

Influence of pacing site on canine left ventricular contraction

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BURKHOFF, DANIEL, ROBERT Y. OIKAWA, AND KIICHI SAGAWA. *Influence of pacing site on canine left ventricular contraction*. *Am. J. Physiol.* 251 (Heart Circ. Physiol. 20): H428–H435, 1986.—We investigated the influence of pacing site on several aspects of left ventricular (LV) performance to test the hypothesis that “effective ventricular muscle mass” is reduced with direct ventricular pacing. All studies were performed on isolated supported canine hearts that were constrained to contract isovolumically. To determine the influence of pacing site on magnitude and time course of isovolumic LV pressure (P) generation, LVP waves were recorded in eight isolated hearts paced at 130 beats/min. Pacing was epicardially from atrium, LV apex, LV free wall, right ventricular free wall (RVF), and endocardially from right ventricular endocardium. In a given heart, peak LVP was greatest with atrial pacing and smallest with RVF pacing, the difference being on average $26 \pm 10\%$ (mean \pm SD) of the former pressure. The other pacing sites produced intermediate peak LVPs. When instantaneous LVP waves, obtained while pacing from each of the five sites, were normalized by their respective amplitudes, they were virtually superimposable up to the time of peak pressure and only slightly different during the remainder of the cardiac cycle. With changes in pacing site there was a linear negative correlation ($r = 0.971$) between changes in peak pressure and changes in duration of the QRS complex of a bipolar epicardial electrogram with an average slope of -0.51 mmHg/ms. Compared with atrial pacing, the slope of the end-systolic pressure-volume relation, E_{es} , was decreased with ventricular pacing, but V_0 , the volume axis intercept, was relatively constant. Decreases in peak LVP with ventricular pacing were associated with decreases in myocardial O_2 consumption such that metabolic efficiency was preserved. These results support the hypothesis that with ventricular pacing, the effective mass of muscle that actively participates in chamber contraction is reduced.

myocardial pacing; end-systolic pressure-volume relation; ventricular oxygen consumption; pressure-volume area; time-varying elastance; isolated canine heart

IT HAS LONG BEEN RECOGNIZED that when the heartbeat is initiated from a ventricular site instead of from the atrium the strength of ventricular contraction diminishes, independent of changes in ventricular preload (23); that is, ventricular pacing diminishes ventricular chamber contractility. Experimental results indicate that the influence of ventricular pacing site on ventricular performance results from a decrease in the degree of synchrony of myocardial contraction (11). Electrophysiologi-

cal mapping studies have shown that with myocardial pacing, as opposed to atrial pacing, there is an increase in the activation time of the ventricle with an accompanying prolongation of the QRS complex of the body surface electrogram (5, 10, 11, 15). Sonomicrometer and cineradiographic measurements have indicated significant and characteristic changes in the time course of local ventricular segmental wall shortening with ventricular pacing (2), and changes in the dynamic geometry of the left ventricle have been noted (9, 13). Finally, it has been shown, surprisingly, that despite the increased dispersion in electrical activity, the duration of ventricular contraction is little affected by ventricular pacing (3), a finding whose significance has not been recognized.

Results of previous studies indicate that with epicardial ventricular pacing the muscle fibers in the epicardial layers near the pacing site are activated earlier than the remainder of the left ventricle. We further hypothesize that as the propagating electrical impulse travels through myocardial tissue, the activated muscle fibers undergo unloaded contractions (i.e., they shorten but generate little force) and therefore do not contribute significantly to the generation of pressure in the ventricle. Once the electrical activation front reaches the Purkinje system, however, the fibers in the remainder of the ventricle are activated quickly, and the resulting contractions of these fibers are more nearly simultaneous, as with supraventricular pacing. In essence, this hypothesis predicts that pacing from a ventricular site reduces the effective mass of muscle, which contributes to the generation of active contractile strength in the ventricular chamber.

Although this hypothesis is not directly testable, there are at least five predictions on how ventricular chamber properties would be influenced by a pacing site that can readily be tested in an isolated heart preparation. First, it is predicted that ventricular chamber contractile strength should be different when pacing is from different ventricular sites. Second, despite the changes in absolute contractile strength with myocardial pacing, the time course of chamber stiffening and relaxation should be independent of pacing site. Third, there should be a negative correlation between chamber contractile strength and the dispersion of ventricular electrical activity that can be measured by the duration of the QRS complex. Fourth, changes in chamber contractility

should result in a change in the slope (E_{es}) of the end-systolic pressure-volume relation (ESPVR), without a change in the volume-axis intercept (V_0) of the ESPVR. Finally, there should be a reduction in ventricular O_2 consumption ($\dot{V}O_2$) with ventricular pacing in proportion to the reduction in mechanical strength so that chamber metabolic efficiency remains the same as with atrial pacing.

