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Functional Abnormalities in Patients With Permanent Right Ventricular Pacing

The Effect of Sites of Electrical Stimulation

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OBJECTIVES We sought to evaluate the long-term effects of alternative right ventricular pacing sites on myocardial function and perfusion.

BACKGROUND Previous studies have demonstrated that asynchronous ventricular activation due to right ventricular apical (RVA) pacing alters regional myocardial perfusion and functions.

METHODS We randomized 24 patients with complete atrioventricular block to undergo permanent ventricular stimulation either at the RVA (n = 12) or right ventricular outflow (RVOT) (n = 12). All patients underwent dipyridamole thallium myocardial scintigraphy and radionuclide ventriculography at 6 and 18 months after pacemaker implantation.

RESULTS After pacing, the mean QRS duration was significantly longer during RVA pacing than during RVOT pacing (151 ± 6 vs. 134 ± 4 ms, p = 0.03). At six months, the incidence of myocardial perfusion defects (50% vs. 25%) and regional wall motion abnormalities (42% vs. 25%) and the left ventricular ejection fraction (LVEF) (55 ± 3% vs. 55 ± 1%) were similar during RVA pacing and RVOT pacing ($p > 0.05$). However, at 18 months, the incidence of myocardial perfusion defects (83% vs. 33%) and regional wall motion abnormalities (75% vs. 33%) were higher and LVEF (47 ± 3 vs. 56 ± 1%) was lower during RVA pacing than during RVOT pacing (all $p < 0.05$). Patients with RVA pacing had a significant increase in the incidence of myocardial perfusion defects ($p < 0.05$) and a decrease in LVEF ($p < 0.01$) between 6 and 18 months, but patients with RVOT pacing did not ($p > 0.05$).

CONCLUSIONS This study demonstrates that preserved synchronous ventricular activation with RVOT pacing prevents the long-term deleterious effects of RVA pacing on myocardial perfusion and function in patients implanted with a permanent pacemaker. (J Am Coll Cardiol 2002;40: 1451–8) © 2002 by the American College of Cardiology Foundation

Asynchronous ventricular activation during ventricular pacing is associated with abnormal regional myocardial blood flow and metabolism and reduces systolic and diastolic left ventricular (LV) function (1–5). Furthermore, these functional abnormalities of ventricular pacing appear to have potential deleterious effects over time. Experimental studies have demonstrated that long-term right ventricular apical (RVA) pacing induces abnormal histologic changes with myofibrillar disarray, as well as asymmetrical LV hypertrophy and thinning (6–9). In a previous clinical study, we have shown that long-term RVA pacing leads to regional myocardial perfusion defects and wall motion abnormalities, which become more pronounced as the duration of pacing increases, and subsequently impairs LV function (10). In animal studies, pacing at the right ventricular outflow tract (RVOT) to decrease the asynchrony of activation ameliorated the reduction in LV function and prevented the development of myofibrillar disarray (11,12). However, clinical studies of RVOT pacing have yielded inconsistent results (13–16), and the long-term effects of RVOT pacing on myocardial perfusion and function are unclear.

The purpose of this prospective, randomized study was to evaluate the long-term effects of RVA pacing and RVOT pacing on myocardial perfusion and function in patients implanted with a permanent dual-chamber pacemaker.

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METHODS

Patients. The study included 30 consecutive patients (14 men and 16 women; mean [±SEM] age 78 ± 2 years [range 59 to 88]) with complete atrioventricular (AV) block admitted for pacemaker implantation. Patients with a history of coronary artery disease, significant valvular disease, congestive heart failure, hypertension or LV hypertrophy, or a left ventricular ejection fraction (LVEF) <50% on the baseline screening echocardiogram were excluded from the study. Their mean LVEF was 59 ± 3% by echocardiography.

Study protocol. All patients underwent implantation of a dual-chamber pacemaker using one passive fixation atrial lead and one active fixation ventricular lead (commercially available bipolar leads could be used). Patients were randomized, using a randomization table at the time of implantation, to receive a ventricular lead at either at the RVA or RVOT position. Atrial leads were positioned to the right atrial lateral wall. Surface limb leads (I, II, III, aVR, aVL, and aVF) of the electrocardiogram (ECG) were recorded with a paper speed of 100 mm/s during the procedure, and the QRS duration was measured from the

