Observations on the Relation Between Ventricular Activation Sequence and the Hemodynamic State

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The cardiac contraction sequence which follows the course of electrical excitation is one of the determinants of the hemodynamic state. The best known example of this relation is the sequence of atrial and ventricular contraction. Hemodynamic conditions are influenced by the contribution of atrial systole to ventricular filling and by the role of atrial contraction in normal closure of the atrioventricular valves. Hemodynamic effects of the activation sequence within individual cardiac chambers are also likely but are less clearly established. For example, it seems possible that the normal atrial activation and contraction sequence advancing toward the atrioventricular valves contributes to proper expulsion of blood through these orifices. In the case of the ventricles, the relation between activation order and cardiac performance has not been defined adequately and a variety of conflicting findings have been reported. Evidence of delayed contraction of the ipsilateral ventricle has been found in some but not all instances of bundle branch block. In several studies different sites of ventricular stimulation were associated with different intracardiac and vascular pressure levels and with different values of cardiac output. Other investigations, however, have shown no significant relation between the ventricular activation pattern and ventricular function.

In view of these findings the relation of ventricular activation order and the hemodynamic state needs further investigation. Definition of this relation would be a worthwhile addition to physiologic knowledge and may also add to the understanding of disease states. Abnormalities of ventricular activation are well known manifestations of heart disease and their recognition by electrocardiographic examination has proved to be diagnostically helpful. It is possible that such disorders also have significant hemodynamic consequences and are important functionally as well as diagnostically.

This report presents a variety of observations which appear to contribute to a definition of the relation between ventricular activation order and the hemodynamic state.

Methods

Experiments were performed on 18 mongrel dogs weighing 10 to 20 kg and anesthetized by means of pentobarbital 30 mg/kg or thiopental 20 mg/kg followed by barbital 250 mg/kg. During artificial respiration, the chest was opened in the midline and the heart cradled in the opened pericardium. Bipolar stimulating electrodes were placed on the right atrium and at selected sites in the superficial layers of the ventricles.

Stimulating electrodes were placed in approximately comparable positions in different experiments. The electrodes on the posterior base were placed at the atrioventricular sulcus midway between the right and left posterior cardiac borders. The apical electrodes were placed at or near the apical dimple and those near the pulmonary conus were located anteriorly at the junction of the right ventricle and pulmonary artery. In three experiments additional stimulating electrodes were placed at selected sites. In one experiment a bipolar electrode was manually moved to multiple sites while ventricular press...
pressures were monitored visually. Stimulators were arranged to drive the atria and ventricles with a controlled temporal relation. Electrograms from bipolar electrodes on the right atrium and anterior surface of the right ventricle and one or more body surface ECG leads were recorded. In most experiments the sinus node was crushed and A-V nodal rhythm resulted. In this state normal ventricular activation was present and retrograde atrial activation occurred during or following ventricular excitation. Abnormal ventricular activation was produced by direct ventricular stimulation and independent atrial stimulation was applied. The time of stimulation of atrium and ventricle was chosen to match the time of excitation of these chambers during nodal rhythm. With these conditions, normal and abnormal ventricular activation without preceding atrial contraction was achieved. These conditions also permitted comparison of various abnormal activation patterns produced by ventricular stimulation at different sites with the contribution of atrial contraction to ventricular filling removed. In these experiments the driven rate was adjusted to duplicate that which had existed during A-V nodal rhythm. Such rates were achieved by initiating stimulation out of phase with the A-V nodal rate and could be maintained as long as the nodal rate did not change significantly.

In some experiments normal and abnormal ventricular activation with comparable contributions of atrial contraction to ventricular filling were produced. The state associated with atrial stimulation alone was compared with that which resulted when both the atria and ventricles were stimulated in such a way that atrial activation preceded ventricular with the longest interval short of that permitting normal supraventricular excitation of the ventricles.

