



ORIGINAL ARTICLE

Effect of left ventricular pacing mode and site on hemodynamic, torsional and strain indices



Savvas Toumanidis*, Anna Kaladaridou, Dimitrios Bramos, Elias Skaltsiotes, John Agrios, George Georgiopoulos, Anna Antoniou, Konstantinos Pamboucas, Elektra Papadopoulou, Spyridon Moulopoulos

Department of Clinical Therapeutics, Medical School, National and Kapodistrian University of Athens, "Alexandra" Hospital, Athens, Greece

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KEYWORDS

myocardial infarction; speckle tracking echocardiography; rotation; strain; twist

Abstract *Introduction:* Several reports have indicated that left ventricular (LV) lead placement at an optimal pacing site is an important determinant of short- and long-term outcome. This study investigated the effect of pacing mode (atrioventricular [AV] or ventricular) and site (LV apical or lateral) outside the ischemic region on the LV hemodynamic, torsional and strain indices in the ischemic myocardium.

Methods: Experiments were conducted in anesthetized open-chest pigs ($n = 15$) 30 min after LAD ligation to investigate the hemodynamic effects of temporary epicardial AV and ventricular LV pacing at the LV apical (outside the ischemic region) or lateral wall. LV hemodynamic data were recorded (ejection fraction, stroke volume, dp/dt_{max} , systolic pressure, cardiac output and e/e' ratio) and torsional (twist, rotation), as well as deformation (radial and circumferential strain), indices of LV function were assessed using two-dimensional speckle tracking imaging.

Results: The LV function was highly dependent on the pacing mode and site. LV dp/dt_{max} , systolic pressure and twist decreased significantly during LV pacing in comparison to sinus rhythm ($p = 0.004$, $p < 0.001$, $p = 0.002$, respectively). Torsion in sinus rhythm decreased significantly during AV-pacing at the lateral wall ($0.11 \pm 0.04^\circ/mm$ vs. $0.06 \pm 0.02^\circ/mm$, $p = 0.005$) but did not change significantly during AV-pacing at the apex ($0.07 \pm 0.05^\circ/mm$).

* Corresponding author. Savvas Toumanidis, MD, 80 Vas. Sophias Ave. – Lourou, 115 28 Athens, Greece. Tel.: +30 210 3381481; fax: +30 210 3381497.

E-mail addresses: stouman@otenet.gr, stoumani@med.uoa.gr (S. Toumanidis).

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Conclusions: LV pacing at the apical or lateral wall, in the ischemic myocardium, leads to a suboptimal response in comparison to sinus rhythm. LV pacing at the apex outside the ischemic area exhibits a better response than pacing at the lateral wall, possibly because pacing from this site leads to a more physiological propagation of electrical conduction.

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1. Introduction

There is growing interest in seeking methods that use different pacing modes and/or pacing sites to maximize the benefits and minimize the harmful effects of artificial cardiac stimulation on left ventricular (LV) function. Biventricular or LV pacing has been proposed as an appropriate choice for patients with preexisting LV dysfunction who require ventricular pacing because they are more likely to develop further deterioration of their LV function after right ventricular apical pacing.^{1–3} Previous studies have shown that cardiac resynchronization therapy (CRT) is less effective in ischemic than in non-ischemic cardiomyopathy.^{4–6} The explanation for these observations is that pacing within the necrotic area is a negative predictor for CRT response. The effects on LV function of pacing sites outside the necrotic region are matters that have not been studied explicitly. The identification of the optimal LV lead position remains controversial.⁸ LV lead position at the lateral wall is recommended because this is the site of greatest contractile delay.^{9,10} Conversely, LV apical pacing maintains a closer to normal electric activation pattern as well as mechanic synchrony and coordination.^{11,12}

Two-dimensional speckle tracking echocardiography (STE) allows detailed evaluation of LV mechanics, including LV mechanical dyssynchrony, LV strain and LV torsion.^{13,14} This technique provides important additional information for the selection of the optimal pacing site. The role of STE in the assessment of the effects of RV apical pacing on LV function and the upgrade from RV to biventricular pacing have been evaluated in few studies.^{15,16} Data based on STE comparing the effects of different LV pacing modes (dual chamber vs. single chamber pacing) and sites on the LV mechanics, LV strain and LV torsion are still lacking.

The aim of this experimental study was to investigate the effect of pacing mode (atrioventricular or ventricular) and site (LV apical or lateral) outside the ischemic region on LV hemodynamic, torsional and strain indices in the ischemic myocardium (MI).

2. Methods

The protocol complied with the “Principles for the Care of Experimental Animals” and the “Guidelines for the Care and Use of Experimental Animals” issued by the US National Academy of Sciences and National Institutes of Health (version 85-23, revision 1996) and was approved by

the Scientific Committee of the Alexandra University Hospital.

