European Journal of Echocardiography Advance Access published March 29, 2008

European Journal of Echocardiography
doi:10.1093/ejechocard/jen108

Right ventricular outflow and apical pacing comparably worsen the echocardioghraphic normal left ventricle†

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Received 23 September 2007

KEYWORDS
Echocardiography;
Right ventricular pacing;
Left ventricular function

Aims A depressed left ventricular function (LVF) is sometimes observed during right ventricular apical (RVA) pacing, but any prediction of this adverse effect cannot be done. Right ventricular outflow tract (RVOT) pacing is thought to deteriorate LVF less frequently because of a more normal LV activation pattern. This study aims to assess the acute effects of RVA and RVOT pacing on LVF in order to determine the contribution of echocardiography for the selection of the optimum pacing site during pacemaker (PM) implantation.

Methods and results Fourteen patients with a DDD-pacemaker (7 RVA, 7 RVOT) and normal LVF without other cardiac abnormalities were studied. PM dependency, because of sick sinus syndrome with normal atrioventricular and intraventricular conduction, was absent in all, allowing acute programming changes. Wall motion score (WMS), longitudinal LV strain, and tissue Doppler imaging for electromechanical delay were assessed with echocardiography during AAI pacing constituting baseline and DDD pacing. The WMS was normal at baseline (AAI pacing) in all patients and LV dyssynchrony was absent. Acute RVA and RVOT pacing deteriorated WMS, electromechanical delay, and longitudinal LV strain, but no difference of the deterioration between both pacing sites was present and dyssynchrony did not emerge.

Conclusion Both acute RVA and RVOT pacing negatively affect WMS, longitudinal LV strain, and mechanical activation times, without clear differences between both pacing sites. Thus echocardiographic techniques do not facilitate the selection between RVOT and RVA pacing to exclude adverse effects on LVF during PM implantation in patients with a normal LVF.

Introduction

Chronic right ventricular apical (RVA) pacing has been reported to worsen both left ventricular (LV) systolic and diastolic function.[1,2] Right ventricular outflow tract (RVOT) pacing has been introduced to avoid this apparent and unpredictable complication of RVA pacing, because this pacing site appears to deliver a more physiological electrical activation of both ventricles, visible with a shorter paced QRS complex than with RVA pacing.[3,4] It is assumed that a more normal ventricular activation brings out less worsening of the LV function (LVF). Despite this theoretical advantage, various clinical reports did not show convincing data of the superiority of mid-term RVOT pacing over RVA pacing.[4–8]

Because the decision to insert the pacing lead in the RVOT or RVA during pacemaker (PM) implantation remains arbitrarily and the ventricular conduction pattern varies widely,[9,10] one would prefer to rely on easily achievable information about the influence of right ventricular (RV) pacing position on LVF in the individual patient. To explore this question we performed a pilot non-invasive study for assessing the influence of RVOT or RVA pacing on the normal LVF. For this purpose LV wall motion score (WMS), regional longitudinal LV strain, and tissue Doppler imaging (TDI) of LV wall segments were measured with echocardiography during normal rhythm and conduction, and compared with chronic DDD pacing with either a RVA or RVOT lead.

This study intends a better understanding of how RV pacing acutely effects LVF, and whether echocardiography

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contains sufficient information to guide the quest for the optimum pacing site during PM implantation.

Methods

Patients

For this pilot study, we included consecutive patients followed at the PM Department of the MCRZ Clara Rotterdam, with chronic pacing for sick sinus syndrome and normal atrioventricular (AV) and intraventricular conduction. Patients with a normal LVF on screening echocardiographic assessment were eligible for inclusion. In addition, the ventricular pacing percentage should be $<5\%$ in the preceding three months before the study. RVA or RVOT lead location was confirmed with both 12 lead ECG and bi-plane X-ray. Patients with cardiomyopathy, previous myocardial infarction or percutaneous coronary intervention, cardiac surgery, congestive heart failure, or unstable angina pectoris were excluded. Patients with aortic valve insufficiency or stenosis >20 mm Hg, mitral valve stenosis or $>$ mild regurgitation on screening echocardiogram were also excluded. Patients with atrial or ventricular tachyarrhythmia on the study date, or in who full and stable ventricular capture could not be obtained or without adequate echo-windows were excluded. The study complies with the declaration of Helsinki and all patients gave informed consent.