Left and right ventricular pressure curves were recorded in each experiment. Aortic and/or pulmonary artery pressure curves were recorded in selected experiments. Pressure curves were usually recorded through short cannulae inserted into the desired chamber or vessel but, in some experiments, pressures were recorded through cardiac catheters or with a catheter-mounted strain gage. The rate of change (dP/dt) of left ventricular pressure was recorded in some experiments. In certain experiments carotid flow was recorded with a square wave electromagnetic flow meter and was taken as an indication of directional changes in cardiac output.6

Blockade of sympathetic beta receptors was produced with nethalide, 6 mg/kg, or dichloroisoproterenol, 5 mg/kg, in certain experiments. These agents were employed to permit administration of the large doses of ouabain necessary to block the specialized cardiac conduction system without producing ventricular arrhythmias, but still permitting spread of the excitatory process in ventricular muscle.11,12 These agents made it possible to obtain abnormal ventricular activation patterns other than those which could be produced with a functioning conduction system.

**Results**

Results were divided into three groups.

1. It was demonstrated that the hemodynamic state associated with normal ventricular activation differed in characteristic fashion from that present with abnormal excitation.

2. Hemodynamic differences associated with various abnormal ventricular activation orders were also demonstrated. (3) Observations concerning the role of the specialized conduction system were made. Much more striking hemodynamic differences were associated with ventricular stimulation at various sites when the conduction system was blocked.

**Normal vs. Abnormal Ventricular Activation**

To compare hemodynamic conditions in these states, comparable atrioventricular relations were established as described under Methods. In two experiments atrial stimulation preceded ventricular with the longest possible interval, but still short of that permitting the occurrence of normal A-V conduction. In nine experiments hemodynamic conditions during A-V nodal rhythm were compared with those which existed during ventricular stimulation. In the latter state, ventricle and atrium were driven with the same relation as had existed during nodal rhythm. Comparison of hemodynamic conditions during normal and abnormal ventricular activation gave similar findings in the two types of experiments.

Abnormal ventricular excitation was usually associated with lower peak ventricular pressure levels. With average values of 101 mm Hg in the left ventricle and 23 mm Hg in the right ventricle during normal activation, decreases of 0 to 35% (avg 10%) in the left and 0 to 40% (avg 15%) in the right ventricle occurred with abnormal activation.

The form of ventricular pressure curves differed during normal and abnormal activation. With normal activation the onset of pres-
Records during A-V nodal rhythm with normal ventricular activation and during abnormal activation produced by stimulation of the left ventricle near the base. The recording paper speed was 100 mm/sec and the time lines shown represent 100 msec intervals. With one exception that will be noted, the tracings in subsequent figures have been recorded similarly. Electrograms from the atria (B) and ventricle (C) show the onset of atrial activity after ventricular during both A-V nodal rhythm and ventricular stimulation. As described in the text this atrio-ventricular relation was achieved during ventricular stimulation by separate stimuli delivered to the atria. The body surface ECG lead (A) was recorded from electrodes on the left fore and hind limbs. Aortic, left and right ventricular, and the first derivative of the left ventricular pressure curve (D) are shown. Scales for right and left ventricular pressures are shown at the right of the figure. During abnormal activation, lower peak pressure and slower rate of rise of pressure is present in both ventricles. Onset of pressure rise in the right ventricle is later with abnormal activation and there are differences in the detailed form of both ventricular pressure curves.

Pressure rise in right and left ventricles was sometimes asynchronous but greater asynchrony resulted from ventricular stimulation at all sites except those near the interventricular septum. Stimulation at other sites resulted in earlier pressure rise in the stimulated chamber. Ventricular pressure curves associated with stimulation at almost all ectopic sites showed a slower rate of rise than curves during normal activation. Some of the features described are illustrated in figure 1, in which right and left ventricular pressure curves, together with the rate of change of left ventricular pressure, are shown during normal ventricular activation associated with an A-V nodal rhythm and during ventricular stimulation at a site near the base of the left ventricle. Lower peak pressure in both ventricles is present, and the onset of right ventricular pressure rise is later with ventricular stimulation. The decreased maximum rate of rise of pressure in the right ventricle is apparent by inspection during ventricular stimulation and in the case of the left ventricle this is indicated by the smaller amplitude of the recorded first derivative of the pressure curve.

The body surface electrocardiographic
lead shows the supraventricular form of the QRS complex and the abnormal form resulting from ventricular stimulation. Electrograms from the atria and ventricles show the onset of atrial activity after that in the ventricles during both A-V nodal rhythm and ventricular stimulation.

