. Acute and long-term effects of atrioventricular junction ablation and VVIR pacemaker in symptomatic patients with chronic lone atrial fibrillation and normal ventricular response. *J Cardiovasc Electrophysiol* 2001; 12:303–309.
 46. Blanc J-J, Etienne Y, Gilard M, et al. Evaluation of different ventricular pacing sites in patients with severe heart failure: Results of an acute hemodynamic study. *Circulation* 1997; 96:3273–3277.
 47. De Cock CC, Giudici MC, Twisk JW. Comparison of the hemodynamic effects of right ventricular outflow-tract pacing with right ventricular apex pacing: A quantitative review. *Europace* 2003; 5:275–278.
 48. Cowell R, Morris-Thurgood J, Ilesley C. Septal short atrioventricular delay pacing: Additional hemodynamic improvements in heart failure. *Pacing Clin Electrophysiol* 1994; 17(Pt II):1980–1983.
 49. Giudici MC, Thornburg GA, Buck DL, et al. Comparison of right ventricular outflow tract and apical lead permanent pacing on cardiac output. *Am J Cardiol* 1997; 79:209–212.
 50. Buckingham TA, Candinas R, Schlaepfer J, et al. Acute hemodynamic effects of atrioventricular pacing at different sites in the right ventricle individually and simultaneously. *Pacing Clin Electrophysiol* 1997; 20(Pt I):909–915.
 51. Karpawich PP, Mital S. Comparative left ventricular function

- following atrial, septal, and apical single chamber heart pacing in the young. *Pacing Clin Electrophysiol* 1997; 20(Pt I):1983–1988.
52. De Cock CC, Meyer A, Kamp O, Visser CA. Hemodynamic benefits of right ventricular outflow tract pacing: Comparison with right ventricular apex pacing. *Pacing Clin Electrophysiol* 1998; 21:536–541.
 53. Mera F, DeLurgio DB, Patterson RE, Merlino JD, Wade ME, Leon AR. A comparison of ventricular function during high right ventricular septal and apical pacing after His-bundle ablation for refractory atrial fibrillation. *Pacing Clin Electrophysiol* 1999; 22:1234–1239.
 54. Buckingham TA, Candinas R, Attenhofer C, et al. Systolic and diastolic function with alternate and combined site pacing in the right ventricle. *Pacing Clin Electrophysiol* 1998; 21:1077–1084.
 55. Victor F, Leclercq C, Mabo P, et al. Optimal right ventricular pacing site in chronically implanted patients: A prospective randomized crossover comparison of apical and outflow tract pacing. *J Am Coll Cardiol* 1999; 33:311–316.
 56. Schwaab B, Froehlig G, Alexander C, et al. Influence of right ventricular stimulation site on left ventricular function in atrial synchronous ventricular pacing. *J Am Coll Cardiol* 1999; 33:317–323.
 57. Kolettis TM, Kyriakides ZS, Tsiapras D, Popov T, Paraskevaides IA, Kremastinos DT. Improved left ventricular relaxation during short-term right ventricular outflow tract compared to apical pacing. *Chest* 2000; 117:60–64.
 58. Gold MK, Shorofsky SR, Metcalf MD, Feliciano Z, Fisher ML, Gottlieb SS. The acute hemodynamic effects of right ventricular septal pacing in patients with congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1997; 79:179–681.
 59. Bourke JP, Hawkins T, Keavey P, et al. Evolution of ventricular function during permanent pacing from either right ventricular apex or outflow tract following AV-junctional ablation for atrial fibrillation. *Europace* 2002; 4:219–228.
 60. Kass DA, Chen CH, Curry C, et al. Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. *Circulation* 1999; 99:1567–1573.
 61. Yu C-M, Lin H, Fung W-H, Zhang Q, Kong S-L, Sanderson JE. Comparison of acute changes in left ventricular volume, systolic and diastolic functions, and intraventricular synchronicity after biventricular and right ventricular pacing for heart failure. *Am Heart J* 2003; 145:e23 (G1–G7).
 62. Leclercq C, Walker S, Linde C, et al. on behalf of the MUSTIC study group. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. *Eur Heart J* 2002; 23:1780–1787.
 63. Leon AR, Greenberg JM, Kanuru N, et al. Cardiac resynchronization in patients with congestive heart failure and chronic atrial fibrillation: Effect of upgrading to biventricular pacing after chronic right ventricular pacing. *J Am Coll Cardiol* 2002; 39:1258–1263.
 64. Leclercq C, Cazeau S, Lellouche D, et al. Upgrading from right ventricular pacing to biventricular pacing in previously paced patients with advanced heart failure: A randomized controlled study. Presented at the European Society of Cardiology Congress 2003; August 30–September 3, 2003; Vienna, Austria. Abstract 1965.
 65. Stambler BS, Ellenbogen KA, Zhang X, et al. Right ventricular outflow versus apical pacing in pacemaker patients with congestive heart failure and atrial fibrillation. *J Cardiovasc Electrophysiol* 2003; 14:1180–1186.
