JACC Vol. 3, No. 4
April 1984:986-91

Two-Dimensional Echocardiographic Contrast Assessment of Pacing-Induced Mitral Regurgitation: Relation to Altered Regional Left Ventricular Function

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Two-dimensional echocardiography during agitated saline contrast injections into the left ventricle was applied in eight closed chest dogs to examine the degree of mitral valve regurgitation encountered with pacing from two sites: 1) at the right ventricular apex and 2) within the coronary sinus at the base of the left ventricle. Pacing was at a rate of 10 beats/min above the sinus rate, and ranged from 60 to 120 beats/min. Hemodynamic variables were monitored, and data on global and regional left ventricular function were derived from a series of short- and long-axis cross-sectional echographic images. The degree of valvular regurgitation was assessed independently by two observers, and systolic appearance of echo contrast in the left atrium was graded as 0 to +4.

Although no mitral regurgitation was noted in sinus rhythm, regurgitation was severe with right ventricular apical pacing (3.2 ± 0.7, mean ± standard deviation) and relatively mild (0.9 ± 0.7) with basal pacing ($p < 0.01$ and 0.05, respectively). Relative to sinus rhythm, thermodilution stroke volume was significantly ($p < 0.05$) depressed by both apical and basal pacing (from 32.6 ± 14.6 to 25.0 ± 7.9 and 26.0 ± 7.6 cc, respectively), but there was no significant difference between the two pacing sites. Mapping of regional function at six levels of the left ventricle revealed significant heterogeneities, with maximal dysfunction noted in the vicinity of the pacing site.

It is concluded that significant differences in mitral regurgitation exist depending on the site of pacing, with apical pacing causing severe regurgitation and abnormal regional contraction near the pacing site.

Although anecdotal reports indicate that ventricular pacing can induce significant mitral regurgitation and hemodynamic derangements, systematic investigation is lacking, particularly with regard to any differences due to pacing site and relative to pacing-induced alterations in regional and global left ventricular function. Hence, the objective of the current study with left ventricular contrast injections was to provide data on regurgitation during right apical versus left basal ventricular pacing, and to elucidate possible mechanisms by mapping regional function with two-dimensional echocardiography.

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Methods

Experimental preparation. We studied eight closed chest dogs weighing 26.3 ± 4.8 kg (range 20 to 32), premedicated with morphine (1.5 mg/kg body weight intramuscularly) and anesthetized with sodium pentobarbital (30 mg/kg intravenously). Ventilation was performed using a Harvard respirator and a cuffed endotracheal tube.

A 7F pigtail catheter was placed in the left ventricle by way of a femoral artery and was used for both left ventricular pressure measurements and left ventricular contrast injections. Arterial pressure was measured with a 7F catheter inserted into the aortic root through the left carotid artery. A Swan-Ganz catheter positioned in the pulmonary artery was utilized for thermodilution measurements of cardiac output.

Table 1. Changes With Right Ventricular Apical and Left Ventricular Basal Pacing Compared With Sinus Rhythm

	NSR	RVa-P	LVb-P
MR	0	3.2 ± 0.7*	0.9 ± 0.7†
SV	32.6 ± 14.6	25.0 ± 7.9†	26.0 ± 7.6*
LVEDP	2.7 ± 2.2	6.6 ± 2.6	3.5 ± 2.2
AoP	99.1 ± 13.4	99.4 ± 15.7	92.1 ± 8.0
EDV	57.8 ± 13.8	64.0 ± 22.4	60.0 ± 17.7
ESV	34.6 ± 10.6	40.1 ± 17.2	38.4 ± 13.4
EF	40.6 ± 6.6	38.4 ± 11.6	35.6 ± 9.6

*$p < 0.01$ compared with normal sinus rhythm; †$p < 0.05$ compared with normal sinus rhythm. AoP = aortic pressure; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LVb-P = left ventricular basal pacing; LVEDP = left ventricular end-diastolic pressure; MR = mitral regurgitation; NSR = normal sinus rhythm; RVa-P = right ventricular apical pacing; SV = stroke volume.

