Relative Contributions of the Atrial Systole-Ventricular Systole Interval and of Patterns of Ventricular Activation to Ventricular Function during Electrical Pacing of the Dog Heart

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ABSTRACT

In areflexic canine right heart bypass preparations, little difference in ventricular function was observed as a result of atrial pacing, sequential atrioventricular pacing, or atrial-His bundle pacing at an appropriate atrial systole-ventricular systole (As-Vs) interval. Ventricular function was depressed during ventricular pacing and during atrioventricular pacing with an inappropriate As-Vs interval. In areflexic isovolumic left ventricle preparations, ventricular function was depressed during ventricular pacing compared to atrial pacing, and changes in the As-Vs interval during atrioventricular pacing were accompanied by changes in ventricular function only in association with changing patterns of ventricular activation. In animals with heart block under conditions of right heart bypass, wherein changes in the pattern of ventricular activation were precluded during atrioventricular pacing, ventricular function deteriorated pari passu with shortening of the As-Vs interval. These data indicate that both the temporal relation between atrial and ventricular contraction and the pattern of ventricular activation importantly influence ventricular function during cardiac pacing. The marked changes in ventricular function observed as a function of the As-Vs interval, for any given pattern of electrical activation, suggest that the As-Vs interval is the more important determinant of ventricular function during cardiac pacing.

ADDITIONAL KEY WORDS sequential pacing mitral valve mechanics ventricular synchrony atrial function fusion beats ventricular performance ventriculogenic valve closure

• In 1963 Gilmore and his associates (1) reported that a depression of ventricular performance ensued when atrial pacing was changed to ventricular pacing in a working heart preparation. They concluded that the manner of ventricular activation, as it affects synchrony of ventricular contraction, is an important determinant of ventricular function. This view was given additional support by the studies of Lister and his co-workers (2), who demonstrated that changing the site of epicardial ventricular pacing influenced the output of the heart. Little (3) and Mitchell et al. (4, 5) observed that the temporal relationship between atrial and ventricular contraction is also an important determinant of ventricular performance as this interval may influence both ventricular filling and A-V valve closure. The present investigation was designed to assess the relative contributions to ventricular function of the temporal relation between atrial and ventricular contractions on the one hand, and of differing patterns of ventricular activation on the other.

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Methods

Right Heart Bypass Preparation.—Experiments were conducted in 20 mongrel dogs weighing 14 to 26 kg, anesthetized intravenously with a warmed mixture of urethane, 600 mg/kg, and chloralose, 60 mg/kg. The trachea was intubated and ventilation controlled with an Emerson volume-limited ventilator. Right heart bypass was instituted as reported previously in detail (6). Briefly, the venous return from the cannulated superior and inferior venae cavae was led to a reservoir from which the blood was warmed, oxygenated, and returned to the pulmonary artery through an occlusive calibrated roller pump; the isolated right heart received only the coronary venous drainage which was led from the cannulated right heart to the venous reservoir. Aortic pressure was controlled by adjusting a screw clamp placed about the descending thoracic aorta just distal to the left subclavian artery. Pressures were measured through short, wide-bore cannulas in the ascending aorta, left ventricle, and left atrium with Statham P23db strain gauges. The left ventricular pressure was measured through a rigid metal cannula which was introduced through the apex of the left ventricle. The phase shift of the pressure measurement system varied linearly up to 30 cps, and the amplitude was uniform over this range. The damping coefficient of the pressure measurement system was 1.0 at a time constant of 0.1 second. The 0.1-second constant was imposed through the preamplifier and all recordings were taken at this time constant. The rate of change of left ventricular pressure (dp/dt) was obtained by electronic differentiation of the output of the channel recording left ventricular pressure. The dp/dt differentiator was calibrated by supplying a waveform of known slope to the differentiating circuit, which has a time constant of 0.001 second and a cutoff at 160 cps. Left ventricular circumference and the maximal rate of rise of left ventricular pressure (max dp/dt), of aortic pressure, and circumference and the maximal rate of rise of left ventricular pressure (max dp/dt), of atrial, sequential atrioventricular, and ventricular pacing at constant cardiac input, aortic pressure, and heart rate. Sequential atrioventricular pacing were produced by the administration of mecamylamine hydrochloride (10 mg/kg) and propranolol (0.5 mg/kg), respectively, to minimize reflex influences on the contractile state of the heart. These drugs were admixed in the oxygenator. Beta-receptor blockade was verified at the end of the experiment with a challenge infusion of isoproterenol, 5 μg/min. Ganglionic blockade was demonstrated by observing the absence of heart rate changes to abrupt changes in arterial pressure.