 66. Brignole M, Gammage M, Puggioni E, et al., on behalf of the Optimal Pacing Site (OPSITE) Study Investigators. Comparative assessment of right, left, and biventricular pacing in patients with permanent atrial fibrillation. *Eur Heart J* 2005; 26:712–722.
 67. PAVE Trial. American College of Cardiology Annual Scientific Session, March 2004.
 68. Daoud E, Doshi R, Fellows C, et al. Ablate and pace with cardiac resynchronization therapy for patients with reduced ejection fraction: Sub-analysis of PAVE study (Abstract 181). *Heart Rhythm* 2004; 1(suppl.):S59.
 69. Jansens JL, Jottrand M, Pneumont N, Stoupe E, de Canniere D. Robotic-enhanced biventricular resynchronization: An alternative to endovenous cardiac resynchronization therapy in chronic heart failure. *Ann Thorac Surg* 2003; 76:413–417.
 70. Valls-Bertault V, Mansourati J, Gilard M, et al. Adverse events with transvenous left ventricular pacing in patients with severe heart failure: Early experience from a single centre. *Europace* 2001; 3:60–63.
 71. Jais P, Takahashi A, Garrigue S, et al. Mid-term follow-up of endocardial biventricular pacing. *Pacing Clin Electrophysiol* 2000; 23(Pt II):1744–1747.
 72. Grosfeld MJW, Res JCJ, Vos DHS, de Boer TJM, Bos HJ. Testing a new mechanism for left interventricular septal pacing: The transeptal route: A feasibility and safety study. *Europace* 2002; 4:439–444.
 73. Amitani S, Miyahara K, Sohara H, et al. Experimental His-bundle pacing: Histopathological and electrophysiological examination. *Pacing Clin Electrophysiol* 1999; 22(Pt I): 562–566.
 74. Deshmukh P, Casavant DA, Romanynshyn M, Anderson K. Permanent, direct His bundle pacing: A novel approach to cardiac pacing in patients with normal His-Purkinje activation. *Circulation* 2000; 101:869–877.
 75. Deshmukh PM, Romanynshyn M. Direct His-bundle pacing: Present and future. *Pacing Clin Electrophysiol* 2004; 27(Pt. II):862–870.
 76. Manolis AS, Sousani E, Simeonidou E, Chiladakis J. Alternate sites of permanent cardiac pacing: A randomized study of novel technology. *Hellenic J Cardiol* 2004; 45:147–151.
 77. Vlay SC. Alternatives when coronary sinus pacing is not possible. *Pacing Clin Electrophysiol* 2003; 26:4–7.
 78. Dixit S, Gerstenfeld EP, Callans DJ, Marchlinski FE. Electrocardiographic patterns of superior right ventricular outflow tract tachycardias: Distinguishing septal and free-wall sites of origin. *J Cardiovasc Electrophysiol* 2003; 14:1–7.
 79. Josephson ME, Callans DJ. Using the twelve-lead electrocardiogram to localize the site of origin of ventricular tachycardia. *Heart Rhythm* 2005; 2:443–446.
 80. Barold SS, Herweg B, Giudici M. Electrocardiographic follow-up of biventricular pacemakers. *Ann Noninvasive Electrocardiol* 2005; 10:231–255.
 81. Res JCJ, Bokern MJJA, Vos DHS. Characteristics of bifocal pacing: Right ventricular apex versus outflow tract: An interim analysis. *PACE* 2005; 28:S36–S38.
 82. Lubinski A, Lewicka-Nowak E, Krolak T, et al. Implantation and follow-up of ICD leads implanted in the right ventricular outflow tract. *Pacing Clin Electrophysiol* 2000; 23(Pt II):1996–1998.
 83. Giudici MC, Barold SS, Paul DL, Schrumph PE, Van Why KJ, Orias DW. Right ventricular outflow tract placement of defibrillation leads: Five year experience. *Pacing Clin Electrophysiol* 2004; 27:443–446.
 84. Vlay SC. Alternate site biventricular pacing: Bi-v in the RV-is there a role? *Pacing Clin Electrophysiol* 2004; 27:567–569.
 85. Pachon JC, Pachon EI, Albormoz RN, et al. Ventricular endocardial right bifocal stimulation in the treatment of severe dilated cardiomyopathy heart failure with wide QRS. *Pacing Clin Electrophysiol* 2001; 24:1349–1376.
 86. O'Donnell D, Nadurata V, Hamer A, Kertes P, Mohammed W. Bifocal right ventricular cardiac resynchronization therapies in patients with unsuccessful percutaneous lateral left ventricular venous access. *Pacing Clin Electrophysiol* 2005; 28:S27–S30.
 87. Zamparelli L, Martiniello AR. Right ventricular bifocal DDD pacing as primary choice for cardiac resynchronization in heart failure patients with severe mitral regurgitation (Abstr). *Heart Rhythm* 2005; 2(Suppl.):S250.