Ventricular pacing. A bipolar pacing catheter was positioned in the right ventricular apex and coronary sinus. The latter was advanced deeply enough to provide controlled epicardial stimulation in the left ventricular basal region as judged from the surface electrocardiogram. A pulse generator with a stimulus isolation unit (Bloom Associates Ltd., model DTC-110-C) was used to provide threshold stimuli (2 to 5 mA) for ventricular pacing at heart rates that were 10 beats above the dog's sinus rate. In view of variations in the intrinsic heart rate, right ventricular apical and left ventricular basal pacing was performed at rates from 60 to 120 beats/min.

Echocardiographic imaging. Two-dimensional echocardiographic studies were performed using a 90° mechanical sector scanner (ATL Mark III) equipped with a 3 MHz transducer. All studies were performed as previously reported (1), with the dog on its right side and the transducer placed on the right chest wall, pointing upward. In this manner, high quality images of the left ventricle were obtained in long-axis as well as six short-axis cross sections at the mitral, high, mid and low papillary, as well as lower left ventricular and apical levels.

Quantitation of two-dimensional echocardiographic images was performed using a light-pen system attached to an image analysis computer. Left ventricular volumes were reconstructed using the modified Simpson's formula, and the left ventricular ejection fraction was calculated. In addition, percent systolic fractional area change (FAC) for each short-axis cross plane was computed using the formula:

$$FAC = \frac{EDA - ESA}{EDA} \times 100,$$

where EDA = end-diastolic area and ESA = end-systolic area.

Echo contrast studies. A normal saline solution, agitated by repeated flushing between two 10 cc syringes via a three-way stopcock (2), served as the echocardiographic contrast agent. For evaluation of presence and severity of mitral regurgitation, we hand-injected 2 cc of the contrast agent into the left ventricle while recording two-dimensional echocardiographic long-axis views. All injections were performed by the same investigator, using approximately the same injection force. The tip of the pigtail catheter was positioned near the left ventricular apex to avoid spurious regurgitation that might be encountered by proximity of the catheter to the mitral valve. Two echo contrast injections each were performed during sinus rhythm and right ventricular apical as well as left ventricular basal pacing. Two blinded independent observers assessed the severity of mitral regurgitation by grading the appearance of echo contrast in the left atrium as 0 to 4+, according to criteria used with standard left ventricular angiography (3).

Experimental protocol. After placement of all catheters and stabilization of the dog, baseline measurements of left ventricular end-diastolic pressure, aortic pressure and cardiac output were obtained during sinus rhythm. Two-dimensional echocardiographic recordings were performed in the long-axis as well as in all five short-axis planes. Two injections of echo contrast agent were performed while imaging the left ventricular long-axis plane.

Hemodynamic measurements and the two-dimensional echocardiographic studies with and without contrast were

Table 2. Severity of Mitral Regurgitation With Different Pacing Sites in Individual Dogs

Dog	NSR	RVa-P	LVb-P
1	0	3	0
2	0	3	1
3	0	3.5	1
4	0	3	1
5	0	4	2
6	0	3	1.5
7	0	2	0.5
8	0	4	0
Mean ± SD	0	3.2 ± 0.7*	0.9 ± 0.7†

*$p < 0.01$ compared with normal sinus rhythm; $p < 0.05$ compared with normal sinus rhythm. LVb-P = left ventricular basal pacing; NSR = normal sinus rhythm; RVa-P = right ventricular apical pacing; SD = standard deviation.

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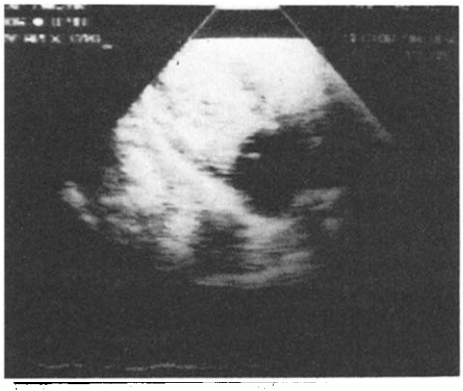


Figure 1. Two-dimensional echocardiographic image of a left ventricular contrast injection during normal sinus rhythm (NSR). There is no evidence of mitral regurgitation. LA = left atrium; LV = left ventricle; MV = mitral valve.

repeated during right ventricular apical and left ventricular basal pacing.