The purpose of the present study, therefore, was to test the hypothesis that myocardial pacing reduces the effective mass of muscle contributing to contraction by determining whether the five predictions outlined above could be demonstrated experimentally. Experiments were performed on isolated, supported, canine hearts, which allow for the study of left ventricular properties under isovolumic conditions. In contrast to studies performed on in situ hearts, measurements made with isovolumic contractions are not influenced by changes in the atrial contribution to ventricular performance, by afterloading conditions, nor by the arterial and cardiopulmonary baroreflexes that might occur when pacing site is changed in vivo.

METHODS

Surgical Preparation

The procedures used to isolate and support a canine heart were similar to those described by Suga and Sagawa (19). Briefly, a pair of mongrel dogs (approx wt, 20 kg each) was anesthetized with pentobarbital sodium (30 mg/kg iv). A heart isolated from the "donor" dog was metabolically supported by arterial blood from the second "support" dog. A water-filled balloon positioned inside the left ventricular chamber of the isolated heart, connected to a volume servosystem, was used to control and measure ventricular volume. Details of the design and performance of this volume servosystem have been reported by Suga and Sagawa (20) and Sunagawa et al. (21).

In all experiments the coronary perfusion pressure was maintained between 80 and 100 mmHg by a servo-controlled finger pump (Harvard Apparatus model 1215). The temperature of the perfusate was maintained between 37 and 39°C.

Measurement of $\dot{V}O_2$

The coronary perfusion flow was estimated by cannulation of the coronary sinus and measurement of venous outflow with an electromagnetic flowmeter (Narco Biosystems model RT-400). The difference between arterial and venous O_2 content [(A-V) O_2 difference] was continuously measured by an A-VOX meter (A-VOX Systems). The principle of operation of this device has been described in detail (16). O_2 consumption is equal to the product of mean coronary sinus flow and (A-V) O_2 difference.

Electrical Stimulation and Recordings

Epicardial pacing leads were placed at five different sites on the heart: the atrium, right ventricular endocar-

dial septum, right ventricular epicardial free wall, left ventricular apex, and left ventricular epicardial free wall. The hearts were paced with square pulses of duration between 1 and 2 ms long and of amplitude approximately twice threshold. The site of pacing was changed using a manually controlled multiplexing switch box.

An A-C coupled bipolar epicardial electrogram was measured between one electrode placed on the left ventricular free wall and another on the right ventricular free wall. The duration of the QRS complex of this electrogram was used as a rough measure of the degree of electrical dyssynchrony over the heart while pacing from different sites. The QRS duration was defined as the time interval between the Q- and S-wave inflection points.

All signals were recorded on an eight-channel pen recorder (Gould 2800), digitized on-line at a rate of 200 Hz, and analyzed off-line.

Protocols and Data Analysis

All studies were performed in isovolumically contracting ventricles to obviate the influences of afterloading conditions on ventricular performance. The aforementioned five predictions were tested using the two basic protocols described below.

Magnitude and time course of pressure generation. In the first series of measurements, the hearts were paced at a constant rate of 130 beats/min. The pacing site was switched from one site to the next in a random order while ventricular volume was maintained at a constant value of ~25 ml. After pacing sites were switched, all recorded signals were allowed to reach steady state. Representative pressure waves and ECG signals for each pacing site were digitized. From these, we determined the peak developed pressures, the duration of the pressure wave at a level of 10% peak developed pressure, and the duration of the QRS complex as defined above, obtained with each pacing site in each of nine ventricles.

To determine the influence of pacing site on the time course of chamber stiffening and relaxation, we compared the shapes of the isovolumic pressure waves. For each heart, a steady-state pressure wave [$P(t)$] was measured while pacing from each of the five pacing sites. Each of these five pressure waves was normalized in amplitude according to the following equation

$$P^*(t) = \frac{P(t) - P_{\min}}{P_{\max}} 100(\%) \quad (1)$$

where t is time, $P(t)$ is the directly measured isovolumic pressure wave, P_{\min} is the minimum pressure, and, P_{\max} is the maximum developed pressure attained during the beat. Then each of the five curves obtained from a given heart were aligned in time at the point when $P^*(t)$ was equal to 50%. The shapes of the resulting normalized, time-shifted curves were quantitatively compared by determining the root-mean-square difference (D_{rms}) between each curve obtained with ventricular pacing and that obtained when atrial pacing (i.e., atrial pacing was considered the "control" curve to which all the others were compared). The physiological significance of this

shape comparison will be discussed in more detail below.

ESPVR and $\dot{V}O_2$. The ESPVRs measured with atrial and right ventricular free wall pacing were compared. At a given volume, the peak isovolumic pressure was determined while pacing from each site. The volume was then changed in a random manner, and the pacing site variation was repeated. In each heart studied, the volume was varied between approximately 5 and 35 ml at 5-ml increments. Linear regression analysis was used to determine the E_{es} and V_0 of the relations between the end-systolic pressures and volumes measured with each pacing site. E_{es} and V_0 obtained with atrial and right ventricular free wall pacing were compared.

