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Influence of Right Ventricular Stimulation Site on Left Ventricular Function in Atrial Synchronous Ventricular Pacing

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OBJECTIVES The study investigates the correlation between left ventricular function and QRS duration obtained by alternate right ventricular pacing sites.

BACKGROUND 1. Right ventricular apical pacing is associated with alterations of left ventricular contraction sequence. 2. A stimulation producing narrow QRS complexes is supposed to provide for better left ventricular contraction patterns.

METHODS Fourteen patients with third degree AV block received one ventricular pacing lead in apical position. The alternate lead was attached to that site on the septum that produced the smallest QRS complex as measured from the earliest to the last deflection in any of the orthogonal Frank leads (xyz). During atrial synchronous ventricular pacing, the AV delay was optimized individually and for each stimulation site using mitral valve doppler or impedance cardiography. By radionuclide ventriculography, the phase distribution histogram of left ventricular contraction was evaluated as area under the curve (AuC); systolic function was determined as ejection fraction (EF) and as absolute ejected counts (EC) in random order. The difference (Δ) in QRS duration between apical and septal stimulation (Δxyz) was correlated with the difference in phase distribution (ΔAuC) and ejection parameters (ΔEF, ΔEC).

RESULTS QRS duration was shorter with septal than with apical pacing in 9 out of 14 patients (64%); it was longer in 4 (29%), and no difference was seen in 1 patient. There was a significant positive correlation between the change in QRS duration (Δxyz) and phase distribution (ΔAuC: $r = 0.66393$, $p = 0.010$) and a significant negative correlation to systolic function (ΔEF: $r = 0.70931$, $p = 0.004$; ΔEC: $r = 0.74368$, $p = 0.002$).

CONCLUSIONS In atrial synchronous right ventricular pacing, if the AV delay is adapted individually, decreased QRS duration obtained by alternate pacing sites is significantly correlated with homogenization of left ventricular contraction and with increased systolic function in acute tests. (J Am Coll Cardiol 1999;33:317–23) © 1999 by the American College of Cardiology

As a result of the early work of Koch (1920) and Wiggers (1925), it is well known that artificial stimulation of the heart results in asynchronous, prolonged contraction with lower dP/dt and reduced pressure maximum (1,2). Animal studies have revealed that right ventricular apical (RVA) pacing alters diastolic (3) and systolic (4) function, changes regional tissue perfusion, increases tissue catecholamine activity (5) and produces histologic abnormalities (6,7) in the left ventricular myocardium. Investigations on alternate pacing sites, however, have yielded inconsistent results. Some researchers reported that right ventricular outflow tract (RVOT) and right ventricular septal (RVS) pacing increased systemic arterial blood pressure and cardiac output (8–11), that it normalized biventricular activation and contraction patterns and that it preserved normal cellular morphology (12). Others did not find any significant differences in left ventricular function or blood pressure when using these stimulation sites in animals (13–17).

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In humans, chronic RVA pacing has been reported to impair diastolic function (18,19,20), to reduce systolic contraction (18,21) and to alter myocardial perfusion (21). Data about alternate pacing sites, again, are conflicting. During VVI pacing, Benchimol et al. (22) and Barold et al. (23) did not reveal any advantage of RVOT pacing, whereas Giudici et al. (24) and De Cock et al. (25) demonstrated a significant increase in cardiac output and cardiac index as compared with RVA pacing. With AV sequential (DDD)

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Abbreviations and Acronyms

AuC = area under the curve
AAT = atrial pacing is triggered by atrial sensing
VDD = atrial synchronous ventricular pacing
AV = atrioventricular
DDD = AV sequential pacing
ROI = region of interest
RVA = right ventricular apical
RVOT = right ventricular outflow tract
RVS = right ventricular septal

pacing, Buckingham et al. reported similar results for cardiac output measured during RVOT and RVA pacing in patients with normal (26) or reduced left ventricular function (27) and in patients after coronary bypass surgery (28). Raichlen et al. (29) showed that RVA pacing resulted in a significant higher cardiac index as compared with RVOT pacing in DDD mode after coronary bypass surgery. Just one study revealed a significant hemodynamic benefit during atrial synchronous RVS pacing in patients with reduced left ventricular function as compared with RVA pacing (30).