Statistical analysis. All results are expressed as mean ± standard deviation. Friedman's analysis of variance and the Newman-Keuls test were used to assess the significance of differences between sinus rhythm, right ventricular apical pacing and left ventricular basal pacing for mitral regurgitation score (graded 0 to 4+), thermodilution stroke volume, left ventricular end-diastolic pressure, aortic mean pressure, left ventricular end-diastolic volumes and ejection fraction, as well as fractional area changes in the two-dimensional echocardiographic short-axis sections. The Kappa test was utilized to evaluate the reliability of mitral regurgitation scoring; all generated scores were used to study reproducibility between two observers for the same injection, as well as the reproducibility between two different injections scored by one observer.

Results

Mitral regurgitation (Tables 1 and 2). Mitral regurgitation was not found to be present in any of the eight dogs during sinus rhythm (Fig. 1). The severity of regurgitation with right ventricular apical pacing was judged to be 3.2 ± 0.7 (mean ± standard deviation), ranging from 1+ to 4+; with basal pacing it measured 0.9 ± 0.7 ranging from 0 to 2+ (Figs. 2 and 3). Compared with no regurgitation during sinus rhythm, both right ventricular apical ($p < 0.01$) and left ventricular basal (probability [p] < 0.05) pacing resulted in a significant increase in the regurgitation score. Furthermore, the valvular insufficiency with right ventricular apical stimulation was significantly greater than with left ventricular basal pacing ($p < 0.05$).

Interobserver reproducibility for the scoring of mitral regurgitation was good, resulting in a Kappa value of 0.95 (perfect agreement being indicated by Kappa value of 1.0), as was reproducibility between two different injections assessed by the same observer (Kappa = 0.96).

Hemodynamic changes (Table 1). Thermodilution-derived left ventricular stroke volume measured 32.6 ± 14.6 cc during sinus rhythm, 25.0 ± 7.9 cc with right ventricular apical pacing and 26.0 ± 7.6 cc with left ventricular basal pacing. Thus, ventricular stimulation from either site resulted in similar decreases in stroke volume, both of which were significant ($p < 0.05$) when compared with sinus rhythm. Left ventricular end-diastolic pressure increased slightly (but not significantly) from 2.7 ± 2.2 mm Hg with sinus rhythm to 6.6 ± 2.6 mm Hg with right ventricular apical pacing and 3.5 ± 2.2 mm Hg with left ventricular basal pacing. No significant changes in mean aortic pressure were seen with right ventricular apical pacing (99.4 ± 15.7 mm Hg) or with left ventricular basal pacing (92.1 ± 8.0 mm Hg), as compared with sinus rhythm (99.1 ± 13.4 mm Hg).

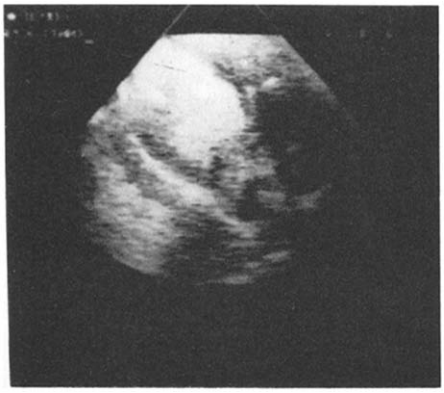
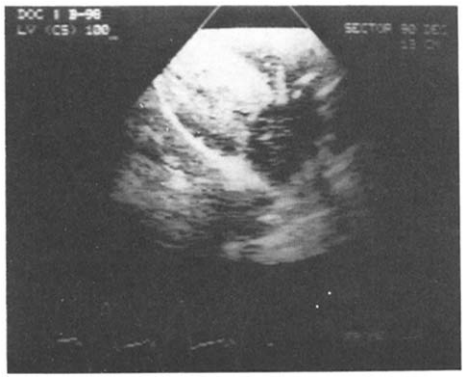


Figure 2. Diastolic two-dimensional echocardiographic image of a left ventricular contrast injection during right ventricular (RV) apical pacing. The left atrium (LA) is almost completely opacified by contrast material, indicating severe mitral regurgitation. Other abbreviations as in Figure 1.