Isovolumic Left Ventricle Preparation.—Experiments were also performed in ten mongrel dogs of weights similar to those used in the right heart bypass preparation. The isovolumic left ventricle preparation, as employed in our laboratory, has been previously described in detail (8). A distensible latex balloon was affixed to the tip of a Y-shaped metal cannula introduced through the left ventricular apex. The balloon could then be filled with known amounts of saline. Subsequently, left ventricular systolic and diastolic pressures corresponding to a given balloon volume were recorded. At the end of the experiment, the balloon was removed from the left ventricle and its distensibility was checked by instilling known amounts of saline while recording pressure developed within it. Over the range of balloon volumes used, no discernible elevation of pressure occurred within the balloon, that is, the distensibility of the balloon was not exceeded. The mitral valve was closed by a multiholed plastic button sutured to the atrial side of the valve to prevent herniation of the ventricular balloon. Drains were placed in both the left ventricle and left atrium. Aortic pressure was maintained at a level higher than the peak developed left ventricular pressure to preclude balloon herniation through the aortic valve. The latter could be recognized by distortion of the aortic or left ventricular pressure tracings. Aortic pressure and left ventricular pressures, dp/dt, and the electrograms were recorded as in the right heart bypass preparation.

Experimental Protocol

Right Heart Bypass Preparation.—Experiments were first done in eight dogs to determine the effects on left ventricular end-diastolic pressure and circumference and the maximal rate of rise of left ventricular pressure (max dp/dt), of atrial, sequential atrioventricular, and ventricular pacing at constant cardiac input, aortic pressure, and heart rate. Sequential atrioventricular pacing were produced by the administration of mecamylamine hydrochloride (10 mg/kg) and propranolol (0.5 mg/kg), respectively, to minimize reflex influences on the contractile state of the heart. These drugs were admixed in the oxygenator. Beta-receptor blockade was verified at the end of the experiment with a challenge infusion of isoproterenol, 5 μg/min. Ganglionic blockade was demonstrated by observing the absence of heart rate changes to abrupt changes in arterial pressure.
was effected with an As-Vs interval 40 to 60% shorter than the prevailing As-Vs interval during atrial pacing. Ventricular function curves (9) were constructed from data obtained by increasing cardiac input while aortic pressure and heart rate were held constant.

Subsequently, in seven dogs, the As-Vs interval during sequential atrioventricular pacing was either progressively shortened or lengthened in steps of 20 msec between the prevailing P-R interval and zero msec, with cardiac input, aortic pressure, and heart rate held constant. The ventricular epicardial pacing site was the mid-right ventricle. In this group of experiments, attention was directed both to ventricular performance and to the relationship between LVEDP and mean left atrial pressure.

In three animals, both atrial-His bundle pacing and atrial-right ventricular pacing were compared and, again, the As-Vs interval was studied over a wide range. In two animals, heart block was induced acutely (10) to preclude alterations in the manner of ventricular activation from influencing hemodynamic observations, namely, partial ventricular activation from the ventricular epicanal pacing site and through the His-Purkinje system (fusion beat) (11). Experiments on the hemodynamic effects of the As-Vs interval

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**FIGURE 1**

Hemodynamic effects of atrial (A Pace), sequential A-V (A-RV2, Pace), and ventricular (RV2) pacing on ventricular performance at constant cardiac input, heart rate, and aortic pressure. LVP = left ventricular pressure; LVC = left ventricular circumference; LVDP = left ventricular diastolic pressure; AP = aortic pressure; LV dp/dt = rate of change of left ventricular pressure; P-R = atrial stimulation— to the R wave of electrogram interval during atrial pacing; HR = heart rate; CI = cardiac input; RHBP = right heart bypass preparation. Note the changes in left ventricular end-diastolic circumference, left ventricular end-diastolic pressure, and max LV dp/dt as a function of pacing mode. LV circumference tracing, while directionally valid, shows some damping.
were carried out in the animals with heart block on right heart bypass as described above.