Abbreviations and Acronyms

AV	= atrioventricular
ECG	= electrocardiogram/electrocardiographic
LV	= left ventricle/ventricular
LVEF	= left ventricular ejection fraction
RV	= right ventricle/ventricular
RVA	= right ventricular apex
RVOT	= right ventricular outflow tract
Tl-201	= thallium-201

earliest to latest deflection of the QRS complex. After pacemaker implantation, optimization of the AV delay was performed by using pulsed Doppler echocardiography of the transmitral blood flow, as previously described (17). All patients underwent 24-h Holter monitoring, dipyridamole thallium-201 (Tl-201) myocardial scintigraphy, and radionuclide ventriculography at 6 and 18 months after pacemaker implantation. Patients with Tl-201 perfusion defects were referred for a coronary angiographic study. Patients with significant coronary artery stenosis (>50%) were excluded from the study. The study protocol was approved by the local Ethics Committee, and all patients gave written, informed consent.

Lead implantation. The ventricular pacing lead was inserted into the RV through a left cephalic vein cutdown or subclavian puncture. Under fluoroscopic guidance, the ventricular lead was positioned in the RVA in those patients randomized to RVA pacing. In patients who underwent RVOT pacing, the ventricular lead was advanced through the tricuspid valve and then withdrawn far enough to position the tip against the interventricular septum, as verified by multiple fluoroscopic views (Fig. 1). Then, mapping of the interventricular septum was performed by using the screw-in tip of the lead with a custom-shaped stylet. The optimal RVOT lead position was confirmed by fluoroscopy and the limb leads of the ECG demonstrating an inferior axis in the frontal axis and the narrowest QRS complex available (Fig. 2). An external pacing system analyzer was used to measure the ventricular capture threshold at a pulse duration of 0.5 ms, R-wave amplitude, and lead impedance. All the ventricular pacing leads were positioned at a stable position to obtain a satisfactory pacing threshold value (mean 1.1 ± 0.2 V [range 0.5 to 1.5]) at a pulse width of 0.5 ms and R-wave sensing value (mean 12.3 ± 0.1 mV [range 6.5 to 20.5]).

Holter recording. Bipolar ECG leads were fixed to the chest at V_1 and V_6; all ECGs were recorded for 24 h with an Oxford Medilog recorder (Oxford Medical Instruments, Oxford, U.K.). The ECG complexes of the first minute of each hour were printed and reviewed at a paper speed of 25 mm/s. Complete ventricular capture was defined by the presence of a pacing spike followed by QRS complexes with a QRS width equal to that during VVI pacing without fusion. The percentage of QRS complexes with ventricular capture during each observation minute was averaged to obtain the 24-h percentage of complete capture.

Dipyridamole Tl-201 myocardial scintigraphy. All patients were instructed to fast for 6 h and to avoid medications containing methylxanthine and beverages containing caffeine for 24 h before the test. Dipyridamole (0.56 mg/kg body weight) was infused for 4 min, and 3 min later, 2 mCi of Tl-201 chloride was injected intravenously. Thallium-201 single-photon emission computed tomographic imaging was performed at 15 min and at 4 h after the injection. An additional 1 mCi of Tl-201 was injected before the rest study at 4 h. If a fixed defect was detected in the 4-h image, imaging was also performed at 24 h. Sagittal, short-axis, and long-axis tomograms were constructed from the raw scintigraphic data. These constructed stress and rest images were then analyzed qualitatively using the 20-segment/5-point scoring system (18). The 20-segment scoring system is based on three short-axis slices (apical, mid, and basal) to represent the entire LV, with the apex represented by one segment visualized by a mid-vertical long-axis image. Perfusion was scored qualitatively by two experienced observers, in blinded manner, using a 5-point scale: 0 = normal; 1 = slight reduction of uptake (equivocal); 2 = moderate reduction of uptake; 3 = severe reduction of uptake; and 4 = absence of radioactive uptake.

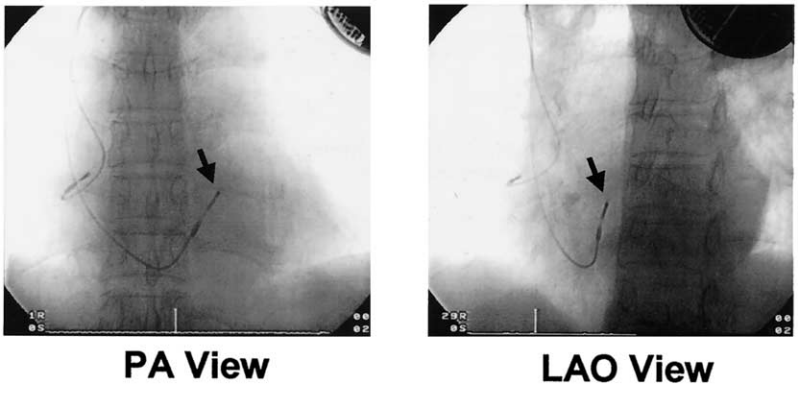

Figure 1. Fluoroscopic images of the **(left)** posteroanterior (PA) and **(right)** left anterior oblique (LAO) projection, showing the position of the active ventricular pacing lead at the right ventricular outflow tract **(arrow)**.

