Direct Current Make and Break Thresholds for Pacemaker Electrodes on the Canine Ventricle

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ABSTRACT

Thresholds to anodal make, anodal break, cathodal make and cathodal break have been studied throughout the cardiac cycle in 13 dogs under pentobarbital anesthesia.

Unipolar direct current pulses were applied through epicardial pacemaker electrodes to the left ventricle. Make and break responses were separated by letting the break and make occur in the refractory periods of the following and preceding cycle, respectively.

Four distinct threshold interval curves were obtained from each of 17 electrodes. The anodal break and cathodal break curves showed an early diastolic dip. Dips were deepest in the anodal break curves. These also had the shortest effective refractory period. Thresholds for cathodal make and anodal make first dipped steeply, then gradually sloped down towards end-diastolic levels. The magnitude of end-diastolic mean threshold values increased in the following order: cathodal make, anodal make, cathodal break, anodal break.

Comparison of threshold interval curves for make and break responses with those for shorter rectangular anodal and cathodal curves throughout the cardiac cycle supports the hypothesis that the threshold behavior to a short rectangular pulse is determined by whichever of two thresholds is lowest: make or break at that particular cycle interval.

ADDITIONAL KEY WORDS anode dip-phenomenon cathode myocardium electrical stimulation cardiac pacing
non was studied by placing the preceding make phenomenon early in the absolute refractory period of the preceding normal heart beat. Similarly the make phenomenon could be studied separately by allowing the break phenomenon to occur in the refractory period of the following normal heart beat.

Subsequent gradual shortening of pulse width gave some indication of the possible mechanism of stimulation with short pulses. Evidence will be presented to support the hypothesis that make and break responses are both operative in determining the threshold behavior of the ventricle to rectangular pacemaker pulses.

**Methods**

Acute experiments were done on 13 adult mongrel dogs anesthetized by intravenous injection of pentobarbital, 25 to 30 mg/kg. After tracheal intubation, ventilation was maintained by a positive pressure respirator. The heart was approached through a median sternotomy and cradled in its pericardium. One or two commercially available electrodes of the type described by Elmqvist et al. (14) were fixed by sutures to the left ventricle. These are platinum epicardial disc electrodes with a diameter of 9 mm. Unipolar stimuli were applied, a needle electrode in the right hind leg serving as the indifferent electrode. Bipolar surface electrodes were fixed to the right atrium. The sinus node was clamp-crushed.

Figure 1 is a schematic representation of timing and shaping of the stimuli. The atria were stimulated with 2-msec pulses at a regular interval chosen between 350 and 400 msec, so as to give a frequency above the spontaneous atrial rhythm. The stimulating current was obtained from a continuously variable voltage supply. A resistor of 30 to 100 kohms was placed in series with the voltage supply, so that for each voltage setting a constant stimulating current was delivered to the pacemaker electrode on the heart. Rectangular current pulses were formed by closing and opening a mercury wetted relay. The current pulse characteristics were as follows. There was a rise time of 0.002 msec with

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...a 5% overshoot in the first 0.008 msec. After opening the relay, 90% of the current drop occurred in 0.006 msec.

A bipolar intramural lead was obtained from the subepicardial terminals of an electrode needle (15) in the left ventricular wall adjacent to the stimulating electrode. This complex, as displayed by the oscilloscope, served to indicate whether the heart was stimulated on current make and break.

The stimulation current was varied by altering the power supply voltage. The pulses were given after each fourth propagated beat. They were monitored and their amplitude was measured on a dual-beam oscilloscope by observing the voltage over a second series resistor of 1000 ohms.

Thresholds were determined by increasing the current until all stimuli were followed by a propagated response. This definition of threshold is relevant to our results, because considerable and strongly variable "hysteresis" was observed when thresholds were determined with decreasing current strengths (7, 9). If the current strength was increased above threshold, an area of no response (4, 8, 10, 13, 18) was sometimes observed. During these studies no special attention was given to this phenomenon, except as a source of possible error to be avoided during the measurement of thresholds. The maximum current strength applied in these experiments was usually limited to 7 mamp because of the risk of provoking ventricular fibrillation.