Ventricular $\dot{V}O_2$ was measured at each of the volumes for both pacing sites. For each series, myocardial $\dot{V}O_2$ was plotted as a function of the total "pressure-volume area" (PVA), which is defined by Suga et al. (20) as the area on the ventricular pressure-volume diagram contained within the end-systolic pressure-volume relation, the end-diastolic pressure-volume relation, and, for isovolumic contractions, the isovolumic pressure-volume line. The relation between $\dot{V}O_2$ and PVA has been described in detail (18) and has been found to be linear and independent of ventricular loading conditions. The PVA- $\dot{V}O_2$ relation obtained from a given heart with both pacing sites were compared by analysis of variance.

RESULTS

Influence of Pacing Site on Peak Systolic Pressure and Duration of Contraction

Original experimental recordings from a typical experiment in which the ventricle was contracting isovolumically at 25 ml are presented in Fig. 1. In this example peak pressure was greatest when pacing from the atrium, intermediate with left apical (LVA) and right ventricular endocardial (RVE) pacing, and minimum with right and left ventricular free wall (RVF and LVF, respectively) pacing, the latter attaining pressures approximately 75% of those obtained with atrial pacing. There was no influence of pacing site on minimum diastolic pressure.

The pacing site dependence of peak developed pressure was studied in eight hearts, and the average results are presented in Fig. 2A. The peak pressures obtained with each site were compared using one-way repeated-measures analysis of variance; multiple comparisons of group means was by the Duncan multiple ranges test. The symbols, explained in the figure legend, summarize the results of this analysis, which indicated that pacing from different myocardial sites generally resulted in significantly different developed peak pressures.

Next we determined the influence of pacing site on the duration of the pressure waves at a level of 10% maximum developed pressure. The results of this analysis are presented in Fig. 2B. Associated with an approximately 25% decrease in peak isovolumic pressure when pacing site was moved from the atrium to the ventricular free wall (Fig. 2A) was an average of only 12.5 ms increase in the duration of contraction. Statistical analysis indicated that in general there were no statistically significant

differences in the duration of contraction among the different pacing sites.

Influence of Pacing Site on the Time Course of Pressure Development

Representative computer-reconstructed pressure curves obtained from a single heart with each of the five pacing sites are presented in Fig. 3A. The peak pressure decreased with ventricular pacing, as described above, and there was no influence on minimum pressure. For this plot, the peak of the R wave of the bipolar electrocardiogram was arbitrarily used to define the starting time (i.e., $t = 0$) of each beat. With this definition of the starting time there was a large difference in t_{max} , the time at which pressure reached its maximal value. To compare the shapes of these pressure waves, they were rescaled in amplitude and aligned in time (see METHODS) as in Fig. 3B. When this was done, all five curves were virtually superimposable during the rising phase of the pressure tracings up to t_{max} , and there were only small differences between them for the remainder of the cardiac cycle. This indicates that the peak of the R wave is a poor indicator of the start of mechanical contraction. The similarity of these curves was quantified by determining the D_{rms} from the atrial curve as outlined in METHODS. All of the normalized pressure waves obtained with ventricular pacing were equally similar to that obtained with atrial pacing, and therefore the average results of this analysis from each heart are reported. When this analysis was carried out for the example of Fig. 3 it was found on average that D_{rms} was only 1.5% up to the time of t_{max} and 4.1% after t_{max} . This pacing site independence of the shape of the pressure wave was observed in all eight hearts studied in this series, and the results are summarized in Table 1.

Correlation of Peak Pressure and Epicardial QRS Duration

In the original recordings of Fig. 1 it can be seen that there are marked differences in the configuration of the epicardial ECG recorded while pacing from different sites. When the heart was paced from the atrium the pressure development was maximal and the QRS complex was short in duration. With ventricular pacing the pressure development was less and the QRS duration was longer. The relationship between pressure development and QRS duration measured in each of the eight hearts studied is presented in Fig. 4. As indicated in the figure, there was a linear, negative correlation between these two parameters in all hearts studied. The mean (\pm SD) slope was -0.51 ± 0.19 mmHg/ms, and the average correlation coefficient was 0.971 ± 0.029 .