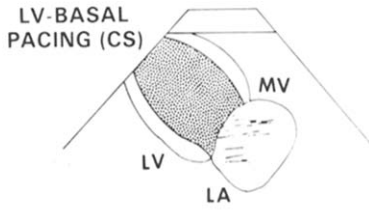


Figure 3. Two-dimensional echocardiographic image of a left ventricular (LV) contrast injection during left ventricular basal pacing. Some contrast appears in the left atrium (LA), although to a much lesser degree than with right ventricular apical pacing. CS = coronary sinus.

Left ventricular function (Tables 1 and 3, Fig. 4). Ventricular stimulation from either location resulted in a significant decrease in systolic fractional area change at the left ventricular short-axis view at a level closest to the pacing site. Thus, fractional area change at the mitral valve level decreased from 23.8 ± 1.5% during sinus rhythm to 6.2 ± 4.7% with left ventricular basal pacing ($p < 0.001$), but remained similar (28.4 ± 10.5%) with right ventricular apical pacing. Conversely, fractional area change at the apical level decreased from 56.7 ± 10.1% with sinus rhythm to 5.5 ± 3.6% with right ventricular apical pacing ($p < 0.001$), but was not altered significantly with left ventricular basal pacing (56.3 ± 6.6%). Neither of the two pacing sites had a significant effect on fractional area change at the midportion of the ventricle.

Both left ventricular end-diastolic and end-systolic volumes increased slightly, but not significantly, with pacing from either site, and there was a minor decrease in ejection fraction.

Discussion

Although pacing-induced mitral regurgitation has been reported as a contributory cause for the hemodynamic alterations observed with ventricular pacing, no systematic studies have as yet been undertaken to study this phenomenon. In some patients, pacing resulted in acute heart failure and angiographically documented severe mitral regurgitation, which was not present during sinus rhythm (4). Walston et al. (5) angiographically documented pacing-induced mitral regurgitation in dogs, but did not investigate it further because its occurrence was actually considered to be a reason for exclusion from their study. A number of investigators (6–8) based the presence of regurgitation on changes in left atrial pressure tracings during ventricular pacing. Others (9,10) hypothesized its existence to account for observed changes in left ventricular function.

We used two-dimensional echocardiography and left ventricular chamber injections of echo contrast material, as previously described (2), to study mitral regurgitation. None of the dogs studied had evidence of valvular insufficiency during sinus rhythm; however, it was almost always present during pacing, although in varying degrees. With right ventricular apical pacing, mitral regurgitation tended to be more severe than with left ventricular basal stimulation, although the pacing-induced decrease in stroke volume, as assessed with the thermodilution technique, was similar for both sites.

Possible mechanisms of pacing-induced mitral regurgitation. A decrease in forward output with ventricular pacing is well recognized and has been attributed to a number of mechanisms other than mitral regurgitation. Thus, loss of synchronized atrial contribution has been implied (6,8,9,11,12), particularly in patients with heart disease (13). Reports on the effects of different ventricular pacing sites on left ventricular performance are conflicting.

Table 3. Changes in Two-Dimensional Echocardiographic Short-Axis Fractional Area Change With Right Ventricular Apical and Left Ventricular Basal Pacing

LV Short-Axis Level	NSR	Rva-P	LVb-P
MV	23.8 ± 1.5	28.4 ± 10.5	6.2 ± 4.7*
HP	29.0 ± 6.4	32.3 ± 9.6	14.9 ± 10.4†
MP	33.9 ± 7.5	33.7 ± 9.4	27.9 ± 12.5
LP	39.0 ± 9.0	33.9 ± 14.7	39.1 ± 9.0
LLV	46.9 ± 5.3	20.0 ± 13.3*	43.9 ± 9.4
Ap	56.7 ± 10.1	5.5 ± 3.6*	56.3 ± 6.6

*$p < 0.001$ compared with normal sinus rhythm; †$p < 0.01$ compared with normal sinus rhythm. Ap = apical; HP = high papillary; LLV = lower left ventricular; LP = low papillary; LV = left ventricular; LVb-P = left ventricular basal pacing; MP = mid-papillary; MV = mitral valve; NSR = normal sinus rhythm; Rva-P = right ventricular apical pacing.