Most of these studies have major limitations: the location where RVS or RVOT pacing was performed has not been clearly specified (22,25), and patients being in sinus rhythm were paced nonphysiologically in the ventricle only (22–25). All studies with atrioventricular (AV) sequential pacing used arbitrary AV delays (26–30) that were mostly identical for septal and apical stimulation (26–29), and, in all the studies cited (22–30), alternate pacing sites were defined topographically.

Using a more functional definition in this study, the lead was attached to that particular site on the interventricular septum that provided for the shortest QRS duration in the surface ECG. All measurements of left ventricular function were performed with the AV interval optimized individually and separately for septal and apical stimulation (31–35). The aim of this prospective study was: 1) To test whether this technique of right ventricular septal implantation is feasible with commercially available pacing leads, and 2) to investigate the interrelation between surface QRS duration and left ventricular function.

METHODS

Fourteen consecutive patients, 6 men, 8 women, mean age 71 ± 8 yr (range 63–87 yr) were included. All were in sinus rhythm and were paced with a DDD system for third degree AV block (Table 1). The study protocol was approved by the local ethics committee, and patients gave informed consent.

Implantation. Half an hour before and 12 hours after the operation, patients received 1.5 g cefuroxim (Zinacef; Hoechst AG, Frankfurt/Main, Germany) intravenously. When an exhausted pulse generator was replaced and the chronic ventricular lead had previously been implanted in the right ventricular apex, the temporary pacing lead was fixed in septal position. During a new implantation, the temporary pacing lead was conventionally implanted in apical position and the permanent electrode was attached to the septum. All septal leads were implanted by the same cardiologist using active fixation leads only (permanent lead: YP60BP, Biotronik, GmbH, Berlin, Germany; temporary lead: TUS2/5F bipolar, Sulzer Osypka, GmbH, Grenzach-Whylen, Germany). Mapping of the interventricular septum was performed by means of custom shaped stylets until the smallest QRS complex available was recorded. Atrial leads were attached to the right atrial lateral wall.

QRS duration. During operation, surface ECG was recorded with a paper speed of 100 mm/s (Mingograph 7; Siemens, Erlangen, Germany). To determine the spatial width of the ECG, the orthogonal leads of Frank were used (xyz; [36]). QRS duration (ms) was manually measured from the earliest to the latest deflection of the QRS complex in any of the Frank leads. The difference in QRS duration between septal and apical pacing (Δxyz; [ms]) was calculated in every patient.

Instrumentation. Measurements were performed during atrial synchronous ventricular (VDD) pacing with the basic rate well below the patients sinus rate. Permanent ventricular leads were driven by the pacemaker implanted; temporary leads were attached to the ventricular connector of an external dual chamber pulse generator (model 5345; Medtronic Inc., Minneapolis, Minnesota). Atrial synchronous ventricular function of this unit was established by connecting skin electrodes to the atrial port which were able to detect atrial pacing spikes from the internal device operating in atrial pacing is triggered by atrial sensing (AAT) mode at high output settings.

Optimization of AV delay. The optimum AV delay was determined by maximizing left ventricular stroke volume equivalents from impedance cardiography ([34]; Cardiomed 30; Cardiomed, Homburg, Germany) or by maximizing left ventricular filling time using pulsed Doppler echocardiography of the transmitral blood flow as previously described [37]; Ultramark 9 HDI; ATL, Inc., Bothell, Washington). Optimization was performed in every patient and for each stimulation site.