2.1. Surgical preparation

The experiments were performed on 15 pigs weighing 37 ± 2 kg. The animals were sedated with an intramuscular administration of midazolam 5 mg/kg and ketamine hydrochloride 5 mg/kg, anesthetized with intravenous (IV) sodium thiopental 5 mg/kg, intubated and controlled by mechanical ventilation (Sulla 808V, Dräger Medizintechnik GmbH, Germany). Anesthesia was maintained with IV propofol 0.1–0.2 mg/kg. During the experiment, analgesia was maintained with an intravenous infusion of fentanyl 3 μ g/kg/h. Additional anesthetic was administered during the experiment as needed. A 7F sheath was inserted into the right internal jugular vein for the delivery of drugs and fluids. Through the left external carotid artery, a 6F pigtail catheter was placed into the LV cavity and used for LV pressure monitoring. Lead II of the standard electrocardiogram (ECG), LV pressure, and hemoglobin oxygen saturation were monitored throughout the experiment as previously described in detail.¹⁷ A regular median sternotomy was performed after thymic resection, followed by a longitudinal pericardiectomy. Two 3–0 Prolene (Ethicon, Johnson & Johnson Co., European Logistics Centre, Sint-Stevens-Woluwe, Belgium) sutures were placed after the origin of the first diagonal branch of the left anterior descending coronary artery (LAD) to be used for future ligation.

Temporary myocardial pacing leads (Medtronic, type 6500, Minneapolis, Minnesota) were attached to the surface of the right atrium and to the epicardium of the LV apex in the territory of the LAD and of the LV lateral wall (approximately 2 cm below the base). The apical pacing lead was placed outside the region where epicardial ischemia was observed. The leads were connected to an external pacemaker (Medtronic AV Pacing System Analyzer Model 5311B). The two LV electrodes were connected to a two-channel external pulse stimulator (Medtronic model 2883), allowing setting of thresholds for each electrode separately and pacing through each of the electrodes separately. Pacing was unipolar with an indifferent electrode positioned in between the intercostal muscles. During atrioventricular (AV) pacing, the AV delays were short enough to produce an activation wave originating from the ventricular pacing lead and were not modified between the different pacing configurations. Under all conditions, pacing was performed at about twice the stimulation threshold. The pacing rate was set at 10 beats/min above the intrinsic heart rate in each case.

2.2. Standard echocardiography

The echocardiographic study was performed using a Vivid i digital ultrasound system (GE Medical Systems Ultrasound Israel Ltd., Tirat Hacarmel, Israel) and a 3.5-MHz phased array transducer. Two-dimensional gray-scale echocardiographic images were obtained using 2nd harmonic imaging. Instrument settings were held constant for each experiment. A soft silicone pad, placed between the probe and the epicardium, acted as a cushion for the moving heart and as an offset to prevent near-field artifacts. The following parameters were measured 30 min after LAD ligation¹⁸: LV end-diastolic and end-systolic long- (Ld, Ls) and short-axis (Sd, Ss) dimensions. The eccentricity index, Ld/Sd and Ls/Ss ratios, the LV end-diastolic (EDV) and end-systolic (ESV) volumes, and the EF (modified Simpson's rule) were subsequently calculated. Stroke volume (SV) and cardiac output (CO) were measured and calculated from a subxiphoid epicardial apical four-chamber view. Mitral early (e) diastolic flow velocity was measured and the early diastolic (e') wave of the lateral mitral annulus was obtained by tissue Doppler imaging from the apical 4-chamber view. The ratio e/e' was calculated. To determine the timing of cardiac events, mitral inflow and LV outflow were recorded using pulsed Doppler echocardiography. Three consecutive cardiac cycles were stored in a cine loop format for offline analysis. Averaged values were calculated for each parameter.

2.3. Two-dimensional speckle tracking echocardiography

Assessment of LV rotation and twist were obtained by a well-established method.¹⁹ The frame rate range was 65–80/s. In each phase, three consecutive cardiac cycles' cine loop images were stored for offline analysis with a dedicated platform EchoPac PC (version 7.3.0, GE Medical Systems). LV twist was defined as the net difference between apical and basal rotation in degrees (°). Because the degree of rotation for the same amount of LV torque increases as the distance from the mid-ventricular level increases, the LV twist is expected to vary with the distance between the planes at which the basal and apical short-axis images are obtained. LV torsion (°/mm) was calculated as LV twist/Ld longitudinal length (measured between the locations of the base and apex of the LV in the end-diastolic phase).^{20,21} The opposite rotation after LV twist was defined as LV untwist, and the time derivative of LV untwist was designated as the LV untwisting rate (°/s). The following parameters were measured: (1) peak apical and basal rotations (Figure 1) and rates, (2) peak LV twist, torsion, torsion rate and peak LV untwisting rate, and (3) peak apical and basal systolic radial and circumferential strains.

