EFFECT OF PACEMAKER SITES ON CONTRACTILE FORCES OF THE LOCAL MYOCARDIUM AND BLOOD FLOW IN THE MAJOR BRANCHES OF THE LEFT CORONARY ARTERY IN ANESTHETIZED OPEN-CHEST DOGS

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Decreased cardiac performance during ventricular tachycardia or ventricular pacing has been ascribed to the lack of synchrony due to altered ventricular contraction. However, the direct effect of the pacemaking site on blood flow in the major coronary arterial branches and on regional contractile forces has not been adequately examined. In this investigation, twelve dogs were used to assess coronary flow in the left anterior descending (LAD) and circumflex coronary arteries (LCx) and the regional myocardial function in response to ectopic electrical pacing. The sites were the outflow tract of the right ventricle (RV pacing), the anterior left ventricular wall supplied by the LAD (LAD pacing), and the lateral wall perfused by the LCx (LCx pacing). Strain gauge arches were transmurally fixed to myocardial segments of the anterior and lateral walls of the left ventricle. The mechanical forces generated were measured while simultaneously recording blood flow in the LAD and LCx. RV pacing diminished developed-tension similarly in both areas. LAD flow was further decreased during anterior pacing as was the developed-tension in the LAD supplied area. A similar relationship was observed between LCx flow and developed-tension in the LCx area during lateral pacing. Compared to RV pacing, anterior pacing did not affect LCx flow and local myocardial force in the lateral wall of the left ventricle, and lateral pacing did not cause further changes in LAD flow and anterior myocardial function. The decrements in blood flow were closely related to decreased myocardial function ($p < 0.01$). These findings indicate that ventricular pacing decreases ventricular performance with attenuated regional myocardial function at the pacing area, in addition to causing altered ventricular contraction sequence.

HEART beats originating from ventricular sites are not as efficient in ejecting blood as beats of supraventricular origin. Decreased cardiac performance of ventricular beats has been

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attributed to lack of synchronous ventricular activation and contraction.^{1,2} The altered ventricular contraction sequence would affect force generation and oxygen requirement of the myocardium. Coronary circulation normally responds to altered myocardial oxygen demand by changing coronary blood flow.²⁻⁴ Thus, simultaneous measuring coronary flow in a major arterial branch and contractile forces generated

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TABLE I HEMODYNAMIC DATA DURING SINUS RHYTHM, AND ATRIAL AND VENTRICULAR PACING

	Heart rate (beat/min)	Blood pressure (mmHg)	Coronary flow (ml/min/100g)		LVmax dp/dt (mmHg/sec)	LVmin dp/dt (mmHg/sec)	LVEDP (mmHg)
			LCx	LAD			
Sinus rhythm	146±27	91±10.0	81±6.1	80±7.7	2049±470	2295±918	6.6±2.5
RA pacing	159±33	93± 8.5	80±8.6	84±6.8	2185±363	2335±852	7.7±2.7
RV pacing	159±33	77± 8.1	77±6.8	76±9.3	1782±483	1641±763	11.5±3.8
Anterior pacing	159±33	77± 8.5	76±7.4	69±5.0*	1805±541*	1742±636	11.2±4.4
Lateral pacing	159±33	80± 5.9	70±8.7** #	76±9.2 #	1928±361** #	1834±728	10.4±4.2

LCx = the left circumflex coronary artery; LAD = the anterior descending coronary artery; LVmax dp/dt = maximum rate of left ventricular pressure rise; LVmin dp/dt = maximum rate of left ventricular pressure fall; LVEDP = left ventricular enddiastolic pressure; RA = right atrium; RV = right ventricle. Significantly different from values obtained during RV pacing at the level of ** $p < 0.01$, and from anterior pacing values at the level of # $p < 0.05$.

All measurements except heart rate obtained during ventricular pacing were significantly different from values during sinus rhythm at the level of $p < 0.01$.

in the supplied myocardium would aid in clarifying the relationship between local myocardial performance and energy supply. However, there have been few reports concerning the effect of ventricular pace-making sites on localized myocardial performances^{5,6} and local coronary blood flow.⁷ In the present investigation, blood flow in the left anterior descending and left circumflex coronary arteries and myocardial forces generated in each region were measured during electrical pacing from both atrial and ventricular sites. The effect of the various sites on cardiac performance and oxygen supply was determined.