Pacing methods

Baseline measurements were acquired with AAI pacing and normal intraventricular conduction. RVOT or RVA pacing was programmed with DDD pacing and AV interval <120 ms to obtain full ventricular capture in the same session. It was previously shown that increased paced heart rates decrease myocardial perfusion in the absence of coronary artery disease,[11] but LVF was not assessed. To evaluate any rate dependency of deterioration of LVF, a faster pacing rate was also evaluated. A low pacing rate was defined pacing with 10 pulses per minute (ppm) above the resting spontaneous heart rate. Faster paced heart rates were evaluated at a rate of 90 ppm. Thus, the study consists of four pacing settings; baseline (AAI) and AAI pacing at a faster pacing rate, and DDD pacing with full ventricular capture at low and faster pacing rates. After PM programming, a 5-min waiting time was allowed for cardiac adaptation to the new pacing setting. Each pacing mode was randomized and during each pacing mode a complete cardiac ultrasound data set was acquired and the paced QRS duration and morphology were assessed on a 12 lead ECG.

Echocardiography methods

Using a GE-Vingmed 7 ultrasound system, parasternal long axis, apical 2, 3, and 4 chamber images were acquired. LV end diastolic dimension, interventricular septum diameter during end diastole, and left atrial diameter were measured during the four pacing settings.

(i) LV wall motion abnormalities were evaluated using the standard 16-segment model.[12] Electromechanical delay was acquired using pulsed wave TDI. The wall motion was scored using a four-point scoring system, 0, normal; 1, hypokinetic; 2, akinetic; 3, dyskinetic. LV ejection fraction was calculated using Simpson bi-plane method at baseline for every pacing setting.

(ii) The electromechanical delay was calculated for the septum and lateral wall from the apical 4-chamber image, and for the inferior and anterior wall using the apical 2-chamber view. The start of the S2-wave with TDI was considered the start of mechanical activation. An electromechanical delay of >40 ms in between the septum and the lateral wall or the anterior and inferior walls was considered to reflect dyssynchrony.[13]

(iii) The regional longitudinal LV-strain curves as parameter of LV contractility were acquired for the septum, lateral, anterior, and inferior walls form the apical 4-chamber and 2-chamber views using a narrow sector.[14,15] A minimum frame-rate of 200 frames per second was used. Regional longitudinal LV end systolic strain was measured at the mid-section of each of the four LV walls. The average longitudinal LV strain was calculated as the sum of the regional longitudinal LV strain of the four assessed walls divided by 4.

All images were stored digitally and then assessed off-line. For intra-observer variability each parameter was measured twice with an interval of 3 weeks. For all TDI measurements, the absolute value of Observer1 (T.J.F.T.C.)−Observer2 (M.G.S.) divided by the mean of the two measurements was used. For the actual study, all parameters were again measured by consensus of the two experienced observers who were blinded to patient and pacing characteristics.

Statistical analysis

All data are presented as mean value $\pm$ SD. The χ^2 test was used to compare categorical data. A two-sided Student *t*-test was used to compare echocardiography values for each pacing mode and pacing setting. The unpaired *t*-test was performed when applicable. A *P*-value <0.05 was considered statistically significant. Bland–Altman method of comparison was used to assess inter-observer variability.

Results

Patients

Sixty-nine patients who presented at the outpatient clinic of the MCRZ Clara location with sick sinus syndrome were initially screened. An abnormal LVF on screening echocardiogram was reason for exclusion in 4 patients, 6 had valvular heart disease that did not meet the inclusion criteria, and 16 were excluded because the echowindow was inadequate for complete analysis. Previous myocardial infarction was present in 6 patients and 9 underwent a percutaneous coronary intervention. Atrial fibrillation was present in 8 patients at screening echocardiogram and 6 had a ventricular pacing percentage $>5\%$ of the time. The clinical and pacing characteristics of the 14 study patients fulfilling the intake criteria, demonstrate shorter chronic pacing ($P < 0.05$) for the RVOT paced group, whereas other characteristic did not differ significantly (*Table 1*). Two patients with RVA pacing could not be studied at faster pacing rates because full ventricular capture could not be achieved. Thus, the study consisted of 14 patients who were studied at low pacing rates, and 12 who were studied both at low and faster pacing rates.