2.4. Experimental Protocol

Throughout the experiment, surface ECG lead II from the limb lead electrodes was monitored and recorded at a speed of 100 mm/s by a multichannel device (Dynamap Plus Vital Signs Monitor, Criticon, Tampa, FL, USA). A pigtail catheter was placed through an arterial sheath and advanced retrogradely across the aortic valve into the LV cavity for the

measurement of LV pressure and peak rate of LV pressure increase (dP/dt_{max}). After completion of the surgical preparations, a steady-state period of 15 min was allowed. Baseline measurements were obtained in sinus rhythm 30 min after ligation and then repeated during ventricular pacing at the LV apex or the LV lateral wall, and during dual AV pacing at the LV apex and the LV lateral wall, in random order. The ligation was placed in the same position in all animals. One animal was excluded from the post-MI analysis due to unsuccessful recovery from ventricular fibrillation immediately after LAD ligation. Measurements were performed after two-minute pacing at each site separated by two-minute intervals in sinus rhythm.

For 10 animals, the analysis of peak systolic strain and LV twist data was repeated after two weeks by the same observer on the same two dimensional echocardiographic loop and the same cardiac cycle to define the intraobserver variability in the analysis. In addition, a second independent observer analyzed the same cardiac cycle to define the interobserver variability in the analysis of tissue tracking-derived deformation and rotational parameters. For each segment, the differences in strain and twist data were calculated and given as the relative deviation between these two measurements.

After death, the heart of each animal was excised, and the LV was divided into 1-cm-thick short-axis slices, incubated in triphenyltetrazolium chloride 1 mg/mL for 15 minutes at 37°C, and photographed. The infarct size (% LV mass) was determined by multislice planimetry.

2.5. Statistical analysis

Statistical analysis was performed on absolute values as well as percent changes during pacing relative to sinus rhythm values. Each experiment served as its own control. The normality of the distributions for each variable was checked using the Kolmogorov–Smirnov test or graphically assessed by P-P plots. Pearson correlations were performed to define the relationship between parameters. Subsequently, one-way analysis of variance for repeated measurements was used to evaluate the significance of the effect of the pacing mode and site on each variable. The Bonferroni correction was used for post hoc comparisons. Univariate linear regression models were performed to define the association between parameters of interest across predefined subgroup analysis (atrioventricular versus ventricular pacing mode). The level of statistical significance was set at $p < 0.05$. The statistical software package SPSS for Windows, version 20, was used for the analysis (SPSS Inc., Chicago, IL, USA).

3. Results

LV systolic pressure and dP/dt_{max} (Table 1, Figure 2) decreased significantly during pacing ($p < 0.001$ and $p = 0.004$, respectively). Additionally, the torsional parameters, torsion ($p = 0.008$, Figure 3) and twist ($p = 0.002$), rotation of the apex ($p = 0.02$) and the base ($p = 0.002$) and apical peak systolic rotation rate ($p = 0.02$), as well as the deformation variables, radial strain of the apex ($p < 0.05$) and the base ($p = 0.006$) together with circumferential strain of