METHODS

Fifteen mongrel dogs, weighing 12–18 kg each, were premedicated with ketamine HCl (1 mg/kg, i.m.), and then anesthetized with pentobarbital sodium (25–30 mg/kg, i.v.). A left thoracotomy was performed in the fifth intercostal space; the dogs were ventilated by a intermittent positive pressure respirator. Small polyethylene catheters, placed in the femoral vein and the aortic root, served for drug infusion and aortic blood pressure monitoring, respectively. Left ventricular pressure and its first derivative were obtained with a catheter inserted into the left ventricle via the apex. The proximal left circumflex coronary artery and the anterior descending coronary artery immediately distal to the first diagonal branch were exposed by a blunt dissection; and electromagnetic flow probes and pneumatic occluder cuffs were placed around the

TABLE II TENSION DEVELOPED DURING SINUS RHYTHM, AND ATRIAL AND VENTRICULAR PACING

	LCx area (g)	LAD area (g)
Sinus rhythm	28.4 ± 5.63	30.0 ± 6.21
RA pacing	26.4 ± 3.81	26.3 ± 4.48 ^a
RV pacing	25.8 ± 4.47 ^a	24.0 ± 3.51 ^a
Anterior pacing	26.6 ± 3.92	20.3 ± 3.08 ^b
Lateral pacing	21.1 ± 3.19 ^d	25.9 ± 3.45 ^c

LCx, the left circumflex coronary artery; LAD the anterior descending coronary artery; RA, right atrium; RV, right ventricle.

a, significantly different from values obtained during sinus rhythm at the level of $p < 0.01$.

b, significantly different from values obtained during sinus rhythm and from RV pacing values at the level of $p < 0.01$.

c, significantly different from values obtained during sinus rhythm and from anterior pacing values at the level of $p < 0.01$.

d, significantly different from values obtained during sinus rhythm, RA pacing, RV pacing and anterior pacing at the level of $p < 0.01$.

vessels. Local myocardial forces were measured with strain gauge arches (modified Model TH-602T, Nihonkoden, Tokyo). The gauges were placed on the left ventricular anterior and lateral walls, fixed in place with transmural needles. Pacing electrodes were sutured onto the surface of the right atrial appendage, the right ventricular outflow tract, the left ventricular anterior wall perfused by the anterior descending coronary artery (anterior pacing), and the lateral wall perfused by the circumflex coronary artery

(lateral pacing). The experimental design is shown in Fig. 1.

Pressure, coronary blood flows and local myocardial forces were recorded using a Mingograph Model 804 recorder (Siemens-Elema Co., West Germany) at a paper speed of 2.5 mm/sec and 100 mm/sec. After control data were recorded, right atrial pacing was initiated. After three minutes of pacing hemodynamic measurements were recorded. The site of pacemaker activation was then randomly switched to an ectopic site. After 3 minutes when hemodynamic equilibrium was resumed the parameters were measured. Between pacing at the various sites, the heart was maintained under atrial control for 5 minutes. Regardless of site, hemodynamic measurements reached steady-state within two minutes, therefore data were recorded at three minutes. Each dog was paced at all three experimental sites with recording being made at the end of each course of pacing. The pacing rate at all sites was set at 10% above the control sinus rate. If stability of the preparation could not be maintained during the control periods, the entire experiment of that dog was invalidated (3 cases). The strain-gauges were calibrated in vitro immediately before and after completion of each experimental series.

RESULTS

Right atrial pacing caused no significant changes in any of the parameters (Table I). However, ventricular pacing altered many parameters as compared with atrial pacing. Systemic blood pressure fell by approximately 15%, the maximum rate of left ventricular pressure rose (LVmax dp/dt) by 16–20% and the maximum rate of left ventricular pressure fall (LVmin dp/dt) by 23–30%. These parameters showed higher values during left ventricular pacing than during right ventricular pacing. The values obtained during lateral and anterior pacing were comparable. Ventricular pacing elevated left ventricular end-diastolic pressure (LVEDP) and lowered coronary blood flow regardless of ventricular site. Right ventricular pacing resulted in a similar decrease in the flow through LAD and LCx, the anterior pacing decreased the LAD flow more than the LCx flow, and the lateral pacing showed the opposite tendency—LCx flow was greater than the LAD flow. Compared to right ventricular pacing, anterior pacing decreased LAD flow by 19%, and lateral pacing LCx flow

Fig. 1. Schematic illustration of instrumentation.

Fig. 2. Reduced coronary blood flow is related to diminished myocardial tension. Open circles (○) represent LAD-supplied area; closed circles (●) LCx.

	slope	x-intercept	correlation coefficient	p
LAD:	+0.77	-4.82	0.77	< 0.01
LCx:	+0.49	-8.04	0.73	< 0.01
whole:	+0.59	-7.06	0.74	< 0.01

by 11%; these changes were statistically significant.