Inter and intra observer variability

Bland–Altman analysis showed a 3 ms absolute difference between observer 1 (T.J.F.T.C.) and observer 2 (M.G.S.) and narrow limits of 95% agreement of ± 19 ms. Likewise, intra-observer mean difference was 1 ms with narrow limits of 95% agreement of ± 11 ms. In addition, variability in TDI time-delay measurements was calculated as the absolute difference in repeated measurements, which is expressed as percentage of the average of these

measurements. The inter- and intra-observer agreement was 3.1 ± 3.6 and 1.3 ± 2.0%, respectively.

Echocardiographic results: low pacing rates

WMS was normal in all patients at baseline and worsened to 3.2 ± 2.6 and 2.1 ± 1.9 during RVA and RVOT pacing, respectively ($P < 0.01$) (*Table 2*). Wall motion abnormalities were mainly located in the inferior, inferoseptal, and apical regions during RVA pacing, and in the septum, posterolateral, and posterior wall during RVOT pacing.

Compared with baseline, the LV electromechanical delay increased significantly in the septum and lateral wall with both RV pacing sites and also in the inferior wall with RVA pacing (*Table 2*). TDI indices showed no LV dyssynchrony during RVA or RVOT pacing. The average absolute delay between onset of mechanical activation between the septum and the lateral wall was 19 ± 6 ms for RVA pacing and 12.5 ± 8.5 ms for RVOT pacing.

The average longitudinal end systolic LV strain, calculated as the sum of the 4 LV segments divided by 4, was 22.1 ± 2.4% at baseline and diminished to 17.2 ± 2.6 and 18 ± 1.9% for RVA and RVOT pacing, respectively ($P < 0.01$) (*Table 2*). No statistical significant difference was observed between RVA and RVOT pacing. Examples of the effects of RVA pacing and RVOT pacing on septal longitudinal strain are shown in *Figures 1* and *2*.

To summarize, all indices of LVF significantly diminished with RVA or RVOT pacing compared with baseline, but no difference was observed between the two RV pacing sites.

Table 1 Patient and pacing characteristics

	RVA ($n = 7$)	RVOT ($n = 7$)
Age (years) ± SD	69.22 ± 7.9	69.33 ± 9.7
Female/men (*n*)	5/2	3/4
Spontaneous QRS duration (ms) ± SD	85 ± 9.4	91.6 ± 9.5
Paced QRS duration (ms) ± SD	135 ± 13.2	130 ± 22
Mean pacing duration (months) ± SD	53.5 ± 45	21 ± 29.3*
LVEDD (mm) ± SD	48.11 ± 6.8	40.6 ± 9.4
LVESD (mm) ± SD	30.6 ± 7.1	24.9 ± 9.9
LA diameter (mm) ± SD	34.6 ± 6.9	34.3 ± 5.5

LA, left atrium; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic dimension; RVA, right ventricular apex; RVOT, right ventricular outflow tract; SD, standard deviation. *$P < 0.05$.

Echocardiographic results: faster pacing rates

Although the WMS further worsened at faster paced heart rates compared with low pacing rates of RVOT or RVA pacing (*Table 2*), this deterioration was not statistically significant between low and faster paced heart rates. However, pacing at faster paced heart rates significantly increased the number of affected segments of RVOT paced patients in contrast to RVA paced ones.

The electromechanical delays measured at the four sites did not significantly change between low and faster paced heart rates of RVOT and RVA pacing.

The average longitudinal LV strain was not significantly different between low and faster paced heart rates for any of the pacing sites, but regional longitudinal septal strain significantly worsened for both pacing sites. The regional longitudinal lateral strain significantly worsened only for RVOT paced patients.

Discussion

This study demonstrated that the normal LVF as assessed with three echocardiographic parameters worsened when RV pacing was instigated. Faster RV pacing resulted in further worsening of WMS with more segments being affected. The average regional longitudinal LV strain also further worsened. However, LV dyssynchrony was not observed at low or faster paced heart rates. Most importantly, no significant differences of LV deterioration were observed between RV outflow and apical pacing.