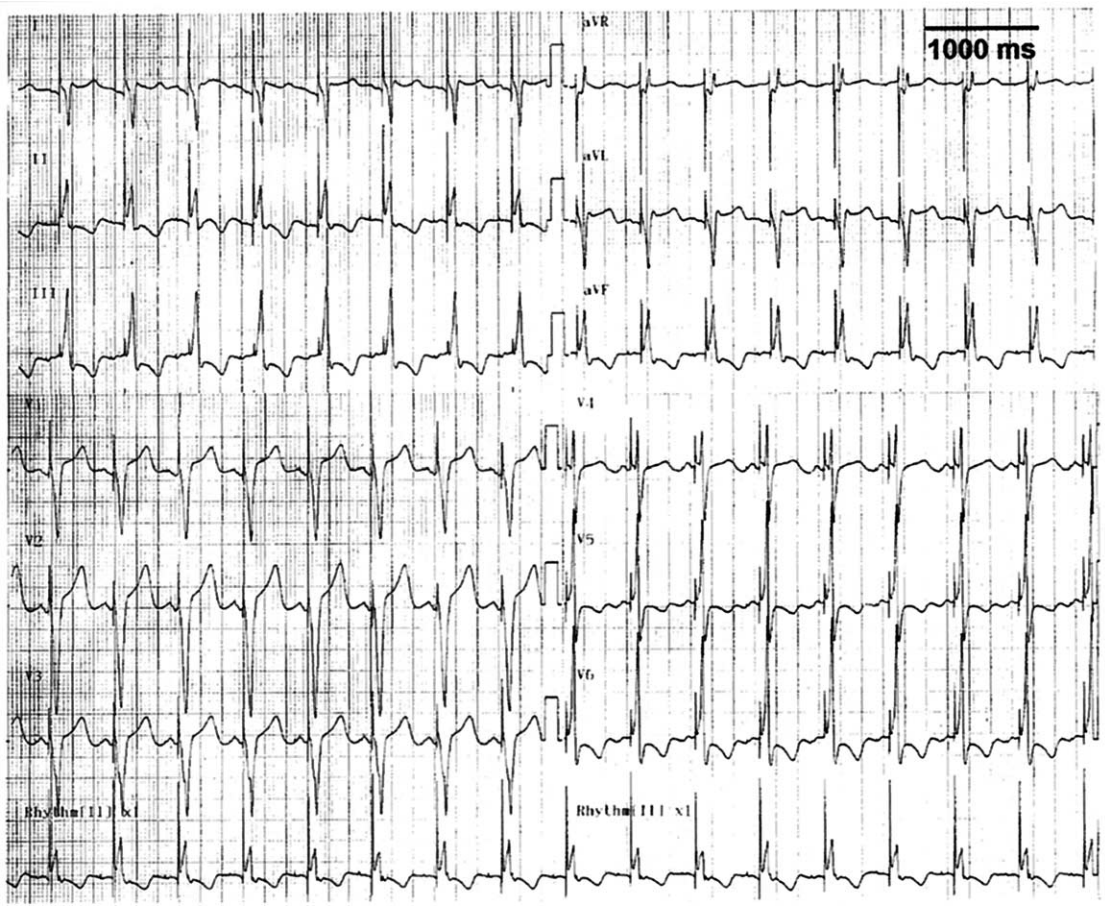

Figure 2. Twelve-lead electrocardiogram of a patient who underwent right ventricular outflow tract pacing, showing a QRS duration of 135 ms with a left bundle branch block pattern and inferior axis.

