Relation of Variations in Activation Order to Intraventricular Pressures during Premature Beats

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ABSTRACT
A comprehensive study on open chest anesthetized dogs was done to investigate the influence of intraventricular activation order on cardiac performance and to evaluate the degree to which entry into the conduction system might contribute to the synchrony of contraction in the ventricle opposite the stimulus site. Intraventricular pressures were measured during premature beats from several ventricular sites and over the entire range of the cardiac cycle. For each site, intraventricular pressures during the premature beats were plotted vs. time of delivery of the stimulus and also vs. time of onset of pressure rise in the ventricle being considered. The prior observation that higher ventricular pressures occur during premature beats initiated in the opposite ventricle was confirmed. Evidence is presented that the major factor responsible is the increased filling and recovery interval permitted by the conduction time of the activation front arriving from the opposite ventricle. After correction for filling and recovery time, there were still differences due to site of origin of the premature beat, with those delivered to the apex resulting in the highest left ventricular pressures. The hypothesis that a more synchronous contraction results from stimulation of sites on the contralateral, rather than the ipsilateral ventricle, was not substantiated.

ADDITIONAL KEY WORDS
ventricular premature beats
artificial pacemaker site
anesthetized dogs

The sequence of ventricular activation as a determinant of cardiac performance has been the subject of recent investigation in this and other laboratories. Reports are conflicting, with some investigations showing marked differences in cardiac function dependent on excitation order and others showing little or no difference. Although Klotz et al. have reported differences in cardiac output with regular pacing from various ventricular sites,1 two other groups using regular ventricular pacing found only small variations in cardiac performance.2,3

While there is lack of agreement that cardiac performance is significantly altered by stimulus site during ventricular pacing at a fixed rate, there is general agreement that variations in performance related to stimulus site do occur with ventricular premature beats. During premature ventricular beats, marked and systematic differences in the intraventricular pressure in the stimulated and contralateral ventricle have been noted, with the directly stimulated ventricle attaining a smaller fraction of the systolic pressure in that ventricle during the preceding normally conducted beat.4,5 Wiggers noted this difference and suggested that the excitation pattern is more
mally abnormal in the directly stimulated ventricle and that there is a more nearly normal activation sequence with greater participation of the specialized conduction system in the contralateral ventricle, resulting in a more synchronous and more effective contraction.

The present study was undertaken in an attempt to define the reasons for the apparently conflicting findings summarized above and to further evaluate differences in hemodynamic performance associated with various ventricular activation orders.

Methods

Observations were made on 8 mongrel dogs anesthetized with pentobarbital (30 mg/kg iv). The chest was opened in the midline and the heart exposed, using the opened pericardium as a cradle. The sinus node was crushed. Bipolar surface and endocardial electrodes applied to four to six sites on the two ventricles were used to deliver premature beats. Figure 1 illustrates the location of the ventricular stimulating electrodes. The right atrium was driven regularly at the minimum rate necessary to maintain control, between 120 and 150 beats/min. Similar recording electrodes were applied to one atrial and one ventricular site to observe temporal relations. At least one body surface lead was recorded. Premature stimuli ($S_2$) were delivered to the ventricular sites at a controlled time after the previous stimulus to the atrium ($S_1$). By use of a selector switch a premature beat from each of the ventricular sites was obtained with the $S_1$-$S_2$ interval held constant. The $S_1$-$S_2$ interval was then changed by a few milliseconds and the series of premature beats repeated. In this way, a series of premature beats scanning the cardiac cycle was obtained for each site of premature ventricular stimulation. Premature contractions with the same $S_1$-$S_2$ interval, but from different sites, could be identified and compared. For each site, 6 to 43 premature beats (average 23 beats) were measured.

Pressures were recorded with Statham strain gauges, model P23Db, through cannulas 13.5 cm long (i.d. 3 mm) introduced directly into each ventricle near the apex. Electrograms, body surface electrocardiograms, and pressures were recorded simultaneously on an Electronics for Medicine recorder at a paper speed of 150 mm/sec.