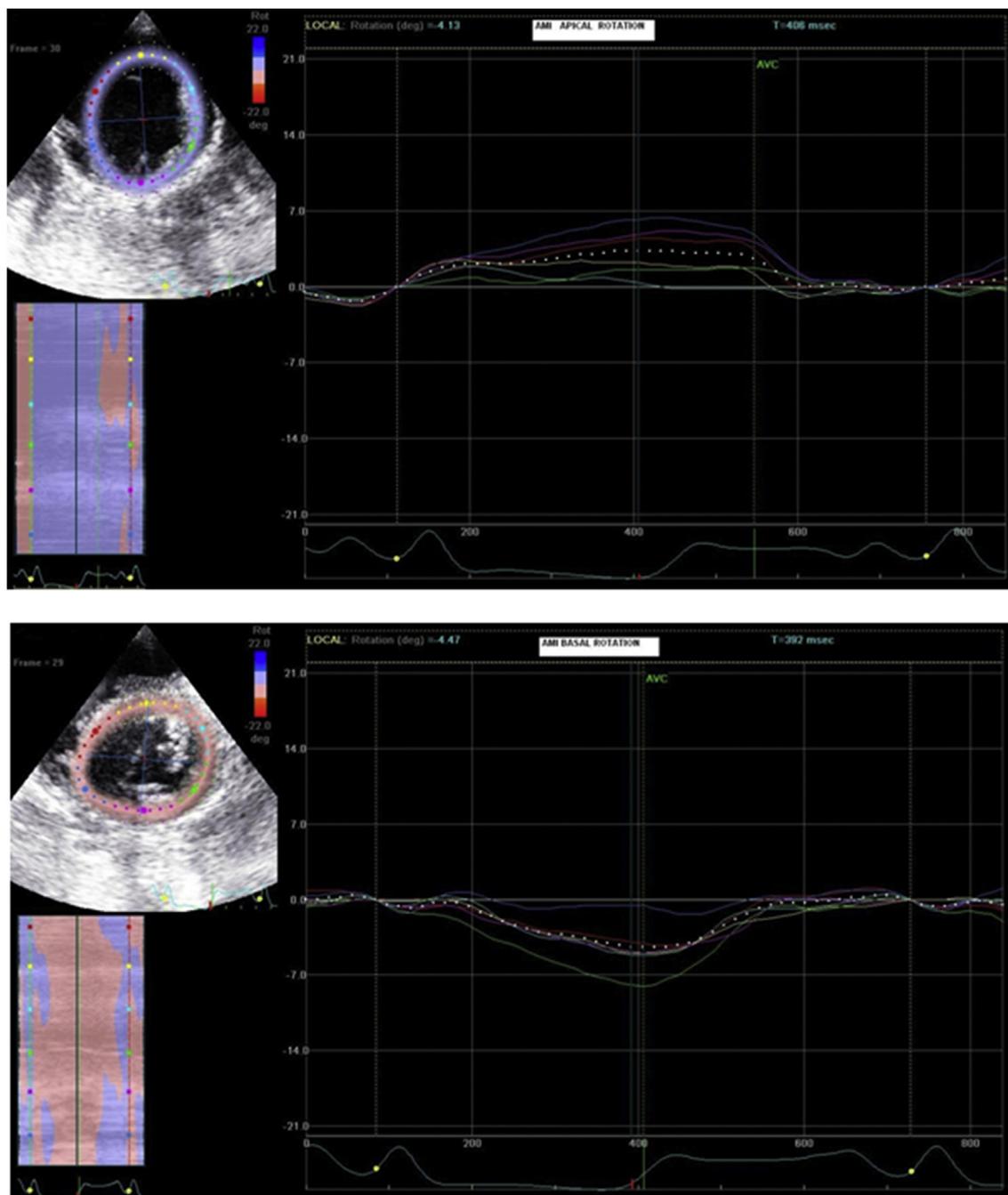


Figure 1 Representative short-axis view tracings of apical (upper panel) and basal (lower panel) rotation post acute myocardial ischemia (AMI). There are six rotation tracings for the six evaluated segments with inhomogeneous distribution. The dotted line indicates the mean apical and basal rotation of all six segments.

the apex ($p = 0.002$) and the base ($p = 0.02$) deteriorated significantly (Table 2).

3.1. Pacing site

AV-pacing at the apex produced the least change in LV function in comparison to sinus rhythm (Table 1 and 2). Post MI, AV-pacing at the apex reduced mainly the circumferential strain of the base and the apex (both $p < 0.05$), whereas AV-pacing at the lateral wall reduced the torsion

($p = 0.005$), twist ($p = 0.007$), rotation of the base ($p = 0.02$) as well as the radial ($p = 0.02$), and circumferential ($p = 0.004$) strain of the base.

Ventricular pacing at the apex showed a lesser effect on LV function than pacing at the lateral wall in comparison to sinus rhythm. Post MI, ventricular pacing at the apex ($p < 0.008$) and the lateral wall ($p < 0.001$) both significantly reduced the LV systolic pressure; moreover, ventricular pacing at the lateral wall also significantly reduced the rotation of the base ($p = 0.01$).

Table 1 Effect of pacing mode and site on the hemodynamic and conventional echocardiographic variables in relation to sinus rhythm in the ischemic myocardium.