Dependence of E_{es} and V_0 on Pacing Site

Results of a typical experiment are illustrated in Fig. 5A. The linearity of the ESPVR was not altered by pacing from the RVF. The pacing site dependence of E_{es} was similar to the pacing site dependence of P_{max} at a constant volume. In this case, E_{es} decreased from 4.9 to 4.3

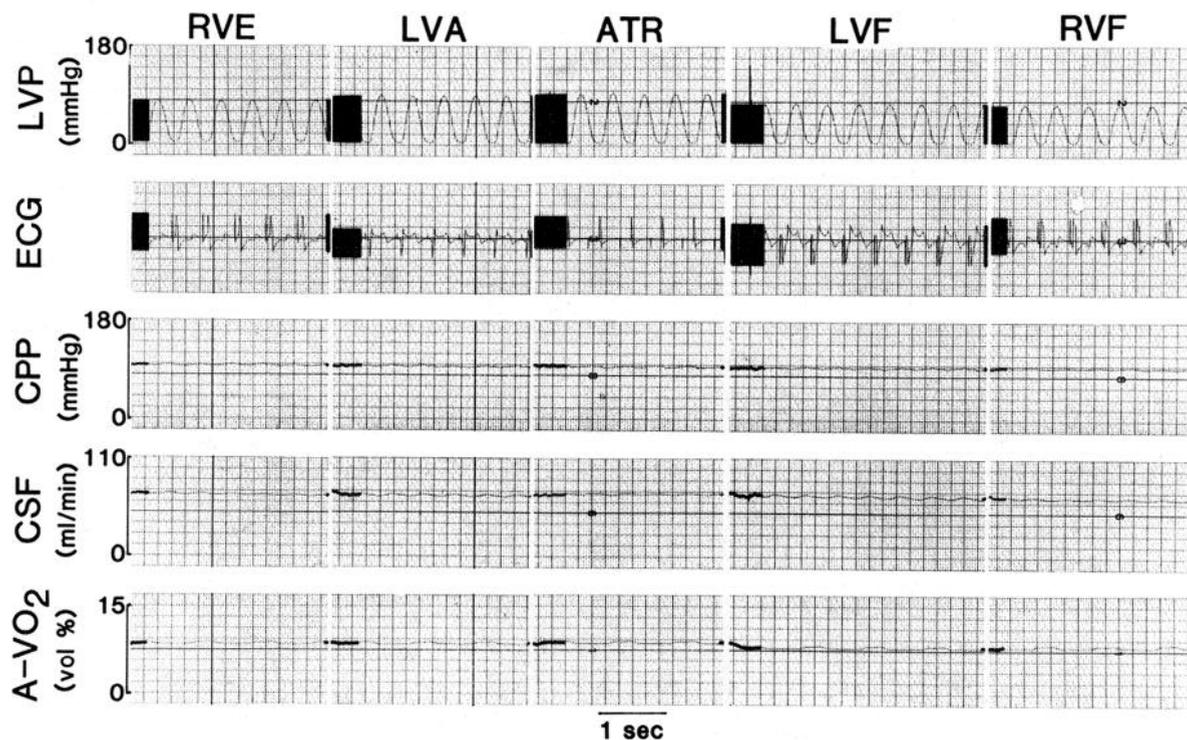


FIG. 1. Typical original recordings obtained from a single heart contracting at a constant volume of 25 ml while being paced from each of 5 pacing sites: right ventricular endocardium (RVE), left ventricular apex (LVA), atrium (ATR), LV free wall (LVF), and right ventricular free wall (RVF). Left ventricular pressure (LVP), Bipolar surface electrogram (ECG), coronary perfusion pressure (CPP), coronary sinus outflow (CSF), coronary arterial-venous O_2 content difference (A- $\dot{V}O_2$). All signals were digitized and analyzed by computer. For this left ventricle, 90 g in weight, the relation between O_2 consumption ($\times 10^5$ ml O_2 /beat) and pacing site was RVE, 5.00; LVA, 5.04; ATR, 5.23; LVF, 4.67; RVF, 4.60. See text for details.

mmHg/ml (a decrease of 12.2%) and V_0 increased from 0.3 to 1 ml. The results of experiments performed in six hearts are presented in Table 2 (data in Fig. 5A are from experiment 4). The data were compared by Student's *t* test, which indicated that the changes in both E_{es} and V_0 were statistically significant at the 1% level.

O_2 Consumption

Original recordings of the signals are presented in Fig. 1; note that the coronary perfusion pressure was held constant at ~ 100 mmHg in this example. Associated with the changes in pressure development with pacing site were alterations in the amount of O_2 consumed by the ventricle. The changes in $\dot{V}O_2$ resulted from changes in both coronary sinus flow and (A-V) O_2 . The magnitude of changes in these signals between pacing sites were small, and $\dot{V}O_2$ was determined accurately by digitizing all signals and averaging several seconds of data by computer. When the developed pressure decreased, $\dot{V}O_2$ decreased; in Fig. 1, this is most clearly illustrated when the pacing site was switched from the atrium to the LVF. The $\dot{V}O_2$ for each panel in the figure, presented in the figure legend, indicate a positive association between peak pressures and the $\dot{V}O_2$.