Radionuclide ventriculography. Multiple-gated equilibrium blood pool imaging was performed at rest to determine global and regional LVEF and to assess regional wall motion. Patients' red blood cells were labeled with 20 to 30 mCi of technetium-99m by using the modified in vivo technique (19). Data were acquired in an ECG-synchronized frame mode (32 frames/cycle with 150,000 to 200,000 counts/frames) in a 64 × 64 computer matrix. Global LVEF was computed from the left anterior oblique image by means of a semi-automated, operator-assisted method to define the border of the LV and background and by using validated and standardized software (20). The LVEF was determined from the fitted curve in the usual manner: (end-diastolic counts − end-systolic counts)/end-diastolic counts. The reproducibility of LVEF measurements using this software is excellent (21). Left ventricular diastolic function was assessed by measuring the peak ventricular filling rate derived from the gated equilibrium, high-resolution LV time–activity curves (20,22).

Regional LVEF was calculated by segmenting the left anterior oblique view of the LV into five regions: septal, anterior, apical, inferior, and lateral. The stroke counts over end-diastolic counts in each segment were used to determine regional LVEF (23). Furthermore, serial frames of the image were displayed for cineangiographic wall motion assessment. Regional wall motion was scored in each of the five segments as normal, hypokinetic, akinetic, or dyskinetic by two experienced observers in a blinded manner (10).

Statistical analysis. Continuous data are expressed as the mean value ± SEM. Comparisons between the two groups were performed by the Mann-Whitney *U* test for continuous variables and by the Fisher exact test for dichotomous variables. The paired Student *t* test was used to compare the change in variables in each group between the 6- and 18-month evaluations. Multiple comparisons of the regional ejection fraction between the 6- and 18-month evaluations during RVA and RVOT pacing were performed using two-way repeated measures analysis of variance, followed by the Bonferroni *t* test for individual comparisons. A p value < 0.05 was considered as statistically significant.

RESULTS

Patient characteristics. At baseline, 16 patients were randomized to receive RVA pacing and 14 patients to RVOT pacing. There were no significant differences in age, gender distribution, baseline LVEF by echocardiography, ventricular pacing variables, and percentage of ventricular pacing between

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Table 1. Clinical Characteristics

	RVA Pacing (n = 12)	RVOT Pacing (n = 12)	p Value
Age (yrs)	72.3 ± 8	77 ± 5	0.12
Male	4 (33%)	6 (50%)	0.68
Intrinsic rhythm			
LBBB	3 (25%)	4 (33%)	1.0
RBBB	4 (33%)	4 (33%)	1.0
IVCD	2 (17%)	1 (9%)	1.0
Narrow QRS	1 (17%)	2 (17%)	1.0
Not available	2 (17%)	1 (9%)	1.0
Other medical illnesses			
Diabetes	2 (17%)	2 (17%)	1.0
Hyperlipidemia	3 (33%)	2 (17%)	1.0
Medications			
Oral hypoglycemic agents	1 (9%)	2 (17%)	1.0
Lipid-lowering agents	2 (17%)	1 (9%)	1.0
Baseline echocardiography			
LVEF	57 ± 12%	59 ± 14%	0.74
Regional wall motion abnormalities	3 (25%)	2 (17%)	1.0
Pre-discharge echocardiography			
LVEF	56 ± 10%	57 ± 13%	0.36
Regional wall motion abnormalities, n (%)	4 (33%)	3 (25%)	1.0
Cardiac output (l/min)	3.6 ± 0.4	3.8 ± 0.5	0.45
E/A ratio	0.8 ± 0.3	1.0 ± 0.2	0.25
Optimal atrioventricular interval (ms)	140 ± 37	146 ± 36	0.49
Pacing variable at 6 months			
Ventricular pacing threshold (V/0.5 ms)	1.2 ± 0.5	1.4 ± 0.7	0.53
R-wave amplitude (mV)	12.5 ± 5.5	9.1 ± 4.5	0.10
Impedance (Ω)	560 ± 175	587 ± 174	0.73
Percent ventricular pacing			
6-month follow-up	96 ± 11%	96 ± 10%	0.28
18-month follow-up	95 ± 16%	97 ± 14%	0.36
QRS duration (ms)	151 ± 21	134 ± 15	0.034

Data are expressed as the mean value ± SEM or number (%) of patients.
E/A = early transmitral flow velocity to atrial flow velocity; IVCD = intraventricular conduction delay; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; RBBB = right bundle branch block; RVA = right ventricular apex; RVOT = right ventricular outflow tract.

the two groups (all $p > 0.05$). No complications or lead dislodgment was observed during the study. All patients were in sinus rhythm and maintained AV pacing throughout the study period. Of the 30 patients initially included in the study, 20 (67%) had perfusion defects on the dipyridamole Tl-201 myocardial scintigraphic image. Six of them had significant coronary artery disease, as detected by coronary angiography, and were excluded from the final analysis. The mean age of the remaining 24 patients (11 men and 13 women) was 75 ± 5 years. Twelve patients were randomized to RVA pacing and the remaining 12 patients to RVOT pacing. Their clinical characteristics are shown in Table 1. There was no significant difference in age, gender distribution, intrinsic rhythm, baseline LVEF, or prevalence of regional wall motion abnormalities by echocardiography, ventricular pacing variables, and percentage of ventricular pacing between the two groups. However, the mean QRS duration was significantly longer during RVA pacing than during RVOT pacing (Table 1).