To appreciate the results of this study in terms of clinical relevance several aspects need to be commented. We aimed to study patients with a normal LVF at baseline to compare the influence of abnormal intraventricular conduction elicited by pacing at two different RV sites with normal

Table 2 Echocardiographic parameters studied at low and faster pacing rates

	Baseline ($n = 14$)	RVA low ($n = 7$)	RVOT low ($n = 7$)	RVA faster ($n = 5$)	RVOT faster ($n = 7$)
WMS	0	3.2 ± 2.6**	2.1 ± 1.9**	5.3 ± 3**	3.6 ± 2***
Abnormal segments	0	2.7 ± 2.2**	1.5 ± 1.2**	3.6 ± 1.8***	2.9 ± 1.6***
LVEF (%)	58.6	54.3 ± 3.4**	55.4 ± 3**	52.8 ± 2.6***	53.9 ± 1.7***
TDI delay septum ± SD (ms)	92.2 ± 15.6	132.7 ± 8.8***	124.1 ± 18.5**	131.4 ± 18.6**	119 ± 15.8***
TDI delay lateral wall ± SD (ms)	88.7 ± 18.2	113.7 ± 10.1***	115.9 ± 22.7*	130 ± 22.5*	119.4 ± 27.5*
TDI delay inferior wall ± SD (ms)	88.8 ± 14.5	121.8 ± 21.7**	107.4 ± 27.8	131 ± 37.1*	121.4 ± 34.8*
TDI delay anterior wall ± SD (ms)	93.2 ± 19.2	110.5 ± 14.2	104 ± 28.8	118.8 ± 23.6*	111.5 ± 23.6*
Average LV strain ± SD (%)	22.1 ± 2.4	17.2 ± 2.6**	18 ± 1.9***	15.7 ± 1.9**	16.9 ± 2***
Septal strain ± SD (%)	22.7 ± 4.6	17.2 ± 2.6*	18.3 ± 1.8**	15.1 ± 1.6**	15.9 ± 3
Lateral strain ± SD (%)	21.3 ± 2.4	16.8 ± 4.1*	18.9 ± 1.3*	15 ± 2.9***	16.5 ± 1.2
Inferior strain ± SD (%)	22.8 ± 4.9	16.3 ± 3	17.1 ± 3**	16.3 ± 2.3	17.7 ± 1.8**
Anterior strain ± SD (%)	21.2 ± 3.9	16.8 ± 1.7*	17.9 ± 4.3	16.2 ± 3	17.3 ± 4.2**

LVEF, Left ventricular ejection fraction; RVA low, DDD pacing from the RVA at low pacing rate; RVOT low, DDD pacing from the RVOT at low pacing rate; SD, standard deviation; TDI, tissue Doppler Imaging; WMS, wall motion score. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. All *P*-values are given for pacing vs. baseline. No significant statistical difference was observed between RVA and RVOT pacing at low or faster paced heart rates.