Peak right and left ventricular pressures during the premature beats were expressed as a percent of the peak pressure in that ventricle during the previous normally conducted beat. Scattergrams were constructed by plotting percent peak pressures vs. time of stimulation, designated $t_s$. In most cases $t_s$ was the $S_1$-$S_2$ interval measured from the stimulus artifacts in the records. In those experiments where stimulus artifacts were not well seen, $t_s$ was taken as the interval between the onset of atrial electrical activity due to the $S_1$ stimulus and the ventricular electrical activity due to the $S_2$ stimulus. For each dog, values of $t_s$ were obtained from one series of premature beats selected for ease of measurement. In that dog, premature beats delivered to other sites at the same $S_1$-$S_2$ interval were assigned the same value of $t_s$.

Using the same pressure curves and the same percent peak pressure measurements, scattergrams were similarly constructed by plotting percent peak pressure vs. the interval ($t_p$) between the onset of pressure rise during the premature beat and the onset of pressure rise in the same ventricle during the preceding normally conducted beat. Premature beats with the same $t_p$ would be expected to have the same preceding filling and recovery time, although they were produced by premature stimuli at different $S_1$-$S_2$ intervals. The percent ventricular pressures vs. $t_p$ were plotted to repeat the previously reported observation that the ventricular pressure was lower dur-

![Figure 1](https://example.com/figure1.png)

The sites of premature stimulation used in this study are: 1, apex of left ventricle; 2, lateral wall of left ventricle; 3, posterior wall of left ventricle; 4, mid-right ventricular wall; 5, pulmonary conus; 6, endocardium near site 1; 7, endocardium near site 2.


Ventricular pressure recordings due to premature ventricular stimuli delivered to five sites in one animal at the same coupling interval \( t_c \). Numbers 1 through 5 refer to the site of the stimulus, as shown in Figure 1. Left ventricular pressures are higher when premature stimulus sites are on the right ventricle (sites 4 and 5) and lower when sites are on the left ventricle (sites 1-3). Similarly, the sites on the left ventricle gave higher right ventricular pressures than did sites on the right ventricle. For each ventricle the higher pressures resulted from stimulus sites on the contralateral ventricle.

\[
\Sigma y = na + b \Sigma x \\
\Sigma xy = a \Sigma x + b \Sigma x^2
\]

where

- \( y \) = right or left ventricular pressure expressed as a percent of the peak pressure in the previous normally conducted beat,
- \( x = t_p \) or \( t_r \),
- and \( n \) = number of observations for that regression line.

In some experiments the scattergrams for left ventricular pressures showed plateaus. These were analyzed by arbitrarily dividing the curves at the point of greatest change in slope and calculating separate regression lines for the steep part of the curve and, in some, for the plateau.

**Results**

Figure 2 illustrates ventricular pressure recordings obtained when premature stimuli were delivered to five ventricular sites in one animal at the same \( t_c \). Note that each ventricle attains a higher systolic pressure during a premature beat when the stimulus is applied to the opposite ventricle, than when it is applied to the ventricle being considered.

Plots of percent ventricular pressure vs. \( t_r \) were obtained for 6 animals. Figure 3 illustrates a scattergram plot of percent peak left ventricular pressure vs. \( t_r \) for one premature stimulus site. The data were chosen to illustrate the arbitrary division of a curve at the point of greatest change in slope.

In all 6 experiments, the highest left ventricular pressures at the same \( t_r \) resulted from stimulation of sites on the right ventricle. The
apex of the left ventricle gave the next highest pressures. The lowest left ventricular pressures were obtained by stimulating sites on the lateral or posterior wall of the left ventricle. These findings for the left ventricle are in agreement with previous reports that intraventricular pressures are higher during premature beats initiated in the contralateral ventricle at the same \( t_s \). Figure 4 shows regression lines for left ventricular pressure vs. \( t_s \) for the various sites of ventricular premature stimulation in 2 of the 6 experiments.

For the right ventricle, the highest pressures at the same \( t_s \) were obtained in 5 of the 6 dogs when the premature stimulus was applied to left ventricular sites. Sites on the right ventricle gave lower pressures. The left ventricular apex was not tested in 1 of the 5 experiments, but in the other 4 the apex gave right ventricular pressures higher than did sites elsewhere on the left ventricle. In the same experiments the pulmonary conus site gave the lowest pressures in all 3 dogs in which that site was tested. In 1 dog the curves for the right ventricle did not show higher pressures when the left ventricle was stimulated.