At pre-discharge echocardiography, there was no significant difference in LVEF, prevalence of regional wall motion abnormalities, cardiac output, as measured by Doppler echocardiography, optimal AV interval, or transmitral A- and E-wave ratio between the two group (Table 1). Furthermore, there was also no significant difference in LVEF, as measured by echocardiography, between the baseline and pre-discharge follow-up in the two groups ($p > 0.05$).

Dipyridamole Tl-201 myocardial scintigraphy. All patients were paced continuously throughout the study. There were no significant differences between patients with RVA and RVOT pacing in the maximal heart rate during pharmacologic stress at 6 months (87 ± 3 vs. 89 ± 2 beats/min, $p = 0.34$) and 18 months (90 ± 2 vs. 86 ± 3 beats/min, $p = 0.18$).

At six months, six patients (50%) with RVA pacing and three patients (25%) with RVOT pacing showed perfusion defects on the dipyridamole myocardial scintigraphic image ($p = 0.40$). There were also no significant differences in the summed rest score (5.3 ± 1.6 vs. 2.2 ± 0.6 ($p = 0.08$) or summed stress score (8.1 ± 1.8 vs. 4.8 ± 1.0, $p = 0.12$) between the two groups (Fig. 3). Perfusion defects were located in the inferior (83%, n = 5) and apical (67%, n = 4) wall during RVA pacing and in the septum (100%, n = 3) during RVOT pacing.

At 18 months, 10 patients (83%) with RVA pacing and 4 patients (33%) with RVOT pacing showed perfusion defects on the dipyridamole myocardial scintigraphic image

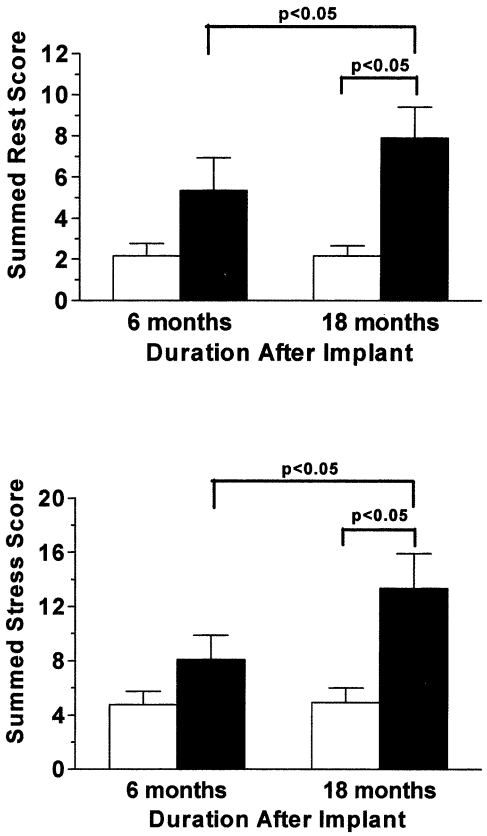

Figure 3. The summed rest **(upper panel)** and stress **(lower panel)** scores for dipyridamole thallium-201 myocardial scintigraphy after 6 and 18 months of right ventricular apex (RVA) **(solid bars)** and right ventricular outflow tract (RVOT) **(open bars)** pacing. The summed rest and stress scores during RVA pacing at 18 months were significantly higher than those during RVOT pacing at 18 months ($p < 0.05$) and during RVA pacing at 6 months ($p < 0.05$).

($p = 0.04$). Pacing at the RVA was associated with a significantly higher summed rest score (7.9 ± 1.5 vs. 2.2 ± 0.5, $p < 0.01$) and summed stress score (13.3 ± 2.6 vs. 4.9 ± 1.1, $p < 0.01$), compared with RVOT pacing (Fig. 3). Perfusion defects were located in the inferior (90%, $n = 9$), apical (80%, $n = 8$), septal (20%, $n = 2$), and lateral (10%, $n = 1$) wall during RVA pacing and in the septal (100%, $n = 4$) and anterior (25%, $n = 1$) wall during RVOT pacing.