Radionuclide ventriculography. Red blood cell labeling was performed in vivo by administration of 2.0 mg tin (II) fluoride/3.4 mg methylene diphosphonic acid (Amerscan Zinn(II)-Agens; Amersham Buchler Inc., Braunschweig, Germany), followed by 800 MBq ^{99m}Technetium-pertechnetate (38). An ECG-triggered, gated scintigraphy of the left ventricle was performed from the left anterior oblique view (45°) by means of a small-field-of-view APEX 210M gamma camera (Elscint, Inc., Haifa, Israel). Using a 32 × 32 pixel matrix, sixty-four frames per cardiac cycle were acquired in phase mode until total counts reached six

Table 1. Patients' Characteristics and Results of the Study

No	Age Sex	Pathol.	ECG in.	AV opti.		HR [bpm]	AV [ms]	QRS [ms]	EF [%]	ΔQRS [ms]	ΔAuC	ΔEF [%]	ΔEC [%]
1	70	DCM	no	Imp	s	74	120	150	45	−40	−323	+6	+17
	F		block		a	76	120	190	39				
2	64	VHD	no in.	Imp	s	70	100	155	64	+15	+157	−7	−6
	m		rhythm		a	70	60	140	71				
3	83	?	no in.	Imp	s	83	150	160	63	±0	+50	−11	−9
	F		rhythm		a	81	95	160	74				
4	63	?	no in.	Imp	s	67	60	160	53	−20	−196	−8	−14
	M		rhythm		a	66	40	180	61				
5	70	HT	comp.	Imp	s	71	120	170	61	+10	+173	−8	−3
	F		LBBB		a	71	80	160	69				
6	66	?	no	Echo	s	65	80	160	55	+10	−139	−9	−10
	F		block		a	64	110	150	64				
7	77	CHD	comp.	Echo	s	89	40	155	43	−25	−53	+3	+14
	F		RBBB		a	87	50	180	40				
8	68	?	no in.	Echo	s	72	60	170	59	−15	−18	+2	+8
	M		rhythm		a	71	40	185	57				
9	66	CHD	no in.	Echo	s	62	100	170	41	−10	−15	−6	+1
	M		rhythm		a	62	130	180	47				
10	68	CHD	comp.	Echo	s	71	60	150	57	+10	+110	−2	−1
	F		LBBB		a	72	70	140	59				
11	87	HT	no in.	Echo	s	78	80	150	49	−5	−99	−7	+4
	F		rhythm		a	76	140	155	56				
12	68	?	no in.	Echo	s	91	100	160	55	−10	−121	−4	−7
	M		rhythm		a	89	140	170	59				
13	68	HT	no in.	Echo	s	80	60	140	40	−50	−115	+2	+24
	M		rhythm		a	83	100	190	38				
14	81	CHD	comp.	Echo	s	55	80	140	43	−10	+119	−7	+8
	F		LBB		a	55	120	150	50				

Demographic data and results of all patients included in the study: No. = number; age in years; sex: F = female, M = male; Pathol. = pathology of the underlying heart disease; DCM = dilated cardiomyopathy; VHD = valvular heart disease; ? = unknown; HT = hypertension; CHD = coronary heart disease; ECG in. = intrinsic QRS morphology; no block = no fascicular or bundle branch block; comp = complete; L = left; R = right; BBB = bundle branch block; AV opti. = method of AV delay optimization; Imp = impedance cardiography; Echo = echocardiography; s = during septal pacing; a = during apical pacing; HR = intrinsic heart rate during radionuclide ventriculography in beats per minute (bpm); AV = optimized AV delay (ms); QRS = QRS duration (ms) measured from the earliest to the latest deflection of the QRS complex in any of the Frank leads (see Methods); EF = ejection fraction (%); Δ = absolute difference of s as compared with a value; AuC = area under the curve of the left ventricular phase distribution histogram; EC = ejected counts (%).

million. Measurements were taken 15 min after randomly programming to the external or internal pacing system.

For evaluation, a master left ventricular region of interest (ROI) was created after standardized background subtraction. This Master ROI was held constant for the processing of all intraindividual studies, and it was used to define the working area for an automatic edge detection creating the ROI on each frame. After generation of the time activity curve, global ejection fraction (EF) and absolute ejected counts (EC) were calculated. Phase images were generated by Fourier analysis, and the peak in phase distribution histogram was evaluated as the area under the curve (AuC) of the ventricular systole. After correction for physical decay, scintigraphic data were evaluated by the same physician who was blinded for the pacing modes. The difference (Δ) in AuC, EF and EC between apical and septal stimulation was calculated (ΔAuC, ΔEF and ΔEC).