Isovolumic Left Ventricle Preparation.—In five animals, the influence of epicardial activation site on the indices of contractility used in this preparation—peak left ventricular pressure and max dp/dt at constant heart rate—was assessed. The sites of epicardial pacing were: right atrium, midright ventricle, right ventricular outflow tract, lowermost area of right ventricle, left ventricular apex (lateral), midleft ventricle, and left ventricular apex (medial to left). In a second group of five isovolumic left ventricle preparations, the As-Vs interval was progressively shortened or lengthened between the prevailing P-R interval and zero msec at constant heart rate during sequential A-V pacing. Statistical significance of the results obtained was determined by Student's t-test for paired comparisons (12).

Results

Right Heart Bypass Preparation.—Figure 1 shows the effect of atrial, sequential A-V, and ventricular pacing on ventricular function in the right heart bypass preparation. At constant cardiac input, aortic pressure and heart rate, sequential atiroventricular pacing at an As-Vs interval 70 msec shorter than the P-R interval which prevailed during atrial pacing caused left ventricular end-diastolic circumference and pressure to increase. A further increase of pressure and circumference followed when the pacing was changed to ventricular pacing. Directionally similar effects on LVEDP (cm H_2O) were consistently noted in 17 experiments in 8 dogs as follows: atrial pace, 11.6 ± 5.0 (mean ± SE); sequential atiroventricular pace, 14.3 ± 4.8; and ventricular pace 18.4 ± 6.7. The difference between the observed LVEDP as a function of pacing mode was statistically significant (P<0.001). In experimental runs of this type ventricular function curves were constructed, and three distinct function curves were obtained, as shown in Figure 2. Ventricular performance in terms of left ventricular end-diastolic pressure and circumference was clearly influenced by changing the site and mode of electrical pacing. Figure 2 also shows that the left ventricle, working against an identical hemodynamic background, developed a greater max dp/dt for any given LVEDP (13) during atrial pacing than during sequential atiroventricular or ventricular pacing.

When the As-Vs interval during sequential atiroventricular pacing was adjusted to more closely approximate the prevailing As-Vs interval during atrial pacing, the difference in left ventricular end-diastolic pressure and circumference and mean left atrial pressure between these two types of pacing was small relative to that encountered during ventricular pacing (Fig. 3). In this type of experiment, the plots of stroke work against LVEDP or mean left atrial pressure (Fig. 4A and B) showed a small difference between atrial pacing and sequential atiroventricular pacing, while the substantial difference in ventricular performance as a function of ventricular pacing still obtained. Also, as shown in Figure 4C, the relation of LVEDP to mean left atrial pressure was very similar for atrial pacing and sequential atiroventricular pacing with an appropriate As-Vs interval, while during ventricular pacing mean left atrial pressure was greater for any given LVEDP than with either of the two former pacing modes.

When comparison was made among atrial, sequential atrial-His bundle pacing, and sequential atiroventricular (right ventricular
epicardial site) pacing at As-Vs intervals of appropriate duration, little difference in left atrial pressure was noted among these three modes of ventricular electrical activation (Fig. 5). However, as expected from the above data, when both sequential atrial-His bundle pacing and sequential atrioventricular pacing were effected through an inappropriately short As-Vs interval, an elevation of mean left atrial pressure was demonstrated.

In eight experimental runs in five dogs in which the As-Vs interval was progressively shortened or lengthened from 100 msec to zero msec during sequential atrioventricular pacing, a progressive elevation of mean left atrial pressure and LVEDP resulted as the As-Vs interval was shortened (Table 1).

To preclude changes in the manner of ventricular activation during pacing, experiments were conducted in two dogs with
surgically induced heart block under conditions of right heart bypass. It was found that even after the interruption of the conduction system, there was still an optimal As-Vs interval, departure from which decreased the level of ventricular performance from that during atrial pacing or sequential A-V pacing at an appropriate As-Vs interval (Fig. 6).

**Isovolumic Left Ventricle Preparation.** In five dogs ventricular pacing was performed from different ventricular epicardial sites. The data from a representative experiment are shown in Figure 7. Pacing from the left ventricular sites resulted in slightly higher peak systolic left ventricular pressure and greater peak velocity of pressure development than did pacing from any of the right ventricular pacing sites (P < 0.001).