To evaluate the influence of pacing site on the balance between ventricular energy consumption and total mechanical work performed by the ventricle, we determined the relation between the total PVA and $\dot{V}O_2$ per beat (see

METHODS). A typical result is presented in Fig. 5B for which the changes in the pressure-volume relation is presented in Fig. 5A (discussed above). As illustrated, despite the fact that both PVA and $\dot{V}O_2$ changed when the pacing site was changed, the relation between these two was the same with both pacing sites. The PVA- $\dot{V}O_2$ relation was quantified by its slope and *y*-axis intercept determined by linear regression applied separately to the data obtained from the two pacing sites. The two regression lines were compared by analysis of covariance. The results from five hearts studied in this series, summarized in Table 3, indicated that in four of the five hearts there was no statistically significant difference in the PVA- $\dot{V}O_2$ relation. In one heart there was a statistical difference at the 1% significance level; however, the magnitude of this difference was small.

DISCUSSION

In the present study we tested the hypothesis that with myocardial pacing the effective mass of muscle that contributes to active ventricular pressure generation is reduced below that which exists when pacing is from the atrium. Five predictions of the hypothesis were validated in isovolumically contracting canine left ventricles.

First, consistent with previous studies, peak isovolumic pressures were smaller with ventricular pacing than with atrial pacing. Furthermore, pacing from different myocardial sites produced different levels of contractile

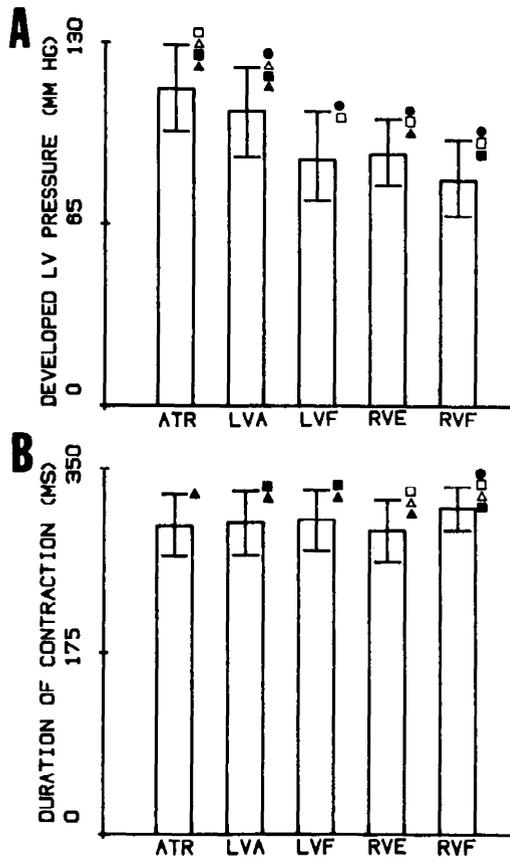


FIG. 2. Average results obtained from 8 ventricles. Influence of pacing site (A) on peak isovolumic pressure and (B) on the duration of contraction at a level of 10% developed pressure. Statistical significance of inter-group differences were determined by repeated measures analysis of variance in combination with the Duncan test. Symbols indicate statistically significant differences ($P < 0.05$) between means of 2 groups: ●, different than with ATR pacing; □, different than with LVA pacing; △, different than with RVE pacing; ■, different than with LVF pacing; ▲, different than with RVF pacing. Abbreviations as in Fig. 1.

strength; atrially paced beats were strongest, followed by (in the order of weakening contractile strengths) LVA, RVE, and finally RVF and LVF, which produced the weakest contractions.

Second, despite the marked influences on ventricular contractile strength and electrical dispersion, there was relatively little influence on the duration of contraction or on the time-course of chamber stiffening and relaxation as judged by the similarity of the shapes of the isovolumic pressure waves. This result is predicted on the basis of a rapid and nearly normal activation sequence of the muscle not rendered "ineffective" by myocardial pacing.

Third, with a change of pacing site in a given heart, there was a highly significant, linear, negative correlation between peak isovolumic pressure and the duration of the QRS complex of an epicardial surface electrogram. The amount of effective muscle mass "lost" with ventricular pacing would be expected to depend directly on the distance between the pacing site and the nearest point of entry of the activation front into the Purkinje system; as this distance increases, the QRS duration increases