The experimental findings for left and right ventricular pressures vs. \( t_s \) are in agreement with previously published reports that the ventricle contralateral to the prematurely stimulated ventricle attains a higher percent of the pressure in that ventricle during the preceding beat.

Measurable changes in left ventricular pressure did not result from very early premature excitation. For premature beats initiated later in the cardiac cycle, there was a time interval during which a slight increase in the \( S_1-S_2 \) interval resulted in a large increase in left ventricular pressure, corresponding to the steep upslope of the calculated regression line. Using Figure 4, if an arbitrary pressure level is chosen, the times of stimulation (\( t_s \)) necessary to achieve that level by stimulation at different sites can be read. It can be seen that a particular level of left ventricular pressure it attained by stimulating the various sites at values of \( t_s \) which differ by 30 to 40 msec, a time interval roughly equal to expected conduction time from one ventricle to the other. With the data viewed in this way it becomes apparent that the appreciable differences during premature beats initiated at different sites but at the same \( S_1-S_2 \) interval might be accounted for by differences in time of arrival of depolarization in that ventricle. That is, the higher left ventricular pressure attained by ventricular beats arising in the right ventricle might be due to the later onset of contraction in the left ventricle rather than

**FIGURE 4**

Regression lines for left ventricular pressure vs. \( t_s \) for 2 experiments. Pressures are higher during premature beats initiated in the contralateral ventricle.

*Circulation Research, Vol. XIX, September 1966*
FIGURE 5
Calculated regression lines for left ventricular pressure vs. the time of onset of pressure rise during the premature beats \( t_p \). Numbers 1 through 7 correspond to ventricular sites in Figure 1. The apex of the left ventricle gave the highest pressures in 6 of the 7 dogs in which that site was tested (C through H). In experiment B, other sites gave pressures as high as the apex. In experiment F, endocardial sites at the apex (site 6) and left lateral wall (site 7) gave pressures higher than did adjacent epicardial sites 1 and 2, respectively. The midright ventricle (site 4) and pulmonary conus (site 5) were both tested in 5 experiments (A, C, D, E, and G). In 4 of these, the midright ventricle gave higher pressure than the pulmonary conus (A, C, D, and E). In experiment G, there was no difference between the two right ventricular sites.

Percent ventricular pressures during the premature beats were plotted vs. \( t_p \) for 8 dogs. Peak pressures for various sites could thereby be compared in terms of their preceding mechanical cycle lengths. Figure 5 shows the calculated regression lines for left ventricular pressures vs. \( t_p \) for all 8 experiments. The stimulus site at the left ventricular apex gave the highest left ventricular pressures in 6 of the 7 dogs in which that site was tested (C through H). The differences in percent pressure with different sites were not great—25 percent or less for late premature beats. In the 1 animal in which endocardial stimulus sites were tested (F), stimulation of those sites resulted in slightly higher pressures for the same \( t_p \) compared to pressures from the corresponding adjacent epicardial sites, suggesting a slight advantage due to immediate entry into the conduction system or due to the endocardial to epicardial activation sequence.

While it is obvious that stimulation at the apex of the left ventricle gave the highest left ventricular pressures when percent peak
pressure was plotted vs. $t_p$ rather than $t_e$, a systematic ranking of other sites is not immediately apparent. To test the hypothesis that a more synchronous contraction results when activation of a ventricle spreads from the contralateral ventricle, the data was displayed in the following way. For each experiment, left ventricular pressure data for all premature beats resulting from epicardial stimulus sites on the right ventricle were combined into one regression line, and the data for all epicardial nonapical sites on the left ventricle were similarly combined, as shown in Figure 6. There was no systematic difference between sites on the right ventricle as compared to the left, when the left ventricular apex was excluded. These data do not substantiate the theory that excitation initiated in the contralateral ventricle results in a more nearly normal activation sequence and more effective contraction.

Because of the finding of highest left ventricular pressures with stimulation of the left ventricular apex, the nonapical sites were reappraised in terms of their distance from the apex, rather than according to their origin in the ipsilateral or in the contralateral ventricle. Both of the nonapical sites on the left ventricle were intermediate in relation to the base or apex, and therefore the influence of distance from the apex could not be evaluated for the nonapical sites on the left ventricle.