	SR	AVA	AVL	VA	VL	p
Ld/Sd ratio	2.42 ± 0.42	2.47 ± 0.46	2.34 ± 0.38	2.33 ± 0.31	2.33 ± 0.22	0.55
Ls/Ss ratio	3.26 ± 0.26	3.55 ± 0.71	3.13 ± 0.83	3.60 ± 0.86	3.35 ± 0.72	0.10
EDV (ml)	60.87 ± 14.85	55.97 ± 10.47	56.32 ± 14.72	54.69 ± 13.40	51.33 ± 13.60	0.06
ESV (ml)	41.46 ± 10.53	36.76 ± 8.89	37.12 ± 11.00	36.69 ± 9.75	35.27 ± 10.52	0.12
SV (ml)	19.42 ± 5.40	19.21 ± 4.96	19.19 ± 5.55	18.00 ± 5.14	16.06 ± 4.38	0.13
EF	0.32 ± 0.05	0.35 ± 0.07	0.34 ± 0.07	0.33 ± 0.05	0.32 ± 0.06	0.41
CO (l/min)	1.96 ± 0.60	2.29 ± 0.50	2.32 ± 0.69	2.24 ± 0.60	1.95 ± 0.53	0.11
LVSP (mmHg)	82.74 ± 7.62	82.10 ± 13.50	79.65 ± 14.32	66.28 ± 14.26* ♦+	66.91 ± 10.64* ♦+	0.001
dP/dt _{max} (mmHg/s)	1.15 ± 0.24	1.09 ± 0.24	1.07 ± 0.24	0.94 ± 0.28	0.92 ± 0.19♦	0.004
dP/dt _{min} (mmHg/s)	-1.30 ± 0.31	-1.22 ± 0.30	-1.06 ± 0.37	-1.08 ± 0.34	-0.95 ± 0.36	0.098
HR (beats/min)	102.54 ± 14.28	113.62 ± 12.55	111.92 ± 11.81	117.33 ± 14.24	116.21 ± 14.80	0.08
QRS (ms)	69.97 ± 7.80	92.51 ± 21.67*	105.79 ± 15.48*	95.79 ± 24.96*	98.24 ± 19.07*	0.001
e/e' ratio	10.33 ± 3.69	11.81 ± 5.16	13.51 ± 7.89	11.47 ± 5.15	11.11 ± 3.98	0.54

(*) Asterisk denotes that the mean difference from sinus rhythm is significant at the 0.05 level.

(♦) Rhombus denotes that the mean difference is significant at the 0.05 level from atrio-ventricular pacing at the left ventricular (LV) apex.

(+) Plus sign denotes that the mean difference is significant at the 0.05 level from atrio-ventricular pacing at the LV lateral wall.

Abbreviations: AVA: Atrio-ventricular pacing at the LV apex; AVL: Atrio-ventricular pacing at the LV lateral wall; CO: Cardiac output; EDV: LV end-diastolic volume; EF: LV ejection fraction; ESV: LV end-systolic volume; e: Mitral early filling velocity; e': early diastolic mitral annulus velocity by tissue Doppler imaging; HR: Heart Rate; Ld: LV end-diastolic long-axis dimension; Ls: LV end-systolic long-axis dimension; LVSP: LV Systolic pressure; Sd: LV end-diastolic short-axis dimension; SR: Sinus rhythm; Ss: LV end-systolic short-axis dimension; SV: LV stroke volume; VA: Ventricular pacing at the LV apex; VL: Ventricular pacing at the lateral wall.

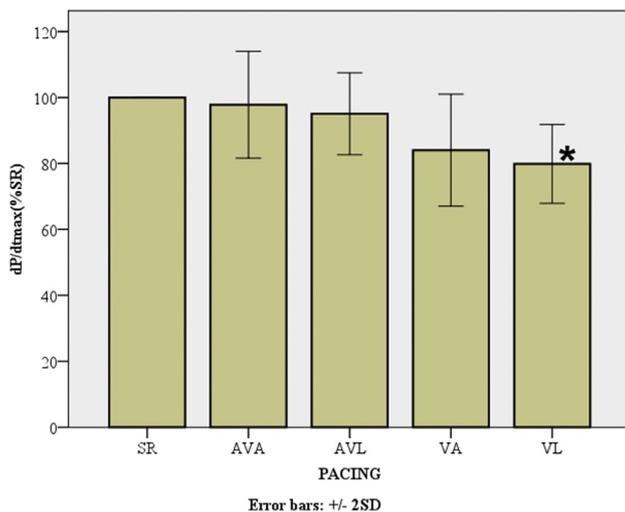


Figure 2 Percentage changes of the maximal rate of rise of the left ventricular pressure (dP/dt_{max}) during different left ventricular pacing modes and sites relative to sinus rhythm (SR), post myocardial ischemia. The asterisk denotes a significant difference from the corresponding values in SR. (AVA: atrioventricular pacing at the apex, AVL: atrioventricular pacing at the lateral wall, VA: ventricular pacing at the apex, VL: ventricular pacing at the lateral wall).