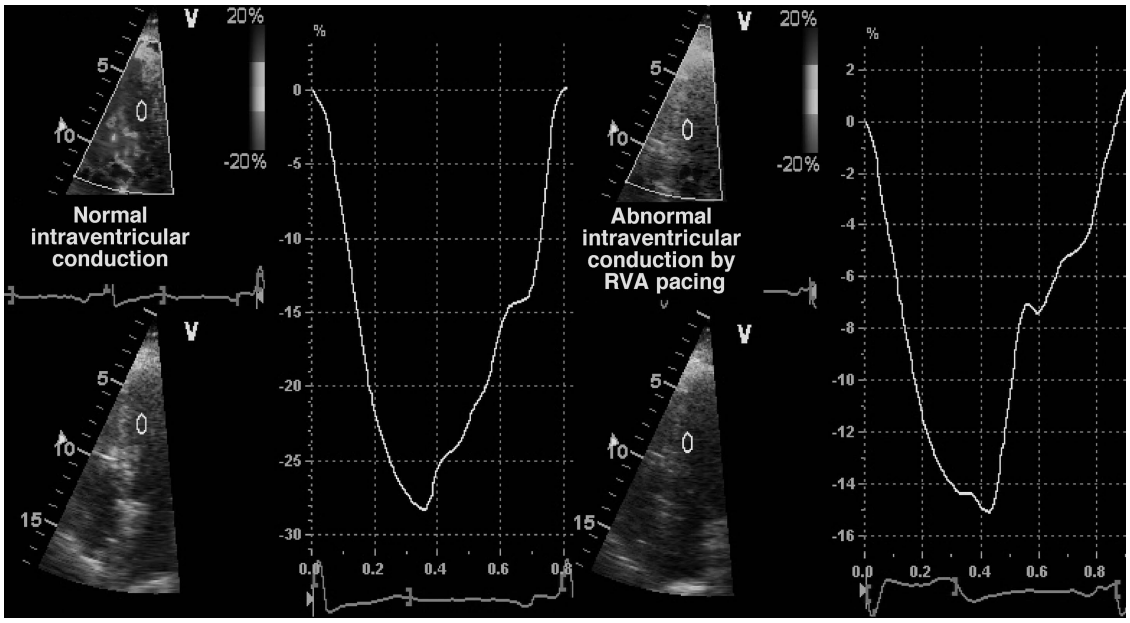

Figure 1 Example of regional longitudinal LV-strain curves of the mid septum for a patients with a DDD-pacemaker with a RVA-lead location. AAI pacing on the left, RVA pacing on the right. Regional longitudinal septum strain decreases with RVA pacing. Note the difference in scale for both LV-strain curves.

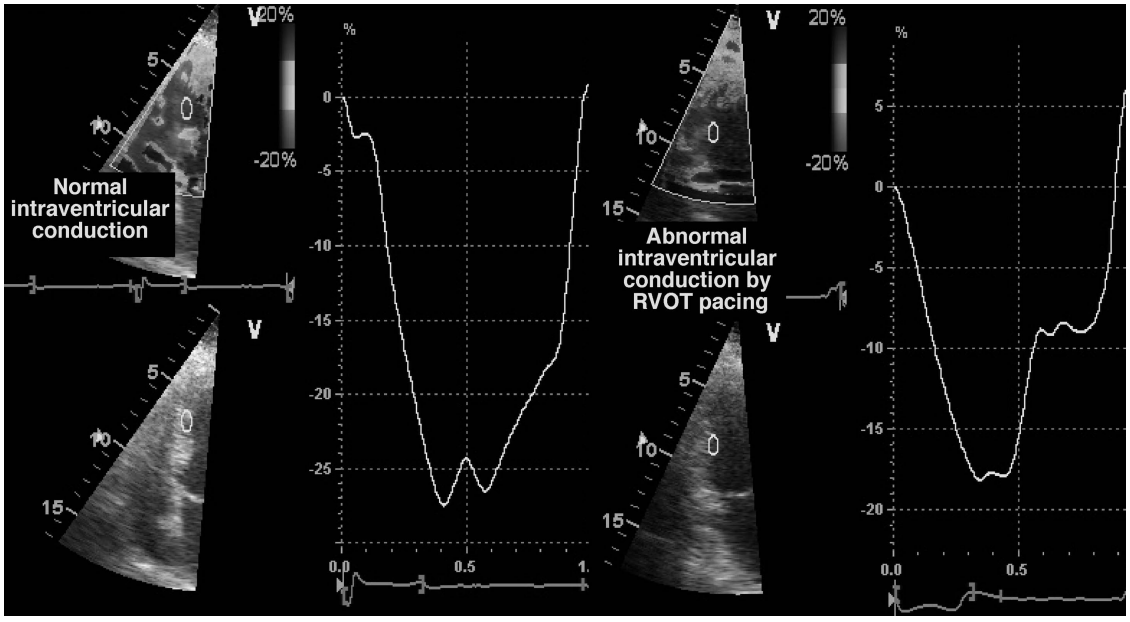

Figure 2 Example of regional longitudinal LV strain curves for the mid septum in a patient with a DDD-pacemaker with a RVOT-lead location. AAI pacing on the left, RVOT pacing on the right. Regional longitudinal septum strain decreased with RVOT pacing. Note the difference in scale for both LV-strain curves.

intraventricular conduction (AAI pacing with normal AV and intraventricular conduction). Previous reports suggest that impairment of LVF in RV pacing is a time-dependent effect.[4,16] In our population, LVF and intraventricular conduction were normal despite a mean chronic pacing duration of more than 36 months. The normal LVF can be certainly attributed to bradytachycardia as pacing indication with a prevailing normal AV conduction during follow-up, and therefore a small percentage of ventricular pacing.