In patients with RVA pacing, the incidence of perfusion defects, the summed rest score, and the summed stress score were significantly higher at 18 months than at 6 months,

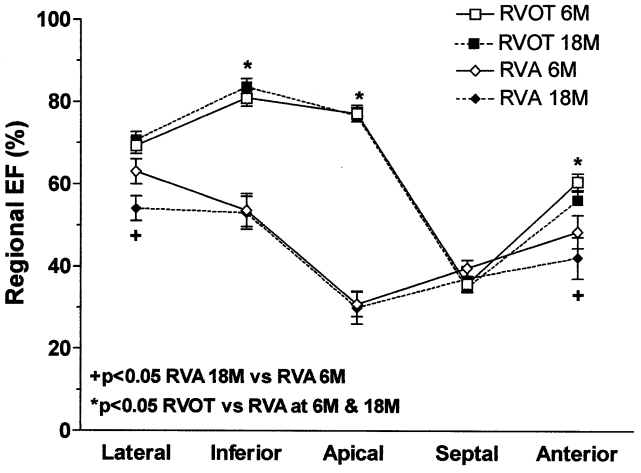

Figure 4. Regional left ventricular ejection fraction (EF) at the lateral, inferior, apical, septal, and anterior regions after 6 and 18 months of right ventricular apex (RVA) and right ventricular outflow tract (RVOT) pacing.

suggesting worsening of myocardial perfusion over time (all $p < 0.05$). These variables were similar at 6 and 18 months in patients with RVOT pacing (all $p > 0.05$).

Radionuclide ventriculography. At six months, five patients (42%) with RVA pacing and three patients (25%) with RVOT pacing showed regional wall motion abnormalities on the radionuclide ventriculogram ($p = 0.20$). During RVA pacing, apical and septal regional LVEFs were significantly diminished compared with those in the anterior, inferior, and lateral regions ($p < 0.05$) (Table 2). During RVOT pacing, the LVEF in the septal region was significantly diminished compared with that in all the other regions ($p < 0.05$), and the LVEF in the inferior region was higher than that in the anterior, lateral, and septal regions ($p < 0.05$) (Table 2). The LVEF in the apical and inferior regions was significantly lower during RVA pacing than during RVOT pacing ($p < 0.05$) (Fig. 4). There was no significant difference in the global LVEF, as measured by pre-discharge echocardiography and radionuclide ventriculography at six months, in patients with RVA pacing ($56 \pm 10\%$ vs. $55 \pm 10\%$, $p = 0.76$) and RVOT pacing ($57 \pm 13\%$ vs. $55 \pm 45\%$, $p = 0.36$). The global LVEF was similar during RVA pacing and RVOT pacing ($p = 0.58$); however, the peak ventricular filling rate was significantly lower

Table 2. Regional and Global Left Ventricular Ejection Fraction (%)

	Regions					
	Global	**Lateral**	**Inferior**	**Apical**	**Septal**	**Anterior**
RVA						
6 months	55 ± 3	63 ± 3†‡	53 ± 4†‡	31 ± 3	40 ± 2	48 ± 4†‡
18 months	47 ± 3*	54 ± 4*†‡	53 ± 4†‡	30 ± 4	37 ± 3	42 ± 5*
RVOT						
6 months	55 ± 1	69 ± 2†	81 ± 2†	77 ± 2†	36 ± 2	60 ± 2†
18 months	56 ± 1	71 ± 2†	82 ± 2†	76 ± 2†	36 ± 2	57 ± 2†

*$p < 0.05$ compared with RVA pacing at 6 months. †$p < 0.05$ compared with the septal region. ‡$p < 0.05$ compared with the apical region. Data are expressed as the mean value ± SEM.

Abbreviation as in Table 1.