**FIGURE 6**

For each experiment, left ventricular pressure data for nonapical sites on the right ventricle were included in one regression line (RV). Data for all epicardial nonapical sites on the left ventricle were similarly combined (LV). There was no systematic difference between the left ventricular pressures due to sites on the right ventricle and those due to sites on the left ventricle, when the apex of the left ventricle was excluded. The apex of the left ventricle gives the highest pressures.
For the right ventricular stimulus sites, however, there was good correlation of higher left ventricular pressures with the site closer to the left ventricular apex. The midright ventricle and the pulmonary conus were tested in the same animal in 5 experiments, as seen in figure 5, curves A, C, D, E, and G. The midright ventricular site gave the higher left ventricular pressure in 4, as shown by curves A, C, D, and E. In 1 experiment, no difference between the two sites was demonstrated, as shown by curve G.

The data for the left ventricular pressures plotted vs. $t_p$ suggest that direct spread of depolarization in the ventricle in which the premature beat is initiated does not significantly alter the pressure attained. The data suggest, rather, that the significant factor is the proximity of the site of origin of the premature beat to the left ventricular apex, and that lower pressures result as the stimulus site is moved toward the base.

Similar plots of percent right ventricular pressure vs. $t_p$ were made for 7 of the 8 dogs. One animal with spontaneous right bundle branch block was not included in evaluation of right ventricular performance, since the purpose of the study was to assess relations between hemodynamics and conduction sequence in the presence of a normal conduction system. The apex of the left ventricle was one of the test stimulus sites in 6 experiments, as shown in figure 7, curves B through G. In 3 of the 6 experiments, that site gave the highest right ventricular pressures (B, D, and E). When the midright ventricle and pulmonary conus were tested in the same animal, as shown by curves A, B, C, F, and G, there was no relation of right ventricular pressure to test site.

There were frequently striking variations in the shape of the right ventricular pressure curves with different stimulus sites without variation of the numerical value of the peak pressure, suggesting the presence of differences due to activation order which were not

![Figure 7](http://circres.ahajournals.org/)

**Figure 7**

Right ventricular pressure vs. $t_p$ for 7 experiments. Numbers 1 through 5 correspond to ventricular sites in Figure 1. See text.
measured by the method of analysis chosen. In individual experiments, the shape of the right ventricular pressure curve was reproducible for each stimulus site, suggesting that the variations associated with different stimulus sites were true differences.

Discussion

In a previous study from this laboratory, little difference in hemodynamic performance resulted from regular drive of various ventricular sites. A chronic experiment reported by Fletcher et al. also failed to show differences due to pacemaker site. It should be noted that measurements of hemodynamic performance were made some time after regular drive was established, with the animals in a stable state. Therefore, differences due to sequence of ventricular activation might have been obscured by a variety of compensatory cardiovascular reflexes. The apparent lack of agreement of the experiments mentioned above with those of Klotz et al., which showed hemodynamic differences related to pacer site, may be due to differences in compensatory phenomena under various experimental conditions and to differences in experimental design.

Wiggers reported more than 40 years ago that higher pressures resulted from apical stimulation than from premature stimulation at other sites. That study also demonstrated higher percent pressure in the opposite than in the directly stimulated ventricle. The latter finding was attributed to differences in synchrony of contraction due to differences in activation order in the two ventricles. Since then, other observations in the literature have noted the higher pressures in the contralateral ventricle.

The present study confirmed previous reports that, during premature beats, a ventricle attains a higher pressure when the excitation begins in the opposite ventricle, and a lower pressure when the excitation begins in the same ventricle, assuming that the timing of the premature stimulus is the same in each case. The major reason for this difference appears to be the greater filling and recovery time available to the contralateral ventricle. This study does give evidence that site of stimulation results in pressure differences in addition to those due to conduction time from the contralateral ventricle, with stimulation of the left apex giving the highest pressures. The hypothesis that a more synchronous contraction results from stimulation of the contralateral rather than the ipsilateral ventricle, was not substantiated.

References

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doi: 10.1161/01.RES.19.3.481

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1966 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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