Similar findings are illustrated in figure 2. The first complex shown in the body surface electrocardiogram has the form resulting from stimulation of a site at the base of the left ventricle. The succeeding three complexes, each of which has a different form, are combination complexes resulting from simultaneous activation of the ventricle from the stimulated site and from the A-V node. In the interval illustrated, the nodal rate was slightly faster than the stimulus rate furnished to the ventricular site. This produced ventricular activation patterns in which successively increasing portions of the ventricle were activated in a normal supraventricular fashion. The last complex shown in the electrocardiographic lead has the normal supraventricular form observed in this animal. The atrial electrogram shows atrial responses to the spontaneous A-V nodal pacemaker. These are followed by stimulus artifacts which have a changing phase relation to the atrial responses. The stimulus artifacts shown were being supplied to the atrium at the same rate and a fixed interval after those furnished to the ventricle. The changing phase described thus illustrates the slightly faster rate of the spontaneous A-V nodal pacemaker as compared to the stimulus rate.

Pressure curves from both ventricles show higher peak pressure with each change of the activation sequence. There are also differences in the detailed configuration of the pressure curves and slightly increased mean carotid flow associated with each successive

**FIGURE 2**

*Records during various patterns of ventricular activation. The first QRS complex illustrated in the ECG lead (C) has the form which resulted from stimulation of the left ventricle near the base. The last complex illustrated shows the form resulting from normal activation of the ventricles in this animal. Intermediate cycles show combination complexes resulting from simultaneous activation of the ventricles from the stimulus site and over normal pathways. As described in the text, this situation occurred during regular ventricular stimulation at a rate slightly lower than the spontaneous A-V nodal rhythm. Records labeled A and B are atrial and ventricular electrograms respectively and record D shows carotid flow. Pressure curves from both ventricles show higher peak pressures with each change of the activation sequence toward the normal.*
Records during three patterns of ventricular activation. The first complex shown in the ECG lead (C) resulted from stimulation of the left ventricular apex. The second is a combination complex resulting from simultaneous activation over normal conducting pathways and from the apical stimulus site. The final complex represents normal supraventricular activation of the ventricles. Both right and left ventricular peak pressures increase with the more normal activation patterns. Records A, B, and D are respectively atrial and ventricular electrograms and a record of carotid flow.

The highest peak pressure and flow were associated with normal supraventricular activation of the ventricles. Comparable findings are illustrated in figures 3 and 4. In the experiments illustrated in these figures, the left ventricle was being driven from a site near the apex. In the experiment illustrated in figure 3, the spontaneous A-V nodal rate increased as in the previous illustration, resulting in a combination complex followed by normal supraventricular activation from the A-V node. In the experiment illustrated in figure 4, the ventricular stimulus was stopped and A-V nodal rhythm occurred at the point indicated. In that figure, the first cycle during nodal rhythm is significantly longer than the stimulated cycle length shown by the first pair of complexes illustrated. These differences of cycle length may be responsible for some features of the pressure curves in the first two beats of A-V nodal rhythm. The nodal rate thereafter is very similar to the driven ventricular rate and it seemed likely that the differences in the pressure curves of the first two cycles illustrated (abnormal activation) and the last two or three cycles shown (normal activation) reflected effects of the ventricular excitation sequence. As in previous examples, normal ventricular activation was associated with (a) higher peak ventricular pressures, (b) differences in the form of pressure curves, including more rapid rate of rise, and (c) slightly higher carotid flow than was the case during abnormal activation.

COMPARISON OF DIFFERENT ABNORMAL ACTIVATION ORDERS

Observations of this type were made in 18 experiments. As described under Methods, the sinus node was usually crushed so that the heart could be driven at reasonably slow rates. However, a systematic study of the effects of rate was not done. Stimuli were delivered to the atria following those furnished to the ventricle in order to eliminate atrial contraction as a factor in ventricular filling.