3.2. Pacing mode

AV-pacing showed a lesser effect on LV function than ventricular pacing in comparison to sinus rhythm (Table 1 and 2). AV-pacing at the apex produced a significant reduction in the circumferential strain of the base and the apex post

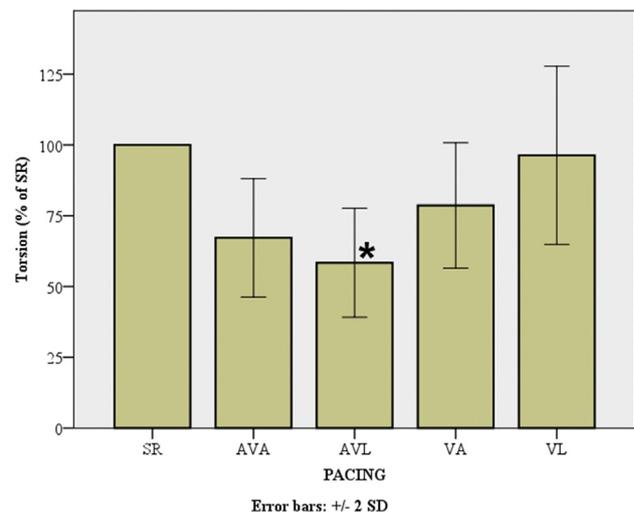


Figure 3 Percentage changes in torsion during different left ventricular pacing modes and sites relative to sinus rhythm (SR), post myocardial ischemia. The asterisk denotes a significant difference from the corresponding values in SR. (AVA: atrioventricular pacing at the apex, AVL: atrioventricular pacing at the lateral wall, VA: ventricular pacing at the apex, VL: ventricular pacing at the lateral wall).

MI. Ventricular pacing at the same site significantly reduced the LV systolic pressure.

AV-pacing at the lateral wall post MI led to a significant reduction in torsion or twist as well as the rotation, and radial and circumferential strain of the base. Ventricular pacing at the same site produced a significant reduction in LV systolic pressure and the rotation of the base.

Table 2 Effect of pacing mode and site on left ventricular torsional and strain parameters in relation to sinus rhythm in the ischemic myocardium.

	SR	AVA	AVL	VA	VL	p
Torsion (°/mm)	0.11 ± 0.04	0.07 ± 0.05	0.06 ± 0.02*	0.10 ± 0.03	0.09 ± 0.04	0.008
Twist (°)	7.18 ± 2.97	4.78 ± 2.99	3.74 ± 1.75*	5.79 ± 1.98	5.24 ± 2.50	0.002
Torsion rate (°/s)	48.40 ± 15.21	51.72 ± 14.12	51.93 ± 21.68	54.13 ± 21.07	50.65 ± 17.27	0.93
Untwisting rate (°/s)	-71.76 ± 21.65	-68.83 ± 27.40	-54.07 ± 11.19	-67.47 ± 20.06	-59.88 ± 31.01	0.27
LV base						
Rotation (°)	-5.81 ± 2.34	-4.48 ± 2.90	-3.97 ± 2.14*	-4.49 ± 1.87	-3.70 ± 1.19*	0.002
Rotation rate (°/s)	-45.74 ± 20.57	-46.21 ± 20.18	-44.80 ± 22.33	-46.70 ± 18.82	-43.84 ± 14.78	0.99
Radial strain	42.31 ± 14.81	27.00 ± 14.29	29.88 ± 11.50*	37.40 ± 14.09	28.54 ± 11.37	0.006
Circumferential strain	-12.08 ± 2.78	-9.27 ± 4.80*	-8.88 ± 3.28*	-11.38 ± 2.02 ⁺	-10.90 ± 2.91	0.02
LV Apex						
Rotation (°)	2.32 ± 1.52	1.24 ± 2.02	-0.02 ± 2.14	2.09 ± 2.14	2.37 ± 1.45	0.02
Rotation rate (°/s)	22.84 ± 11.11	17.40 ± 24.92	-2.36 ± 31.29	27.87 ± 29.95 ⁺	27.04 ± 19.23	0.02
Radial strain	23.21 ± 11.64	15.03 ± 9.28	13.47 ± 7.16	13.57 ± 6.88	17.90 ± 13.04	0.05
Circumferential strain	-11.43 ± 4.19	-6.49 ± 4.21*	-6.91 ± 3.30	-7.54 ± 1.99	-8.22 ± 3.18	0.002

Abbreviations and symbols as in Table 1.

dP/dt_{max} showed a significant positive correlation with torsion and rotation of the base ($r = 0.62$, $p = 0.001$ and $r = -0.73$, $p < 0.001$, respectively) during AV-pacing at the apex and/or lateral wall (Figure 4), whereas during ventricular pacing at the apex and/or lateral wall, this significant correlation was markedly distorted ($r = 0.12$, $p = 0.57$ and $r = -0.27$, $p = 0.20$, respectively). Similarly, torsion was significantly correlated with stroke volume during AV-pacing at the apex and/or lateral wall ($r = 0.43$, $p = 0.036$) but not during ventricular pacing at the apex and/or lateral wall ($r = 0.15$, $p = 0.49$).

The indices of diastolic LV function dP/dt_{min} , e/e' ratio and untwisting rate did not show any significant changes during the different pacing modes and sites (Table 1 and 2).