Resting myocardial tension of the left ventricular wall was not affected by ectopic pacing (Table II). However, right ventricular pacing lowered the developed-tension slightly but significantly in the LAD supplied area; developed-tension in the LCx area was not affected. In comparison with atrial pacing, anterior pacing decreased the LAD-area developed-tension by 23% (pacing area) with no significant change of the force in the LCx area (non-pacing area).

Conversely, a 20% reduction of the developed-tension was observed in the LCx area during the lateral pacing, while the pacing did not affect the developed-tension in the LAD area.

The reduction in the coronary blood flow during the left ventricular pacing was plotted against the segmental myocardial force reduction (Fig. 2). This figure relates flow to the tension developed in the area supplied by the perfused artery. Individual arteries and their areas showed high correlations (LAD correlation coefficient = 0.77; LCx = 0.73). This strongly suggests a causal link between blood flow and developed-tension.

DISCUSSION

The function of the left ventricle as a whole is reflected by a number of parameters: cardiac output, left ventricular end-diastolic pressure, rate of pressure rise and rate of pressure fall. Each of these variables is influenced by the several factors such as heart rate, end-diastolic volume, resistance to ejection, and myocardial contractility^{5,8-10}. The results of this study clearly support the contention that the sequence of ventricular activation is an important determinant of left ventricular function^{11,12}.

Previous work in our laboratory¹³ has shown that myocardial force measurements using a strain gauge arch unaffected by left ventricular end-diastolic volume and pressure, heart rate, and systemic blood pressure. The forces detected increased using isoproterenol infusion in a dose-response manner, and decreased after injection of propranolol. This finding indicates that this gauge is quite sensitive to an alteration of myocardial contractility independent of the left ventricular preload and afterload.

In the present study, myocardial developed-tension was reduced significantly when pacing originated in the left ventricle. The lateral pacing significantly decreased developed-tension in the area perfused by the LCx; and the anterior pacing lowered the force in the LAD area. It is unlikely that changes in preload and afterload were responsible for the reduction in the force because the gauges used in this experiment are known to respond almost entirely to myocardial contractility within the hemodynamic range observed. Although we could not unequivocally demonstrate the basis for the reduced contractility, it is reasonable to postulate that either epicardial electrical stimulation or different

contraction sequence plays a major role. Epicardial stimulation is associated with reversal of the normal sequence of activation and presumably of the sequence of contraction.

Our results are contrary to the findings of Miyazawa et al.¹⁴ who concluded that the developed-tension is unaffected by the ventricular pacing site. Although the reason for this discrepancy is not clear, the experimental design may be a possibility. In the present study the strain gauges were transmurally fixed to insure detection of forces generated across all the myocardial layers, while Miyazawa et al. sutured the gauge only on the subepicardial myocardium. Hood et al.⁹ using a mercury-in-silastic gauge, had demonstrated earlier, that production of a ventricular premature beat at the gauge site resulted in early muscle shortening followed by relaxation with late systolic bulging. This suggested a decrease in developed-tension at the pacing site.

Blood flow changes in normal coronary arteries is related closely to the myocardial metabolic state¹⁵. With right ventricular pacing, in the present study, LAD flow and LCx flow were decreased to the same extent together with a fall in blood pressure. Left ventricular pacing further diminished coronary flow to the pacing area, but not to the non-pacing area. This reduction in flow varied directly with a decrease in developed-tension of the pacing area (Fig. 2). While we did not assess myocardial oxygen consumption, these results strongly suggest that coronary flow to the ventricular pacing site was attenuated (in response to the reduced myocardial oxygen requirement) as a result of diminished developed tension. According to Badeer and Feisal¹⁶ total coronary flow, estimated in a heart-lung preparation, rose significantly during left ventricular pacing when arterial pressure and cardiac output were kept constant at baseline levels. It is well known that the aortic pressure is a major determinant of myocardial oxygen consumption^{4,17}. Allowing the aortic pressure to vary, the ventricular pacing was seen to cause a significant decrease in blood pressure, lowering myocardial oxygen supply. This decreased the coronary flow, and further decreased the myocardial oxygen demand brought about through the lessened myocardial force at the pacing site.