In experiments carried out in a second series of five dogs under isovolumic conditions, wherein atrial influences were precluded, the effect of changing the As-Vs interval during sequential atrioventricular pacing was assessed in terms of peak left ventricular pressure and max dp/dt. The data from two representative experiments of this type are shown in Figure 8. Stepwise lengthening of the As-Vs interval during atrioventricular pacing from zero msec to the prevailing P-R interval during atrial pacing produced initially little difference in ventricular function from that observed during ventricular pacing. For-

### Table 1

<table>
<thead>
<tr>
<th>As-Vs Interval (msec)</th>
<th>MLAP (cm H$_2$O)</th>
<th>LVEDP (cm H$_2$O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>12.5 ± 3.5</td>
<td>11.0 ± 3.3</td>
</tr>
<tr>
<td>80</td>
<td>14.0 ± 3.7</td>
<td>12.6 ± 3.9</td>
</tr>
<tr>
<td>60</td>
<td>15.4 ± 3.1</td>
<td>12.9 ± 3.7</td>
</tr>
<tr>
<td>40</td>
<td>18.1 ± 2.5</td>
<td>15.1 ± 4.2</td>
</tr>
<tr>
<td>20</td>
<td>20.7 ± 3.2</td>
<td>17.1 ± 4.6</td>
</tr>
</tbody>
</table>

MLAP = mean left atrial pressure (n = 8); LVEDP = left ventricular end-diastolic pressure (n = 8); P values (t-test) are significance of the difference between the means for As-Vs interval and the one preceding it. Values are mean ± SE.
other lengthening of the As-Vs interval, however, caused progressive increase of peak left ventricular pressure and max dp/dt up to the level attained during atrial pacing. Simultaneous with this graded change in peak left ventricular pressure and max dp/dt there was
Influence of the ventricular epicardial pacing site on ventricular performance in the isovolumic left ventricle preparation at constant heart rate. Peak LVP = peak left ventricular systolic pressure; RVOT = right ventricular outflow tract; RV = right ventricle; LV = left ventricle; MAD = mean aortic pressure.

Discussion
To elucidate factors affecting ventricular performance during electrical pacing of the heart, investigators have explored in considerable detail the influence of the atrium, and the temporal relationship between atrial and ventricular contraction, on ventricular function. The hemodynamic consequences of the ectopic nature of ventricular depolarization during cardiac pacing have also been the subject of numerous studies. Currently, controversy exists regarding the relative importance of these phenomena in determining the level of ventricular performance during electrical pacing of the heart. The experiments described herein indicate that both the manner of ventricular activation (synchrony) and the As-Vs interval independently influence ventricular performance during pacing. However, the data also show that when the A-V delay during sequential atrioventricular pacing is adjusted to closely match the prevailing As-Vs relation, the ensuing effects on atrial and ventricular dynamics appear to override the consequences of the aberrant nature of ventricular depolarization, and the hemodynamic state approaches that attained during atrial pacing with a normally propagated wave of depolarization.

One important aspect of the temporal relation between atrial contraction and ventricular contraction lies in the negative pressure gradient (left atrial pressure < LVEDP) during atrial relaxation across the mitral valve, permitting the closure of the valve before the onset of ventricular systole. The absence of this gradient may find the mitral valve open at the onset of ventricular systole; the subsequent closure of the mitral valve by the abrupt rise in left ventricular pressure at the onset of ventricular systole may be attended by mitral regurgitation. Skinner and co-workers (5, 14) have documented mitral regurgitation at inappropriately short or long As-Vs intervals using a hydrogen electrode in open-chest dogs with complete heart block. On the other hand, Williams and co-workers (15, 16), using dye dilution and ventriculography, did not observe significant mitral regurgitation in the absence of an appropriately timed atrial systole in normal closed-chest dogs. Braunwald et al. have confirmed the findings of Williams et al. in man (17). A possible explanation for this discrepancy in data is that if the vigor of ventricular contraction is deficient in experiments performed in areflexic dogs under conditions of cardiac bypass, ventriculogenic valve closure may be incompetent, and under these conditions a suitably timed atrial contraction may selectively relieve defective valve closure (15). However, the hemodynamic studies carried out by Samet et al. (18) in normal man show that atrial and sequential atrioventricular pacing at an appropriate As-Vs interval differ little in terms of cardiac output, left atrial pressure, and arterial pressure. Ventricular pacing in these same subjects was associated with depressed cardiac output and arterial pressure, and elevated left atrial pressure. The present experiments in areflexic...
dogs under conditions of right heart bypass clearly show that abnormal patterns of ventricular activation influence ventricular performance little in the working heart if atrial and ventricular contractions are appropriately and sequentially related in time.