Statistics. Linear regression analysis was performed for Δxyz versus ΔAuC, Δxyz versus ΔEF and for Δxyz versus ΔEC, respectively, and ΔAuC, and ΔEF and ΔEC were correlated to one another. In eight patients randomly chosen, radiocardiography was performed twice. The ratio between standard deviation and mean value of double measurements was taken as the coefficient of variation. Paired data were compared by nonparametric Wilcoxon test, frequency distribution of parameters between groups was analyzed by Fisher's exact test. A $p < 0.05$ was considered significant.

RESULTS

There was no complication during surgery. An average of 9 ± 4 attempts (range 3 to 18) were made until final position of the septal lead was reached. By the technique described, QRS duration was shorter in 9 out of 14 patients (64%) with RVS pacing as compared with RVA pacing. In one patient, there was no difference and in four patients (29%), QRS duration was longer despite the septal implantation site. In the whole study group, average QRS duration

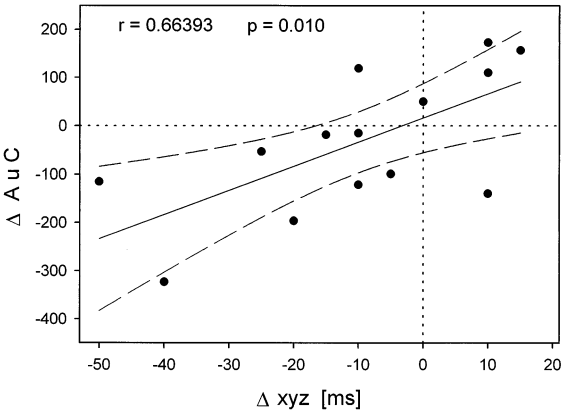

Figure 1. The difference in QRS duration obtained with septal and apical pacing (Δxyz [ms]; see methods) is plotted against the difference in the area under the curve of the phase distribution histogram as obtained with septal and apical pacing (ΔAuC; n = 14). Full line = regression line; dotted line = 95% confidence limit; r = regression coefficient; p = level of significance.

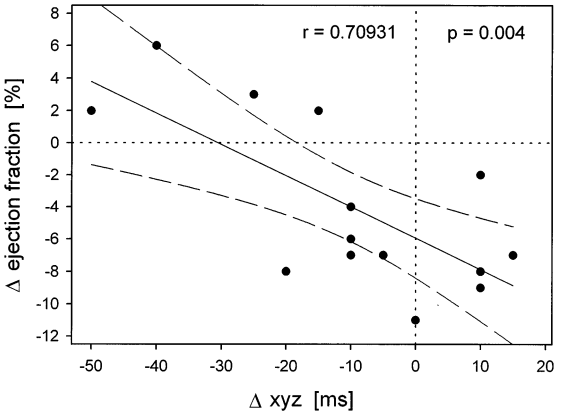

Figure 2. The difference in QRS duration (Δxyz) is plotted against the difference in ejection fraction as obtained with septal and apical pacing (ΔEF [%]; n = 14). Abbreviations as in Figure 1.

did not differ significantly between RVS and RVA pacing (156 ± 10 ms versus 166 ± 18 ms; Table 1).

Optimization of the AV delay was performed by impedance cardiography in five patients and by mitral valve doppler echocardiography in nine. In 8 out of 14 patients (57%), the optimized AV delay was shorter with RVS pacing; in 1 patient, there was no difference and in 5 patients (36%), it was shorter with RVA pacing (Table 1). The mean optimized AV delay did not differ significantly between septal (86 ± 30 ms) and apical (93 ± 36 ms) pacing (Table 1).