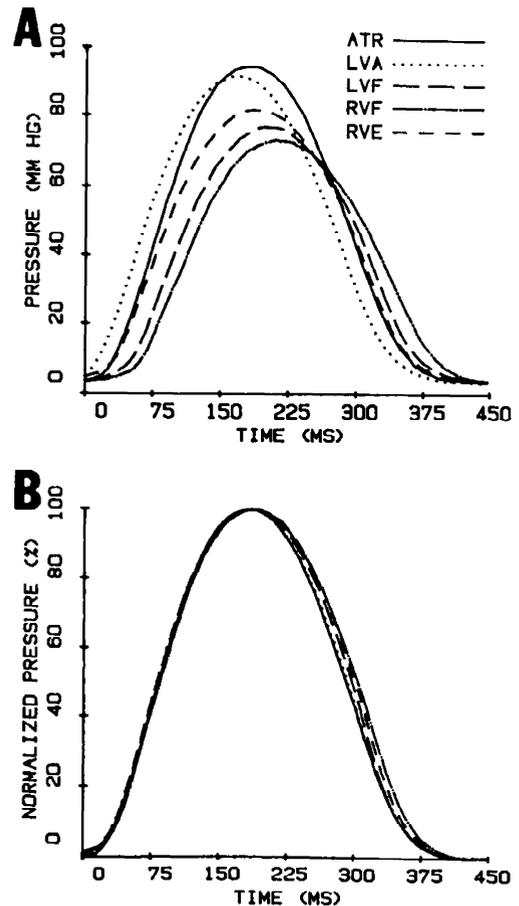


FIG. 3. Influence of pacing site on time course of pressure generation. A: computer reconstructed pressure waves from an isovolumically contracting left ventricle while paced from each site as indicated. B: curves of A were offset, rescaled in amplitude and shifted in time to reveal that time course of pressure generation was independent of pacing site up to time of peak pressure. Average root-mean difference between normalized curves obtained with ventricular pacing, as compared with curve obtained with atrial pacing, was 1.46% up to t_{max} and 4.08% from t_{max} to end of contraction. These curves also illustrate small changes in duration of contraction. Abbreviations as in Fig. 1.

TABLE 1. Root-mean squared difference between normalized pressure waves obtained with ventricular pacing and atrial pacing (%)

Expt	Time Interval	
	0 to t_{max}	t_{max} to 460
1	1.43±0.12	3.60±1.34
2	1.50±0.25	2.18±1.09
3	0.87±0.12	1.80±1.06
4	1.70±0.19	5.38±1.68
5	1.57±0.61	5.03±2.10
6	1.46±0.33	4.08±1.55
7	1.41±0.80	1.92±1.38
8	1.90±0.59	1.73±0.50

Results are expressed as means ± (SD) ms. t_{max} , the time at which pressure reached its maximal value.

and the remaining effective muscle mass (and resulting pressure development) decreases.

Fourth, the ESPVR measured with RVF pacing had a lower E_{es} , and a small increase in V_0 as compared with that measured with atrial pacing. V_0 is predominantly

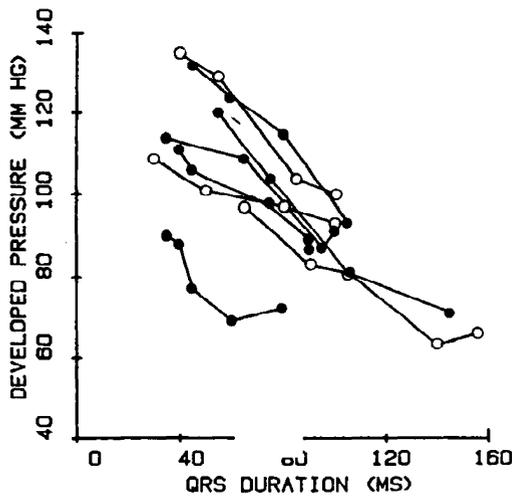


FIG. 4. Summary of results from 8 ventricles on relation between developed pressure and duration of QRS complex of an epicardial electrogram (different symbols used for clarity). In each heart this relation was linear with average (\pm SD) regression slope -0.51 ± 0.19 and correlation coefficient, $r = 0.971 \pm 0.029$.

TABLE 2. Comparison of E_{es} and V_0 obtained with atrial pacing and right ventricular free wall pacing

Expt	Pacing Site			
	ATR		RVF	
	E_{es}	V_0	E_{es}	V_0
1	4.2	0.0	3.6	2.4
2	4.0	8.5	3.6	10.6
3	6.2	11.5	5.1	12.1
4	4.9	0.3	4.3	1.0
5	6.0	15.0	4.6	15.0
6	4.2	8.5	3.9	9.6
Mean	4.9	7.3	4.2*	8.5*
SD	0.97	5.5	0.60	5.1

E_{es} , slope of the end-systolic pressure-volume relation; V_0 , volume axis intercept; ATR, atrial pacing; RVF, right ventricular free wall pacing. * Statistically significant difference of results obtained with atrial pacing at $P < 0.01$ by Student's t test.

TABLE 3. Influence of pacing site on slope and y -intercept of regression of $\dot{V}O_2$ on total pressure-volume area

Expt	Pacing Site			
	Atrium		RV Free Wall	
	A, ml O_2 /beat · mmHg · ml	B, ml O_2 /beat	A, ml O_2 /beat · mmHg · ml	B, ml O_2 /beat
1	2.10×10^{-5}	0.035	1.90×10^{-5}	0.038
2	2.36×10^{-5}	0.035	2.30×10^{-5}	0.032
3	3.18×10^{-5}	0.020	3.11×10^{-5}	0.021
4	3.64×10^{-5}	0.011	3.60×10^{-5}	0.012
5	2.96×10^{-5}	0.025	2.79×10^{-5}	0.031

RV, right ventricle. * Statistically significant difference in regression lines by analysis of variance, $P < 0.01$, present only in Expt 5.