Miyazawa et al.¹⁸ reported a slight reduction in coronary sinus blood flow during pacing, at both the apex and the lateral wall of the left

ventricle. We found that blood flow to the pacing site decreased with no significant changes of blood flow to the remaining ventricular wall. Badeer and Feisal¹⁶ and Miyazawa et al.¹⁸ measured total coronary flow in the left pulmonary artery and coronary sinus, respectively, of the lung-heart preparation but did not measure the blood flow through individual major coronary arteries. Lack of decreases or even increases in flow to the non-paced area may have masked the effect of left ventricular pacing on the reduction of local coronary flow when measuring total coronary blood flow.

In summary, left ventricular pacing decreased regional myocardial function at the pacing site. This probably resulted in a reduced myocardial oxygen requirement and a reduction in local coronary flow. The suppressed regional myocardial function directly contributed to a decrease in left ventricular performance, in addition to its indirect effects on altered ventricular contraction sequence.

REFERENCES

1. FINNEY JO: Hemodynamic alterations in left ventricular function consequent to ventricular pacing. *Am J Physiol* 208: 275, 1965
2. GILMORE JP, ASRNOFF SJ, MITCHELL JH, LINDEN RJ: Synchronicity of ventricular contraction: Observations comparing haemodynamic effects of atrial and ventricular pacing. *Brit Heart J* 25: 299, 1963
3. ECKENHOFF JE, HAFKENSCHIEL JH, LANDMESSER CM, HARMER M: Cardiac oxygen metabolism and control of the coronary circulation. *Am J Physiol* 149: 634, 1947
4. SAITO D, NIXON DG, VOMACKA RB, OLSSON RA: Relationship of cardiac oxygen usage, adenosine content, and coronary resistance in dogs. *Circ Res* 47: 875, 1980
5. COVELL JW, ROSS J Jr, SONNENBLICK EH, BRAUNWALD E: Comparison of force-velocity relation and ventricular function curve as measures of contractile state of intact heart. *Circ Res* 19: 364, 1966
6. ECKENHOFF JE, HAFKENSCHIEL JH, EOLTZ EL, DRIVER RL: Influence of hypotension on coronary blood flow, cardiac work, and cardiac efficiency. *Am J Physiol* 152: 545, 1948
7. PITT B, GREGG DE: Coronary hemodynamic effects of increasing ventricular rate in the unanesthetized dog. *Circ Res* 22: 753
8. BAXTER RH, TAIT CM, McGUINNES JB: Vasodilator therapy in acute myocardial infarction. *Brit Heart J* 39: 1067, 1977
9. HOOD WB Jr, JOISON J, ABELMANN WH, NORMAN JC: Asynchronous contraction due to late systolic bulging at left ventricular pacing sites. *Am J Physiol* 217: 215, 1969
10. SAITO D, YASUHARA K, NISHIYAMA O, KUSACHI S, HARAOKA S: Comparative effects of heart rate and aortic blood pressure on MVO₂ in the anesthetized open-chest dog. *Jpn Heart J* 22: 833, 1981
11. BENCHIMOL A, LIGGETT MS: Cardiac hemodynamics during stimulation of the right atrium, right ventricle, and left ventricle in normal and abnormal hearts. *Circulation* 33: 933, 1966
12. LISTER JW, KLOTZ DH, JOMAIN SL, STUCKEY JH: Effect of pacemaker site on cardiac output and ventricular activation in dogs with complete heart block. *Am J Cardiol* 14: 494, 1964
13. KUSACHI S, SAITO D, NISHIYAMA O, TAKEDA K, HYODO T, ABE H, UCHIDA T, KIMURA S, NISHIHARA M, NAGASHIMA H, KAGAWA K, HARAOKA S: Simple technique for measuring regional contractility by a modified strain gauge arch. *Jpn Circ J* 48: 43, 1983
14. MIYAZAWA K, ARAI T, SHIRATO K, HANEDA T, IKEDA S, HONNA Y, NAKAJIMA T, MIURA T: Regional contraction patterns of the left ventricle during ventricular pacing. *Tohoku J Exp Med* 122: 167, 1977
15. BRAUNWALD E: Control of myocardial oxygen consumption: Physiologic and clinical consideration. *Am J Cardiol* 27: 416, 1971
16. BADDER HS, FEISAL KA: Effect of atrial and ventricular tachycardia on cardiac oxygen consumption. *Circ Res* 17: 330, 1965
17. KATZ LN, FEINBERG H: Relation of cardiac effort to myocardial oxygen consumption and coronary flow. *Circ Res* 6: 656, 1958
18. MIYAZAWA K, SHIRATO K, HANEDA T, HONNA T, ARAI T, NAKAJIMA T: Effects of pacing location on coronary circulation in dogs. *Tohoku J Exp Med* 121: 149, 1977