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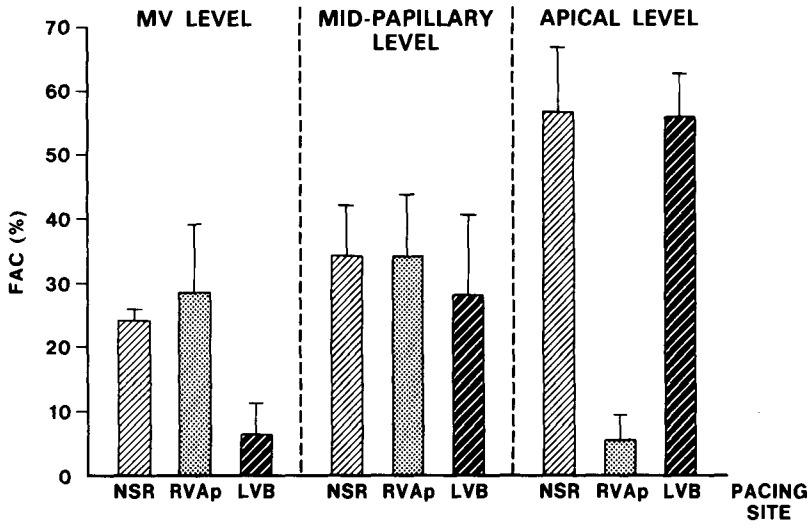

Figure 4. Left ventricular fractional area (FAC) change in two-dimensional echocardiographic short-axis cross sections with different pacing sites (expressed as mean ± standard deviation). Fractional area change decreases significantly with right ventricular apical pacing (RVAP) at the apical level ($p < 0.001$ compared with sinus rhythm) and with left ventricular basal (LVB) pacing at the mitral valve (MV) level ($p < 0.001$ compared with normal sinus rhythm [NSR]).

Although some investigators (13,14) found no differences, others (9,10,15) observed superior left ventricular performance with pacing from left ventricular sites as compared with right ventricular stimulation. In addition, occurrence of hypotension during pacing has been ascribed to stimulation of vagal receptors in the atrial wall by sudden atrial distension in conjunction with cannon waves on the left atrial pressure tracing (16).

The reason why ventricular pacing can cause mitral regurgitation remains unclear. Tsakiris et al. (17) reported mitral regurgitation to occur if a premature ventricular contraction suddenly interrupted leaflet motion toward the ventricle during early diastolic valve opening, during the rebound after diastolic closure or during atrial opening of the valve leaflets. The timing of papillary muscle contraction and relaxation also seems to affect valve competence (18), as elongation of the papillary muscles in late diastole may be necessary to permit proper valve closure. Alterations in timing of contraction between the papillary muscle and the adjacent left ventricular myocardium may play an important role and have been considered a possible explanation for different degrees of regurgitation with different pacing sites (10).

Our findings substantiate previous observations (19–21) of altered regional left ventricular function near a pacing site, because we invariably found markedly decreased two-dimensional echocardiographic systolic fractional area change in the left ventricular short-axis view at a level closest to the stimulating electrode. Such alterations in left ventricular geometry might in themselves conceivably be responsible for regurgitation. Furthermore, in view of the altered pattern of left ventricular contraction, an alteration in the contraction pattern of the papillary muscles would appear likely. It has therefore been assumed that ventricular pacing sites, which best approximate the normal depolarization pattern by their proximity to the conduction system, would produce the fewest contraction abnormalities (10).

Limitations of study. Possible limitations of our study include the subjective grading of mitral regurgitation using the new technique of contrast echocardiography. However, this method appeared highly reproducible. Pacing was performed at different rates because we attempted to stay close to the dog's own sinus rate, which varied among animals. We did not study the role of atrial contraction and only performed short-term studies during the acute stage, which may not be representative of long-term pacing.

Conclusion. Our experimental study demonstrated the frequent occurrence of mitral regurgitation with ventricular pacing. This regurgitation was more severe with right ventricular apical than with left ventricular basal pacing. We observed significant alterations in left ventricular contraction patterns with pacing, which might be responsible for the mitral regurgitation and which may in themselves contribute to hemodynamic changes. Further experimental and clinical studies of these phenomena are needed before these findings can be extrapolated to a clinical setting.

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