Left ventricular systolic function was not severely depressed in the patients studied as indicated by their ejection fraction ranging between 38% and 74% (Table 1). The coefficient of variation of the radionuclide parameters was 0.06 ± 0.08, 0.07 ± 0.05 and 0.05 ± 0.03 for AuC, EF and EC, respectively. The AuC was smaller in eight out of nine patients (89%) in whom septal QRS duration was shorter as compared with apical pacing; however, one out of four patients in whom QRS duration was longer with septal stimulation also showed a reduced AuC (p = 0.052). The ejection fraction (EF) increased in four out of nine patients (44%) with a smaller septal QRS duration. All patients with longer septal QRS duration showed a lower EF than with apical pacing (p = 0.228). Among the patients who had shorter QRS durations during septal pacing, seven out of nine (78%) also exhibited higher ejected counts (EC), whereas all patients with longer septal QRS durations showed reduced EC (p = 0.021).

There was a significant, linear, positive correlation between the difference in QRS duration (Δxyz) obtained by apical and septal pacing and the change in phase distribution histograms of left ventricular contraction, evaluated as the area under the curve (ΔAuC, r = 0.66393, p = 0.010), although seven patients were outside the 95% confidence limit (Fig. 1). The difference in QRS duration was linearly and inversely related to the difference in left ventricular systolic function measured as ejection fraction (ΔEF, r = 0.70931, p = 0.004; Fig. 2) or ejected counts (ΔEC, r = 0.74368, p = 0.002; Fig. 3) with six and four patients, respectively, being outside the 95% confidence limit.

There was no correlation between the difference in phase distribution histograms (ΔAuC) and the difference in ejection fraction (ΔEF: r = 0.42832, p = 0.107) as well as between Δ AuC and the difference in ejected counts (ΔEC: r = 0.22647; p = 0.436). But the correlation between the difference in ejection fraction (Δ EF) and ejected counts (ΔEC) was highly significant: r = 0.80590, p < 0.001.

DISCUSSION

Dual chamber pacing with the preservation of atrioventricular synchrony represents a major advance in the treatment of bradycardia. A clinically relevant problem, although unsolved, is pacing from some right ventricular site which

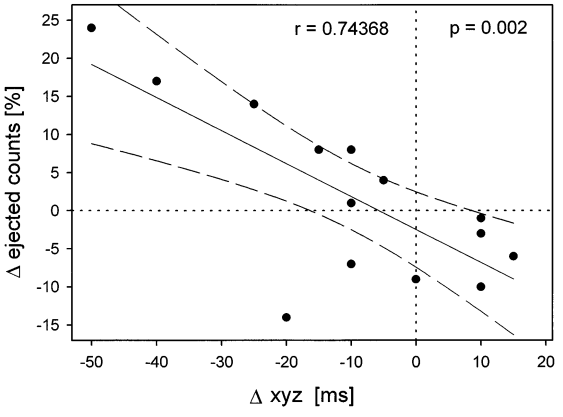

Figure 3. The difference in QRS duration (Δxyz) is plotted against the difference in the ejected counts as obtained with septal and apical pacing (Δ EC [%]; n = 14). Abbreviations as in Figure 1.

may result in nonphysiological contraction and relaxation patterns of the left ventricle (18–21). The present study addresses this issue and tries to avoid methodological pitfalls in the field of septal pacing.

QRS duration obtained by ventricular pacing. A long QRS duration obtained by artificial stimulation suggests that the pathways of left ventricular activation are different from normal. It is supposed that the more myocardium activated by muscle conduction before the ectopic activation front enters the specialized conduction system, the longer the QRS duration (10,39). This is shown by animal studies (8,9,12,17,40) and by a study in humans (30), where the His-Purkinje conduction system was directly paced producing narrow QRS complexes comparable to intrinsic rhythms. It must be emphasized, however, that pacing the bundle of His which is preferable with regard to very narrow QRS complexes may be technically difficult (17) and may not be adequate in patients presenting with infra Hisian conduction problems.