Because studies of echocardiographic LV strain and other parameters can hardly be reliably conveyed during PM implantation, a pilot study comparing patients with either RVOT or RVA pacing lead for DDD pacing was carried out. We assumed that a normal intraventricular and normal interventricular conduction at baseline applied as inclusion criteria, would sufficiently allow for a fair comparison of the effects of pacing of both RV pacing sites to compensate for the missing intra patient comparisons of the various pacing sites.

TDI is a regularly used technique to assess LV dyssynchrony in patients with impaired LVF that are eligible for chronic resynchronization therapy. It has been shown that this technique is powerful to predict responders of this technique in patients with dilated cardiomyopathy, but less in patients with ischaemic cardiomyopathy.[13] In the present study, dyssynchrony was assessed using pulsed wave TDI in patients with pre-existent normal LVF and wall motion. Using this accepted two-dimensional technique dyssynchrony could not be observed during pacing from either the RV apex or the RV outflow tract. The concept to add dimensions to assess dyssynchrony seems better. Liu *et al*.[17] showed that RVA pacing can induce dyssynchrony using three-dimensional echocardiography. However, the gain of spatial resolution by imaging in three-dimensions comes at the cost of a reduced temporal resolution.

Asynchronous LV activation has been proposed to be an important cause of diminished LVF in paced patients[18] reason why chronic RVOT pacing is thought to be a more favourable alternative pacing mode. The presumed beneficial effects of RVOT pacing would even be more prominent when LVF is impaired.[16] However, a large scale randomized trial by Stambler *et al*.[6] failed to show any advantage of RVOT pacing over RVA pacing in patients with pre-existent diminished LVEF and atrial fibrillation. Although in our acute study both RVA and RVOT pacing increased electromechanical delay compared with no pacing (*Table 2*), and lengthened the QRS duration (*Table 1*), LV dyssynchrony (see definition) could not be provoked. Tops *et al*.[19] demonstrated using radial strain in patients with atrial fibrillation that underwent His-ablation and RV PM implantation that dyssynchrony could be provoked with RV pacing and that pacing-induced LV dyssynchrony was associated with a reduced LVF. The differences between the outcome of this study and the present study can be explained by differences in baseline characteristics and the paced QRS complexes. Schwaab *et al*.[3] showed that not the site of pacing but the duration of the paced QRS complex was related to LVF. The paced QRS complexes in the study by Tops *et al*.[19] were $>$160 ms, whereas in our study these were $<$140 ms. This leaves the question whether in presence of impaired LVF dyssynchrony is more provoked by RVA than RVOT pacing.

Limitations

Only patients with normal ventricles participated and thus any information about a reduced LVF cannot be given. Secondly, the results can be influenced by the short pacing intervals, but resynchronization studies showed an immediate and stable response after onset of pacing.[20,21] Finally, the small number of patients can have affected the interpretation of the data.

Clinical relevance

The message of this pilot acute study includes that echocardiography as a guiding tool for choosing the optimal RV pacing site in the individual patient with a normal LVF, appears ineffective. Because both RVOT and RVA pacing sites result in a comparable reduction of LVF when acute pacing is instigated, the decision cannot rely on the three echocardiographic parameters used in this study. In addition, the time spend on echocardiographic data collection and interpretation do not apply with the standard PM implantation because it took 1 h per patient. Furthermore, the acquisition of the images required repositioning of the patient to obtain the best images depending on the desired image. Under the sterile conditions of PM implantation, this is difficult to carry out due to the ability to turn the patient into the left lateral position.

Conclusion

Acute abnormal LV activation form RVA or RVOT pacing results in an acute diminished LVF as assessed with echocardiographic WMS, traced LVEF, electromechanical delay, and regional longitudinal LV strain. No differences were observed between RVA and RVOT pacing. This suggests that any RV pacing sites can negatively affect LVF and that readily available and non-invasive echocardiographic techniques are not helpful to guide the selection of the individual optimum pacing site during implantation.

Conflict of interest: none declared.

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