That the manner of electrical activation of the ventricle may influence ventricular function was first suggested by Wiggers (19) and has been the subject of numerous other studies (1, 2). In our isovolumic left ventricle experiments, changing the site of epicardial pacing significantly altered ventricular contractility. The observation that the level of performance when pacing from the left ventricle in the isovolumic heart is higher than that attained when pacing from the right ventricle is consonant with the observations made by Lister et al. in the working heart (2). In an attempt to assess further the role of ventricular synchronicity in achieving an optimal ventricular performance, and to preclude the effects of left atrial contraction, experiments were carried out in isovolumic preparations in which the As-Vs interval during sequential A-V pacing was varied over a wide range. A substantial increase in peak left ventricular pressure and max dp/dt was observed during sequential A-V pacing as the As-Vs interval was made to approach the prevailing As-Vs interval during atrial pacing. Correlated with this changing contractile state...
was a consistent and progressive alteration in QRS configuration which suggested a changing pattern of ventricular activation, and the development of ventricular fusion beats as the As-Vs interval was lengthened (Fig. 8). QRS configuration came to resemble that observed during atrial pacing, when the performance of the left ventricle was maximal. These data document an effect of differing patterns of ventricular activation (synchrony) on ventricular contractility.

To exclude the possibility that changing patterns of ventricular activation might account for the observed differences in ventricular performance as a function of the As-Vs interval in the working heart, experiments were carried out in dogs with complete heart block under otherwise identical conditions. With an unvarying pattern of ventricular activation effected through sequential A-V pace, it was again observed in the dogs with heart block that left atrial pressure, LVEDP, and max dp/dt (at constant aortic pressure, cardiac output, and heart rate) were directly related to the As-Vs interval. Possible explanations for these data and that of Samet et al. (18) do not include an altered pattern of ventricular activation.

One explanation for this demonstrated direct relation between the As-Vs interval and ventricular function would be that mitral regurgitation was present at inappropriately short As-Vs intervals. Although mitral regurgitation was not directly assessed in these experiments, the wave forms recorded in the left atrium during ventricular pacing and during sequential A-V pacing at inappropriate as-Vs intervals are consistent with this hypothesis (Figs. 3 and 6). Atrial cannonading, that is, premature atrial contraction against a closed mitral valve, is also suggested in these left atrial pressure traces. Atrial cannonading, however, cannot in itself account for the observed direct relationship between the As-Vs interval and ventricular function in the working heart, as left ventricular end-diastolic pressure and circumference (and thus volume) were also observed to increase at inappropriate As-Vs intervals during sequential A-V pacing as well as during ventricular pacing. Similarly, variations in the timing of atrial systole during ventricular pacing as a result of varying retrograde conduction cannot account for the observed results, as the changes in LVEDP at a time when retrograde 2:1 block was evident (Fig. 3) were small relative to the substantial rise of LVEDP as a function of ventricular pacing.

The presence of mitral regurgitation as a hypothetical explanation for the direct relation between the As-Vs interval and ventricular performance (we are unable to provide an alternative explanation) would appear less important than the functional implications of this relationship in determining the manner in which cardiac pacing is applied. Although blockade of autonomic influences and the use of extracorporeal circulation in the present experiments may have exaggerated the results observed, the same cannot be said for the findings of Samet et al. (18), whose experimental subject was normal, awake man. The present data appear to add significantly to the findings of Samet et al. by the measurement of left ventricular dynamics and direct effects thereon of the As-Vs interval. These data appear particularly relevant to selection of pacing modes under conditions of impaired myocardial contractility, in which the efficiency of ventriculogenic A-V valve closure has been shown to be impaired (15).

Although both the temporal relation between atrial contraction and ventricular contraction (as it affects end-diastolic volume, fiber length, and A-V valve closure) and the pattern of ventricular activation (as it influences ventricular synchrony) have been shown to influence independently the performance of the left ventricle during electrical stimulation of the heart, the marked changes in ventricular performance observed as a function of the As-Vs interval for any given pattern of ventricular electrical activation suggest that this mechanism is the more important determinant of ventricular performance during electrical pacing of the heart.

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