With the specialized conduction system intact, there were definite though small differences in the form of ventricular pressure curves and often in the level of peak pressure and carotid flow associated with stimulation.
VENTRICULAR ACTIVATION AND HEMODYNAMIC STATE

at different ventricular sites. As indicated in the previous section, different ventricular stimulus sites were associated with peak pressures which differed from those observed during normal activation by 0 to 35% in the left ventricle and 0 to 40% in the right ventricle. There was no consistent relation between stimulus site and peak pressure level. In some experiments stimulation at the apex of the left ventricle produced higher peak pressure than did stimulation at the left ventricular base or pulmonary conus, but other experiments showed higher pressure associated with stimulus sites at the conus or the left ventricular base than with apical stimulation. Average decreases of left ventricular peak pressures associated with ventricular stimulation as compared to normal activation were: left ventricular base 11%, left ventricular apex 7.5%, and pulmonary conus 14%. Comparable values for the right ventricle were: left ventricular base 14.5, apex 14.5 and pulmonary conus 13%. Figure 5 presents examples in which the body surface ECG displays the different activation patterns associated with stimulation at the sites indicated. The electrograms show the temporal relation between atrial and ventricular activation when the ventricle was activated prior to the atrium. Pressure curves from the ventricles and aorta show differences in the time of onset of pressure rise in the cardiac chambers and differences in the detailed form of the curves associated with different stimulation sites.

Comparable findings are illustrated in figure 6, which indicates also that there was no consistent relation of stimulus site to peak pressure or to carotid flow level. Thus in the experiment illustrated in figure 6A, stimulation near the pulmonary conus was associated with peak pressures in both ventricles higher than those associated with stimulation at the base or apex of the left ventricle. In the experiment illustrated in figure 6B, however, stimulation at the left ventricular apex resulted in higher peak left ventricular pressure than did stimulation of sites at the base of the left ventricle or near the pulmonary conus. In this experiment the highest peak right ventricular pressure occurred with stimulation near the base of the left ventricle. In both experiments illustrated by figure 6,

FIGURE 4

Records during abnormal and normal ventricular activation. A, B, and C are respectively atrial and ventricular electrograms and carotid flow. The first two cycles shown resulted from ventricular stimulation near the apex. The remaining cycles were recorded during A-V nodal rhythm with a normal mode of ventricular activation. The first cycle length during nodal rhythm is longer than that during ventricular stimulation and may be responsible for some of the features of the pressure curves of the first three nodal beats. Thereafter the nodal rate is similar to the driven ventricular rate and the last two pressure curves shown can be compared to those during ventricular stimulation. Abnormal activation produced by ventricular stimulation is associated with lower peak pressure in both ventricles and with slightly lower carotid flow.

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higher levels of mean carotid flow were associated with higher levels of peak left ventricular pressure.

Stimulation at additional sites was associated with pressure curves whose form and peak level were intermediate between those resulting from stimulation at the three routinely employed locations.

ROLE OF THE SPECIALIZED CONDUCTION SYSTEM

On theoretical grounds it seemed likely that the ventricular conduction system played a significant role in the observations which have been described. It seemed probable that activation initiated by stimulation of the right ventricle might invade the conduction system of that side, enter the central portion of the system, and be delivered to the left ventricle in a normal supraventricular fashion. Even on the right side, activation might be distributed to a significant portion of the ventricle in a normal sequence. If the contraction sequence follows that of activation, only minor differences in the hemodynamic states associated with supraventricular and various origins of ventricular stimulation might be expected. The variety of activation patterns possible in the absence of a specialized conduction system might, however, be associated with more marked variability of the hemodynamic state.

Because of these considerations, attempts were made to block the specialized conduction system. As outlined in the Methods section, beta adrenergic blocking agents were given to permit the administration of large doses of ouabain. Differential effects of digitalis preparations on ventricular muscle and specialized conduction system have been reported, e.g., conduction is blocked in the latter but still possible in ventricular muscle. It was recognized that the doses of ouabain employed, as well as the adrenergic blocking agents, might modify excitation in ventricular muscle and also in the conduction system. Despite this, the known effect of digitalis preparations on cardiac conduction tissue and the probable role of that tissue in the phenomena under investigation made it likely that block of the conduction system was a major factor in the results obtained. Observations of this type were carried out in six experiments. In three experiments observations were...
made after 0.5 mg and again after 1.0 mg ouabain and in other experiments observations were made after 1.0 and 1.5 mg ouabain.