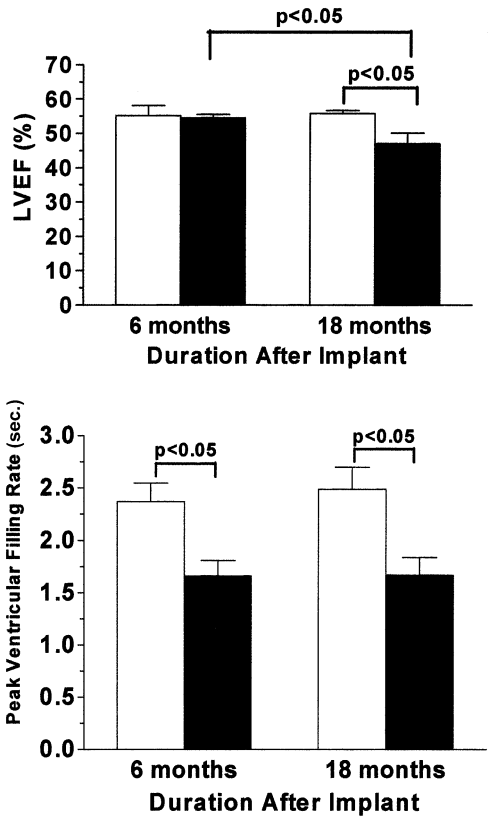

Figure 5. Global left ventricular ejection fraction (LVEF) **(upper panel)** and left ventricular diastolic function **(lower panel)** after 6 and 18 months of right ventricular apex (RVA) **(solid bars)** and right ventricular outflow tract (RVOT) **(open bars)** pacing. The LVEF during RVA pacing at 18 months was significantly lower than that during RVOT pacing at 18 months ($p < 0.05$) and during RVA pacing at 6 months ($p < 0.05$). At both 6 and 18 months, the peak ventricular filling rate during RVA pacing was lower than that during RVOT pacing ($p < 0.05$).

during RVA pacing than during RVOT pacing (1.66 ± 0.50 vs. 2.37 ± 0.64/s, $p < 0.01$) (Fig. 5).

At 18 months, nine patients (75%) with RVA pacing and four patients (33%) with RVOT pacing showed regional wall motion abnormalities on the radionuclide ventriculogram ($p = 0.04$). During RVA pacing, the LVEF in the apical and septal regions was significantly diminished, compared with that in the inferior and lateral regions ($p < 0.05$) (Table 2). During RVOT pacing, the LVEF in the septal region was significantly diminished compared with that in all the other regions ($p < 0.05$), and the LVEF in the inferior region was higher than that in the anterior, lateral, and septal regions ($p < 0.05$) (Table 2). The LVEF in the apical and inferior regions was significantly lower during RVA pacing than during RVOT pacing ($p < 0.05$) (Fig. 4). Both the global LVEF (56 ± 1% vs. 47 ± 3%, $p = 0.02$) and peak ventricular filling rate (1.66 ± 0.16 vs. 2.49 ± 0.21/s, $p < 0.01$) were significantly lower during RVA pacing than during RVOT (Fig. 5).

In patients with RVA pacing, there was a significant interval decrease in regional LVEF over the lateral and anterior regions ($p < 0.05$) (Fig. 4). As a result, global LVEF during RVA pacing was reduced at 18 months versus 6 months ($p < 0.01$). However, there were no interval changes in regional and global LVEF in patients with RVOT pacing ($p > 0.05$) (Table 2). The peak ventricular filling rate was similar at 6 and 18 months in both groups ($p > 0.05$).

DISCUSSION

Main findings. The results of this study demonstrate that RVA pacing leads to a high incidence of regional myocardial perfusion and wall motion abnormalities near the sites of electrical stimulation, which increase with the duration of pacing. These functional abnormalities during RVA pacing are associated with impairment of LV diastolic function and progressive deterioration of regional LVEF over time in regions remote from the site(s) of electrical stimulation, which result in a significant reduction in global LV function. Pacing at the RVOT is associated with more synchronous ventricular activation with a narrower QRS duration and lower incidence of regional myocardial perfusion and wall motion abnormalities, compared with RVA pacing, and it preserves global LV systolic and diastolic function over long-term follow-up.

Previous experimental studies. Asynchronous electrical activation during ventricular pacing has been shown to reduce LV function and to alter regional myocardial blood flow and work (3,11,24). This redistribution of regional myocardial blood flow and work is associated with abnormal structural and histologic changes in the ventricles (6–9). Although the mechanism remains unclear, previous experimental studies have demonstrated that RVA pacing results in greater impairment of ventricular function, as compared with pacing at other sites (3,25,26). Prinzen et al. (3) have demonstrated, by using magnetic resonance imaging tagging, the loss of contractile function in early activated regions with compensatory hyperfunctioning of late activated regions during ventricular pacing. However, pacing at the RVA, but not at the LV basal region, was associated with impairment of global LV function, suggesting that the size of the region with reduced function appears to be too large to be compensated during RVA pacing. Although RVA pacing resulted in more complex and inhomogeneous ventricular activation, with regions of rapid and slower propagation, pacing at the LV basal region showed a steady and consistent propagation of activation (27). This difference in myocardial activation may contribute to the larger hypofunctional area during RVA pacing. Furthermore, RVOT pacing that maintained synchronous ventricular activation preserved myocardial function and prevented the development of myofibrillar disarray (11,12).