For every pacing mode and pacing site in the ischemic myocardium, the QRS duration was significantly longer in comparison to sinus rhythm ($p < 0.001$ for all). None of the pacing modes and sites could improve LV function significantly in relation to sinus rhythm post MI (Table 1 and 2).

The accurate measurement of LV twist/untwist by STE is contingent on high-quality recordings, high tracking

quality, and the correct recognition of anatomic structures that identify the basal and apical short-axis levels. Our results were obtained using a high frame rate that allows for accurate tracking. We also verified the tracking accuracy visually, retracing and repositioning the region of interest as needed. Nevertheless, good speckle tracking and reliable measurements of twist parameters were possible 80% of the time. Pacing tachycardia results in reductions in both systolic twist and diastolic untwisting rates, which were constant in every pacing mode and site.

Intraobserver variability for peak systolic circumferential strain was $4.5 \pm 1.5\%$ and for twist $6.5 \pm 5.5\%$. The interobserver variability was $7.5 \pm 2.5\%$ and $8.5 \pm 5.5\%$, respectively.

The infarct size ranged from 17% to 35% (mean $25 \pm 4\%$).

4. Discussion

The main findings of this experimental study are that LV pacing in every mode examined, either atrioventricular or

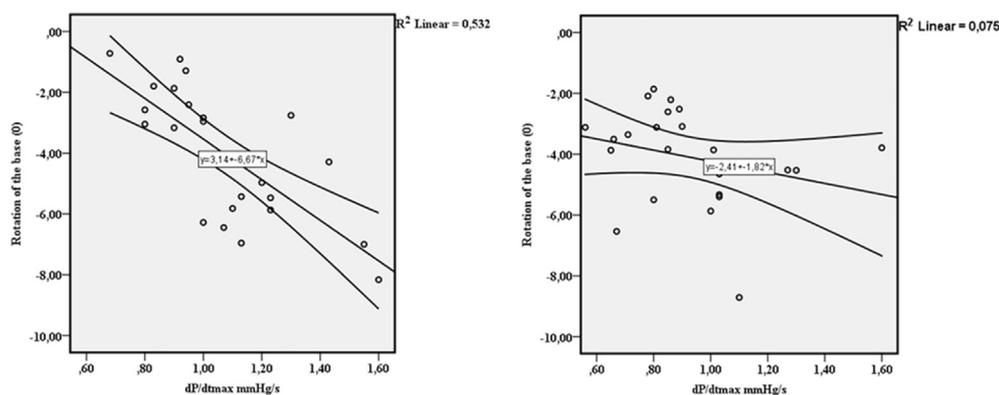


Figure 4 The left panel demonstrates the significant positive correlation between dP/dt_{max} and the rotation of the base ($r = -0.73$, $p < 0.001$) during atrioventricular pacing at the left ventricular apex and lateral wall in the ischemic myocardium. The right panel shows that this significant correlation disappears ($r = -0.27$, $p = 0.20$) during ventricular pacing at the left ventricular apex and the lateral wall.

ventricular, and at every examined site, either apical or at the lateral wall in the ischemic myocardium, produced harmful effects on LV hemodynamic, torsional and strain indices in comparison to sinus rhythm. A comparative evaluation between LV pacing modes and sites showed that AV-pacing at the LV apex (outside the ischemic region) provides the most favorable benefits in terms of LV function.

4.1. Impact of LV pacing mode and site

The present study, performed in pig hearts with normal ventricular conduction, demonstrates that LV function was maintained at largely the same level as in sinus rhythm when AV-pacing was implemented at the LV apex in ischemic myocardium. Basic indices of LV function, such as EF, dP/dt_{max} , SV, torsion or twist, rotation of the base and the apex, did not change significantly in comparison to sinus rhythm, except for circumferential strain of the base and the apex, which decreased significantly. In contrast, AV-pacing at the lateral wall significantly reduced the torsion or twist, the rotation, and the radial and circumferential strain of the base. The importance of the normal electrical activation of the myocardium during sinus rhythm for optimal pump function is well known.²² Moreover, it has been recognized that in addition to AV synchrony, a proper sequence of activation is a highly important parameter. The hemodynamic superiority of LV apical AV-pacing in comparison to AV-pacing at the lateral wall may be explained by a relatively physiological sequence of electrical activation during pacing from this site. During LV pacing, activation is more asynchronous because of the longer QRS duration. This widening of the QRS duration is primarily due to the propagation of the electrical impulse through the slowly conducting myocardium instead of the His-Purkinje system. AV-pacing at the LV apex provides a fairly physiological sequence of stimulation, although activation is more asynchronous because of the longer QRS duration. However, a good sequence of electrical activation is sufficient to allow a near normal LVEF for AV-pacing, although QRS duration did not differ significantly. Several studies using single-chamber pacing showed a significant influence of the pacing site on hemodynamic performance. Ventricular pacing at any site may have an adverse effect on pump function. However, among all LV pacing sites the LV apex generally results in the best maintenance of pump function, in non-ischemic animal hearts and when pacing is applied outside the necrotic region.^{2,7,12,23–28} Ventricular pacing at the apex or lateral wall suffers from the lack of the “atrial kick,” which produces a significant reduction in LV systolic pressure in the ischemic myocardium. Ventricular pacing at the lateral wall created, as did AV-pacing, additional detrimental effects on LV function in comparison to pacing at the apex.