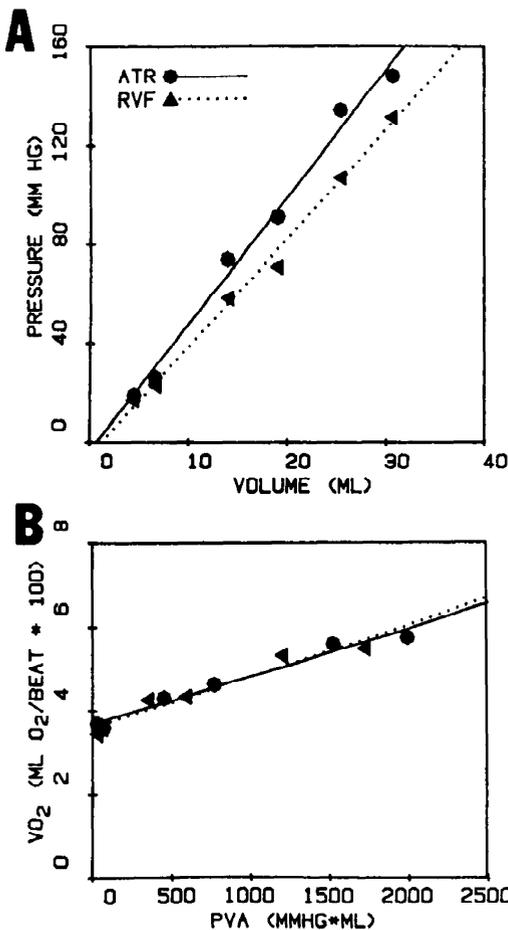


FIG. 5. A: end-systolic pressure-volume relation obtained from a single heart with atrial pacing (ATR) and with right ventricular free wall pacing (RVF). B: ventricular O_2 consumption ($\dot{V}O_2$) and corresponding total pressure-volume area (PVA) were measured for each loading condition and pacing site of A. Pacing site influenced both PVA and $\dot{V}O_2$ but did not alter the PVA- $\dot{V}O_2$ relation.

determined by ventricular structural factors and only mildly influenced by systolic properties. Thus changing pacing site should not significantly influence V_0 .

Finally, reduced ventricular strength created by ventricular pacing was associated with decreased $\dot{V}O_2$. As judged by the constancy of the relation between the total PVA- $\dot{V}O_2$, with atrial and RVF pacing, the decreases in contractile strength and $\dot{V}O_2$ were such that ventricular efficiency, as defined by Suga et al. (18) as the slope of the PVA- $\dot{V}O_2$ relation, was conserved. Theoretically, that part of the myocardium which is rendered "ineffective" by ventricular pacing would be expected (in the extreme case) to produce no mechanical work and consequently consume only the basal amount of O_2 . Therefore, when the contractile strength is reduced by myocardial pacing, $\dot{V}O_2$ measured from the whole heart should decrease by an amount proportional to the mass of "ineffective" muscle, thus preserving the relation between $\dot{V}O_2$ and PVA.

Although the results of some studies have suggested relatively little or no influence of pacing site on systolic ventricular performance (7, 9, 17, 22, 24), most studies have clearly demonstrated, as in the present study, a reduction in ventricular chamber "contractility" with myocardial pacing (1, 3, 4, 6, 8, 11, 14, 23).

The results of the present study are consistent in many respects with those obtained by Boerth and Covell (3) who compared the performance of isovolumically contracting canine ventricles paced from the atrium and right ventricle. However, they reported on average that there was no change in $\dot{V}O_2$, despite reduced pressure development with RVF pacing, and therefore they concluded that there was a reduction in the efficiency in the transduction of chemical energy into ventricular mechanical work. Inspection of their data [see Fig. 5, Boerth and Covell, (3)] reveals that in four of the six hearts studied, switching the pacing site from the atrium to the RVF, which resulted in decreased pressure development, actually decreased $\dot{V}O_2$; in one heart there was almost no change, and in one heart there was an increase. Paired *t* test analysis resulted in no statistically significant difference between $\dot{V}O_2$ with atrial and RVF pacing for that sampling. As indicated in Figs. 1 and 5B of the present study, only small changes in $\dot{V}O_2$ were required to preserve the "efficiency" of energy transduction in association with altered pacing site. We therefore feel that the data of Boerth and Covell are for the most part consistent with our findings.