In these experiments there were marked differences in the form and peak level of pressure curves associated with some sites of ventricu-

FIGURE 6

Records from two experiments showing effects of stimulation at various ventricular sites. Differences in the time of onset of pressure rise in right and left ventricles and differences in the detailed form of pressure curves are associated with different stimulus sites. In the experiment illustrated in A, stimulation near the pulmonary conus was associated with a higher peak pressure in both ventricles and higher carotid flow than was stimulation at the base of apex of the left ventricle. In this portion of the figure the two upper records designated A are atrial and ventricular electrograms and records B and C are a body surface ECG lead and a record of carotid flow. As described in the text, no consistent relation was found between stimulus site and peak pressure or carotid flow. B portion of the figure illustrates this by records from an experiment in which stimulation near the left ventricular apex was associated with higher peak left ventricular pressure and carotid flow than was stimulation at the pulmonary conus. Stimulation of the left ventricle at the base was associated with higher peak right ventricular pressure than was stimulation at the apex or the pulmonary conus. In this portion of the figure records A, B, and C are respectively atrial and ventricular electrograms and records of carotid flow.
Records obtained before (A) and 15 minutes after (B) 1.5 mg ouabain and 5 mg/kg DCI. Tracings in this figure made at paper speed of 200 mm/sec. A, B, and C are respectively body surface ECG leads and atrial and ventricular electrograms. Pressure curves include aortic as well as right and left ventricular records. Records in A show differences in time of onset and detailed form of pressure curves associated with different stimulus sites. Following medications given to block the specialized conduction system differences in the form of pressure curves associated with stimulation at different sites are more striking.

Discussion

As noted in the introductory section, studies of the hemodynamic consequences of abnormal ventricular activation have given conflicting results. This study was not designed specifically to resolve those conflicts but some
of the results may be applicable to their explanation. One of the major findings of the present study was that the various activation patterns possible with an intact conduction system were associated with definite but small differences in the hemodynamic state. When the conduction system was blocked, marked variations of the hemodynamic state were sometimes associated with various activation patterns. It seems possible that some of the conflicting findings in previous studies may have been due to differences in the state of the conduction system in different experimental preparations.

Results of this study support the possibility that disease of the conduction system may be

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

**FIGURE 8**

Records obtained 15 minutes after 1 mg (A) and 1.5 mg ouabain (B) in a dog previously given 5 mg/kg DCl. A, B, and C are respectively atrial and ventricular electrograms and a body surface ECC lead. Differences in peak pressure and form of pressure curves are much more marked after the larger dose of ouabain.
a significant functional factor in heart disease. The minimal hemodynamic effects of driving the ventricle with an intact conduction system may be the counterpart of localized bundle branch block in patients. With the exception of late onset of mechanical events, no definite circulatory abnormalities have been identified in such patients. In the presence of bundle branch block it seems likely that the excitation process enters the otherwise normal conduction system distal to the block and activates the ventricle late, but in a relatively normal fashion. The striking electrocardiographic abnormalities associated with bundle branch block do not exclude such an activation order in the chamber whose bundle branch is blocked. These abnormalities reflect the disturbed phase of right and left ventricular activation but activation within each chamber may be normal or nearly so.

Experimentally, greater pressure and flow alterations were sometimes produced when the ventricles were driven and the conduction system poisoned with ouabain. The clinical counterpart of this situation would be extensive disease of the peripheral conduction system. At the present time it is difficult to separate such disease from bundle branch block due to a localized lesion. Diffuse disease of the conduction system disease must exist, however, and the findings of this study suggest that such disease may be associated with significant hemodynamic alterations.

Summary

Hemodynamic parameters including records of left and right ventricular pressure, aortic pressure, the first derivative of the left ventricular pressure curve, and carotid flow were recorded with different patterns of ventricular activation. Special measures were used to achieve a comparable role of the atrium in ventricular filling with the different ventricular activation patterns.

With an intact cardiac conduction system, definite but small differences in the hemodynamic parameters named were associated with different activation patterns. Normal ventricular activation produced slightly higher peak pressures in both ventricles and higher carotid flow than did abnormal activation. Each different activation pattern was associated with differences in the detailed shape of the ventricular pressure curves and with differences in the relative time of onset of pressure rise in right and left ventricles. When the specialized conduction system was blocked with large doses of ouabain, various patterns of ventricular activation were associated with marked differences of the hemodynamic parameters named. These findings may explain previously published conflicting results. They also suggest that disease of the conduction system may have a significant functional role in cardiac disease.

References


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