 88. Auricchio A, Stellbrink C, Block M, et al. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. *Circulation* 1999; 99:2993–3001.
 89. Turner MS, Bleasdale RA, Mumford CE, Frenneaux MP, Morris-Thurgood JA. Left ventricular pacing improves haemodynamic variables in patients with heart failure with a normal QRS duration. *Heart* 2004; 90:502–505.
 90. Peschar M, de Swart H, Michels KJ, Reneman RS, Prinzen FW. Left ventricular septal and apex pacing for optimal pump function in canine hearts. *J Am Coll Cardiol* 2003; 41:1218–1226.
 91. Vanagt WY, Verbeek XA, Delhaas T, Mertens L, Daenen WJ, Prinzen FW. The left ventricular apex is the optimal site for pediatric pacing: Correlation with animal experience. *Pacing Clin Electrophysiol* 2004; 27:837–843.
 92. Touiza A, Etienne Y, Gilard M, Fatemi M, Mansourati J, Blanc J-J. Long-term left ventricular pacing: Assessment and comparison with biventricular pacing in patients with severe congestive heart failure. *J Am Coll Cardiol* 2001; 38:1966–1970.

HARM FROM RIGHT VENTRICULAR APICAL PACING

93. Blanc J-J, Bertault-Valls V, Fatemi M, Gilard M, Pennec P-Y, Etienne Y. Midterm benefits of left univentricular pacing in patients with congestive heart failure. *Circulation* 2004; 109:1741–1744.
94. Auricchio A, Stellbrink C, Butter C, et al. Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. *J Am Coll Cardiol* 2003; 42:2109–2116.
95. Garrigue S, Bordachar P, Reuter S, et al. Comparison of permanent left ventricular and biventricular pacing in patients with heart failure and chronic atrial fibrillation: Prospective haemodynamic study. *Heart* 2002; 87:529–534.
96. Aonuma K, Yokoyama Y, Seo Y, et al. Tri-ventricular pacing: A novel concept of resynchronization therapy for better left ventricular performance in end-stage heart failure (Abstr). *Heart Rhythm* 2005; 2(Suppl.):S131.
97. Leclercq C, Faris O, Tunin R, et al. Systolic improvement and mechanical resynchronization does not require electrical synchrony in the dilated failing heart with left bundle branch block. *Circulation* 2002; 106:1760–1763.
98. St John Sutton MG, Plappert T, Abraham WT, et al. for the MIRACLE Study Group. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation* 2003; 107:1985–1990.
99. Sogaard P, Egeblad H, Kim W, et al. Tissue Doppler imaging predicts improved systolic performance and reversed left ventricular remodeling during long-term cardiac resynchronization therapy. *J Am Coll Cardiol* 2002; 40:723–730.
100. Lau CP, Yu CM, Chau E, et al. Reversal of left ventricular remodeling by synchronous biventricular pacing in heart failure. *Pacing Clin Electrophysiol* 2000; 23:1722–1725.
101. Giudici MC, Barold SS, Moeller AL, Meierbachtol CJ, Paul DL, Walton MC. Influence of native conduction status on clinical results with right ventricular outflow tract pacing. *Am J Cardiol* 2003; 91:240–242.
102. Prinzen FW, Peschar M. Relation between the pacing induced sequence of activation and left ventricular pump function in animals. *Pacing Clin Electrophysiol* 2002; 25(Pt 1):484–498.
103. Nielsen JC, Pedersen AK, Mortensen PT, Andersen HR. Programming a fixed atrioventricular delay is not effective in preventing pacing in patients with sick sinus syndrome. *Europace* 1999; 1:113–120.
104. Sweeney MO, Ellenbogen KA, Casavant D, et al., for the Marquis MVP Download Investigators. Multicenter, prospective, randomized safety and efficacy study of a new atrial-based managed ventricular pacing mode (MVP) in dual chamber ICDs. *J Cardiovasc Electrophysiol* 2005; 16:1–7.
105. Sweeney MO, Nsah E, McGrew F, et al., and the SAVE PACE Investigators. Reduction in ventricular pacing and its long-term clinical outcomes: Preliminary results of the SAVE PACE trial (Abstr). *Heart Rhythm* 2005; 2(Suppl):S322.
106. Savoure A, Froehlig G, Galley D, et al. A new dual-chamber pacing mode to minimize ventricular pacing. *Pacing Clin Electrophysiol* 2005; 28:S43–S46.
107. Olshansky B, Day J, McGuire M, Pratt T. Inhibition of unnecessary RV pacing with AV search hysteresis in ICDs (INTRINSIC RV): Design and clinical protocol. *Pacing Clin Electrophysiol* 2005; 28:62–66.
108. Baker CM, Christopher TJ, Smith PF, Langberg JJ, Delurgio DF, Leon AR. Addition of a left ventricular lead to conventional pacing systems in patients with congestive heart failure: Feasibility, safety, and early results in 60 consecutive patients. *Pacing Clin Electrophysiol* 2002; 25:1166–1171.