Correlation of QRS duration with left ventricular function. In 1925, Wiggers (2) postulated that the longer the distance from the artificial stimulation site to the entry of the His-Purkinje system the weaker the beats that occur. This was supported by the electrophysiological maps obtained in dogs by Lister et al. (39). In both studies, data were not taken from the surface ECG. Burkhoff et al. (10) found a highly significant, linear, negative correlation between peak isovolumic pressure and QRS duration ($r = 0.971$) during epicardial single chamber ventricular pacing from different sites in canine hearts. In their study, an A-C coupled bipolar ECG was recorded directly from the epicardium between left ventricular and right ventricular free wall, which is hardly comparable to surface ECG data. Another animal study showed a linear positive correlation (r from 0.58 to 0.93) between QRS duration and the rightward shift of the left ventricular endsystolic pressure-volume relation when the pacing mode was changed from atrial to ventricular pacing (16). In that study, a surface ECG was used, but only lead II was considered.

A correlation between the reduction of surface QRS duration and the improvement of left ventricular function by changing a single right ventricular pacing site has not yet been demonstrated in humans. This might be due to the fact that only two dimensional ECG recordings were used in those investigations with detailed ECG technique (26–28). Another reason could be that in the studies cited (26–28), QRS durations were measured after the septal pacing site had been determined topographically, whereas in this study, QRS duration was the criterion for optimizing the right ventricular pacing site. Using this approach, it could be demonstrated that the reduction in QRS duration was linearly related to homogenization of contraction and to an increase in ejection parameters of the left ventricle. However, the lack of correlation between homogeneity of left ventricular contraction (ΔAuC) and systolic function (ΔEF, ΔEC) suggests that homogenization is not sufficient to explain the interrelationship between QRS duration and cardiac output. Several other factors might be important: 1) Homogeneity as assessed by the phase histogram of left ventricular contraction does not reflect the sequence of left ventricular activation and mechanics that might be nonphysiologic despite a narrow phase distribution. 2) In contrast to the radionuclide technique which focuses the ROI on the left ventricular cavity, QRS duration represents the electrical activation of both the left and right ventricles. Hence, homogeneity of left ventricular contraction does not necessarily indicate a normal interventricular timing which was not assessed in this study but may have an influence on left ventricular ejection performance.

AV delay in atrioventricular synchronous pacing. A major determinant of diastolic hemodynamics in DDD pacing is the AV delay programmed (31–35). As the right ventricular stimulation site seems to alter left ventricular diastolic function (18–20), and as it influences beginning of left and right ventricular contraction, an identical AV interval for different pacing sites cannot be appropriate. Timing of AV delay has rather to be adapted on specific diastolic filling patterns obtained with a particular stimulation site. Moreover, this optimization is a prerequisite for adequate systolic function as shown in the studies of Kosowsky et al. (8) and Daggett et al. (14), who clearly demonstrated that the improvement in left ventricular function obtained by an alternate right ventricular pacing site varied with the AV delay programmed. The fact that Buckingham et al. (26–28) used the same AV delay for RVA and RVS pacing might explain why they did not find a significant increase in systolic function.

Cowell et al. (30) used preset AV delays (50, 100, 150 ms), but data were evaluated for that interval giving maximum cardiac output individually and for each stimulation site. These optima showed a trend toward shorter AV delays during RVS as compared with RVA pacing. Data of the present study do not allow a recommendation whether the AV delay has to be shorter with septal than with apical pacing (Table 1). On the contrary, results of this study support the need for optimizing the AV delay individually for patient and pacing site.

Conclusions. Right ventricular lead implantation guided by surface QRS duration is feasible by means of commercially available pacing leads. Using this technique, the reduction of QRS duration obtained by alternate pacing sites is linearly related to homogenization of left ventricular contraction and to improvements of systolic function. Given the small number of patients and the relatively minor effects on ejection fraction, it seems unwarranted that the results of the present study should affect the general practice of lead implantation. Its results do justify initiation of a larger scale study on the mechanisms and long term consequences of different lead placements. However, the alternate stimulation site must be clearly defined, whereby a functional rather

than topographic criterion should be established. In patients with sinus rhythm and AV synchronous pacing, the AV delay should be optimized individually and for each stimulation site. It might be that these methodological issues are responsible for the fact that recent studies failed to confirm any consistent benefit of DDD pacing in severe heart failure using one single alternate pacing site (41) and that at least biventricular (42) or even multisite pacing (43) was needed to achieve this goal.

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