The effect of pacing on diastolic function is not well-established. In the present study, the indices of diastolic LV function did not change significantly during pacing. Studies that address the relationship between diastolic function and pacing show conflicting data.²⁹

4.2. Impact of the presence of MI and lead location

Anterior MI produced a significant deterioration of the hemodynamic and torsional parameters, affecting mainly the

rotational and strain parameters of the LV apex. This effect has been recognized by previous experimental and clinical studies.^{19,30,31} The important contribution of torsion to LV function, evidenced by its close relationship with EF and dP/dt_{max} has been investigated in other studies.^{19,32,33} The findings of the present study revealed that this dynamic correlation is maintained during AV-pacing at the apex and/or lateral wall, whereas during ventricular pacing at the apex and/or lateral wall this significant correlation was markedly distorted. It is worth noticing that AV-pacing at the lateral wall reverses the counterclockwise motion of the LV apex to clockwise. None of the pacing modes and sites tested in the present study was able to improve LV function significantly in relation to sinus rhythm post MI.

There is a common perception, supported by several clinical studies, that reverse remodeling is observed less in patients with ischemic cardiomyopathy than in patients with dilated cardiomyopathy.^{34,35} A justification for this poor response in patients with ischemic cardiomyopathy may be that pacing within the infarcted area limits the response to CRT.^{36,37} A previous study of ours showed that in the intact myocardium, LV pacing at the apex produced a significantly higher EF than pacing at the lateral wall. In contrast, pacing inside the necrotic LV apical zone impairs LV EF compared with pacing at the non-necrotic LV lateral wall.²⁷ This EF deficit was probably due to slow conduction around the pacing site, which induces electromechanical delay and a deterioration of systolic shortening. Similar results have been found by others.^{5,34} In an experimental study performed in canine hearts with LBBB, Rademakers LM et al. found that CRT can improve LV pump function to a similar degree in hearts with and without MI. However, the location of the MI determines the best pacing site.³⁸

4.3. Limitations

Owing to the setup of the study, only the acute effects of pacing at different sites were assessed. The long-term effects in a chronic model of ischemia and cardiac decompensation may be different. The impact of the pacing site in patients with chronic ischemia is more clinically relevant and needs to be further investigated. Moreover, the ideal site of pacing for non-LAD lesions (or for global injury) is not addressed in this study.

4.4. Clinical implications

CRT has been recognized as a valuable therapy for patients with heart failure³⁹. That at least 30% of patients are “non-responders” to this expensive treatment constitutes a medical and a socio-economic problem.⁴⁰ In this article, we have analyzed the impacts of different pacing modes and sites on LV function in order to provide insight into the future perspectives for cardiac pacing therapy. In practical terms, CRT is provided using epicardial pacing electrodes because conventional access for lead positioning (via the coronary sinus or by thoracotomy) results in an epicardial location of the LV pacing electrode. However, in the current study, biventricular pacing was not tested. We suggest that if one wanted to pace only the LV, there appears to be differences depending on the

position of the LV lead, and the status of the myocardium at that site (ischemic or not).

In the present study, we showed that AV-pacing at the apex is the preferred pacing mode and site for ischemic myocardium (outside the ischemic area) in comparison to the lateral wall. The acute hemodynamic response could help guide lead placement outside the scarred area, with a view to optimizing the future responsiveness to CRT.

The discovery of the optimal lead location warrants further investigation, as multiple factors - infarct location and size, lead location and accessibility, single or multiple pacing sites, AV and interventricular delay - constitute an unresolved problem that does not depend only on the pacing mode and site. To date, there is no clear agreement as to the best guideline regarding LV lead placement. Indeed, the quest for an optimal site for all could be a chimera; perhaps individualization is the only solution.

5. Conclusions

This experimental study indicates that in every examined mode, either AV or ventricular, and at every examined site, either apical or lateral wall, LV pacing in the ischemic myocardium produces detrimental effects on LV hemodynamic, torsional and strain indices compared to sinus rhythm. A comparative evaluation between LV pacing modes and sites showed that AV- pacing at the LV apex (outside the ischemic region) provides the optimal benefits in terms of LV function.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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