Previous human studies. Recent clinical studies have demonstrated that asynchronous ventricular activation during RVA pacing is associated with impairment of LV systolic and diastolic function, as well as alteration of regional adrenergic innervation, myocardial blood flow, and perfusion in patients with normal coronary arteries

(1,4,5,28). Furthermore, regional perfusion defects and wall motion abnormalities became more pronounced with an increased duration of RVA pacing and subsequently led to impairment of LV function (10). Therefore, the use of alternate permanent ventricular pacing sites to prevent these potential long-term deleterious effects have been investigated.

Previous studies have demonstrated the long-term safety and efficacy of RVOT pacing as an alternate permanent right ventricular (RV) pacing site (29). However, investigations on the effects of RVOT pacing have yielded inconsistent results. Giudici et al. (13) have revealed a significant early hemodynamic benefit of RVOT pacing versus RVA pacing, whereas Buckingham et al. (14) failed to show any difference between RVOT and RVA pacing. Recently, Victor et al. (15) demonstrated no symptomatic improvement or hemodynamic benefit during RVOT pacing compared with RVA pacing in patients with long-term atrial tachyarrhythmias and complete AV block after three months of pacing. Schwaab et al. (16) showed that a reduction in the QRS duration by RVOT pacing is significantly correlated with homogenization of LV contraction and with increased systolic function. However, most of these studies involved early hemodynamic testing or only had a limited duration of follow-up, and the long-term effects of RVOT pacing on myocardial perfusion and functions have not been evaluated.

Long-term effects of RV stimulation. This is the first prospective study in humans to evaluate the long-term effects of using a different RV stimulation site on myocardial perfusion and function. In this study, RVOT pacing was performed by positioning the lead in that particular site of the interventricular septum to achieve the shortest QRS duration on the surface ECG (16). This resulted in a significant reduction in the QRS duration during RVOT pacing compared with RVA pacing. After six months of pacing, there were no significant differences in myocardial perfusion and global LV systolic function between RVA and RVOT pacing. However, global LV diastolic function diminished with RVA pacing compared with RVOT pacing. During both RVA and RVOT pacing, the regional LVEF decreased at the early activated regions and increased at the regions remote from the stimulation sites. As a result, the global LVEF was not depressed after six months in both groups. This may explain why previous (5) and recent (Right ventricular Outflow tract Versus Apical pacing [ROVA] trial) (30) clinical studies, which lasted less than six months, failed to show a benefit of RVOT pacing.

However, after 18 months of pacing, the number of myocardial perfusion defects and regional motion abnormalities were significantly higher and global LV systolic and diastolic function was significantly lower during RVA pacing compared with RVOT pacing. Furthermore, there was also a significant interval increase in the number of myocardial perfusion defects and regional motion abnormalities and a decrease in global LVEF (~14%) during RVA pacing after one year, but not during RVOT pacing. These data provide further evidence to support our previous findings (10) that asynchronous electrical activation during RVA pacing is associated with progressive worsening of myocardial perfusion and function over time. Most importantly, this study demonstrates that decreased asynchronous ventricular activation with RVOT pacing is associated with a lower incidence of regional myocardial perfusion and wall motion abnormalities, and it preserves global LV systolic and diastolic function over long-term follow-up.

Study limitations. First, only patients without coronary artery disease and normal LV function were included in this study. Therefore, whether the findings of this study are applicable to patients with underlying heart disease or LV dysfunction, or both, remains unclear. Second, the small number of patients in this study is a limitation. This was due to the strict screening criteria used in this study to exclude other factors that might affect LV function. Third, the clinical outcome and functional assessment, such as exercise capacity, quality of life, and hospital admission for heart failure, were not assessed in this study. Final, the lead position was optimized during RVOT pacing, but not during RVA pacing. Therefore, the result may simply demonstrate that the minimization of QRS duration, not the location of pacing, is important.

Conclusions. The present study demonstrates that permanent RVOT pacing that preserves ventricular activation prevents the long-term deleterious effects of "conventional" RVA pacing on myocardial perfusion and function in patients implanted with a permanent pacemaker. The long-term clinical benefit of using RVOT pacing for routine pacemaker implantation and resynchronization therapy for congestive heart failure requires further study.

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