Previous studies (11, 23) have shown that pacing from different myocardial sites resulted in different intensities of ventricular performance. To explain this phenomenon, Wiggers (23) originally proposed that the greater the distance the excitation wave front had to travel from the pacing site to the Purkinje system, the greater would be the degree of asynchrony of contraction and thus the weaker the contractile strength. That is, the more muscle activated by "muscle conduction" prior to the arrival of the activation front at the Purkinje system, the weaker the beat. The electrophysiological maps of Lister et al. (11) support this concept.

Results of the present study further support this position in two ways. First, the observed similarity of the time course of pressure generation suggests the existence of a common final sequence of myocardial activation that is independent of pacing site; this is presumably the Purkinje system. The second line of evidence is based on the observed inverse linear relation between QRS duration and peak developed pressure. With atrial pacing this duration was between 35 and 45 ms, which is approximately the time of activation obtained in previous studies of canine hearts (10, 15). With ventricular pacing, the activation front propagates more slowly through the myocardium until it ultimately enters the Purkinje system and is conducted rapidly. A longer QRS duration would therefore imply the involvement of a greater amount of myocardial tissue during the activation process. As already discussed, the greater the distance of conduction through ventricular myocardium, the weaker the contraction. Hence the inverse relation between QRS duration and peak pressure.

Recently, Park et al. (14) very carefully studied the influence of pacing site on the ESPVR of closed-chest chronically instrumented dogs. Their data differ from ours in that they found a significant increase in V_0 with little influence on E_{\max} when pacing is switched from atrium to myocardium. There are many methodological

differences between our study and theirs, making direct comparison difficult. Because the isolated heart preparation allows for direct measurement of volume and strict control of loading conditions and coronary perfusion pressure, we believe that the changes in the ESPVR we observed reflect direct effects of pacing site on ventricular mechanical properties. In contrast, the changes detected in a closed-chest dog preparation may reflect the responses of the more complex in situ cardiovascular system in which influences of autonomic reflexes and changes in coronary perfusion pressure may be present. Additionally, the ESPVR is measured by transient vena caval occlusion in the closed-chest dog, and in the isolated heart by stepwise decreases in ventricular volume, allowing establishment of a steady mechanical state at each volume setting. However, it is possible, although it seems unlikely, that the difference may result from some altered properties of the electrical activation system created when the heart is studied in isolation.

The observed shape invariance of the isovolumic pressure wave has an interesting physiological implication pertinent to the "time-varying elastance" theory of ventricular contraction (19). According to this theory, under isovolumic conditions, instantaneous pressure [$P(t)$] and volume [$V(t)$] are related by the equation

$$P(t) = E(t) [V(t) - V_0] \quad (2)$$

where $E(t)$ is the time-varying volume elastance of the ventricle, and V_0 is the volume at which the peak systolic pressure is 0 mmHg. $E(t)$ can be expressed as follows

$$E(t) = E_{\text{es}}e(t) + E_{\text{min}} \quad (3)$$

where E_{min} is the minimum elastance, E_{es} is the maximum developed elastance attained at end-systole, and $e(t)$ describes the time course of change of elastance (i.e., the time course of stiffening and relaxation) and has a value of zero at end diastole and a value of 1 at end systole. Under isovolumic conditions, [i.e., $V(t) = \text{constant}$ in Eq. 3], the shape of the pressure wave [$P^*(t)$ in Eq. 1] is determined by the shape of the elastance curve, which, as defined in Eq. 3 is described by $e(t)$; that is, $e(t) = P^*(t)$. Thus the relative shape invariance of the isovolumic pressure wave suggests that the asynchronously contracting "ineffective" mass of muscle created by direct myocardial stimulation does not contribute significantly to the total elastance of the ventricle during the period of synchronous activation of the "effective" muscle mass. Any such influence, if it does exist, was beyond the sensitivity of our measurements. The only consistent alteration in the pressure waves with pacing site was that observed during relaxation, i.e., the significant prolongation of contraction. This observation suggests that the contribution of the "ineffective" muscle mass to overall chamber elastance may not be negligible during the relaxation phase of the cardiac cycle.

The pressure wave-shape invariance further indicates that reductions in the maximum rate of rise of isovolumic ventricular pressure (dP/dt_{\max}) observed with ventricular pacing are not due to a reduced rate of chamber stiffening per se, but rather are due to a decreased magnitude of pressure generation.

In summary, we observed significant influence of pacing site on the magnitude, but not the time course of isovolumic ventricular pressure waves. Pacing from different sites of the ventricle resulted in different chamber contractile strengths. There was a linear inverse relation between changes in QRS duration and changes in contractile strength. The decreased chamber contractility manifests itself as a decrease in F_{cs} and a small increase in V_0 . The relation between ventricular $\dot{V}O_2$ and PVA was independent of pacing site. These results are consistent with the hypothesis that the effective mass of muscle that participates in the generation of active contractile strength is reduced when the pacing site is moved from the atrium to the ventricle.

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