Make and break pulses for the relay were provided by a variable delay stimulator which could be adjusted in steps of 1 msec. For the study of break phenomena, the relay was closed 30 msec after the beginning of the QRS complex of the preceding propagated beat. Thresholds to break phenomena were then plotted as a function of the time interval between the beginning of QRS and the opening of the relay. Thresholds to make phenomena were similarly measured by placing the break impulse in the absolute refractory period of the following beat.

In another series of experiments, much shorter rectangular anodal and cathodal pulses were used. Thresholds were first determined in the classical way in which rectangular stimuli are treated as a single entity. The pulse width was then gradually increased and the threshold interval curves thus obtained were compared with the threshold interval curves to make and break stimuli.

These experiments were designed to yield some indirect information about the respective contribution of make and break phenomena to the overall response to rectangular impulses.

FIGURE 2

Multiple exposure tracings showing the effect of rectangular anodal pulses during the end-diastolic period. In the upper half of both figures the myocardial response is shown as obtained from bipolar needle electrodes at a distance of approximately 10 mm from the center of the stimulating electrode. The recordings of the myocardial responses are placed in the same vertical order as the current pulses shown below them. Current strength was fixed at 2 mamp, slightly above the threshold for the longest pulses (1.5 mamp). Pulse duration was varied in two different ways: A: instead of current break was fixed in the cardiac cycle and the current make was moved progressively later in the cardiac cycle. The myocardial response was seen to shift with the current make. B: instant of current make was fixed in the cardiac cycle and the current break was moved progressively later. The myocardial response arrived with a fixed delay after current make, irrespective of the timing of current break both before and after the response. Such response behavior was interpreted as anodal make stimulation.

More direct information was obtained from inspection of the response to rectangular pulses of

Tektronics 502 A.

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Myocardial thresholds in milliamperes are plotted as a function of the interval in milliseconds after the preceding normally conducted QRS complex for each mode of stimulation—anodal make, anodal break, cathodal make and cathodal break. a through d each gives a set of

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intermediate duration. If a rectangular impulse caused a QRS response to occur before the break, it could not have been caused by this break and was thus counted as a make response. Moreover, a make response could be recognized by the observation that its timing in the cardiac cycle would move with the timing of the current make whereas it was independent of the timing of the break (Fig. 2).

Identification of a break response was more uncertain. A break response was assumed to occur if the response not only followed the break, but if it could also be moved to and fro by changing the break interval while remaining stationary after small changes in make interval.

**Results**

**Threshold Studies with Direct Current**

It was found that the left ventricle of the dog could be excited by direct current in all four modes: cathodal make, cathodal break, anodal make, and anodal break. Each of these excitation modes was found to have a different threshold interval curve. For each of 17 electrodes, a set of four threshold interval curves was obtained. Considerable variation was found among individual animals and even between two electrodes in one animal. Figure 3, a to d, illustrates this variability.

There is, however, a common trend which will be discussed for each of the following periods: end-diastole, effective refractory period, and relative refractory period.

**End-Diastolic Thresholds**

These were invariably lowest for cathodal make excitation. Anodal make, cathodal break, and anodal break excitation increased usually in that order, with respective mean values of 0.4, 1.3, 2.2, and 3.0 mamp. There were exceptions to this rule, however. The cathodal break end-diastolic threshold was almost equal to the anodal make threshold in 3 of 17 electrodes tested. In five instances the cathodal break threshold was higher than the anodal break threshold.

During measurements of threshold interval curves for break phenomena in end-diastole, it was sometimes observed that the timing of the excitation became independent of the timing of the current break even to the extent that the excited beat preceded the break phenomenon. It was concluded that in those instances the direct current in itself excited the heart with a threshold lower than that of the break stimulus. Whenever this was observed, the results were discarded.

**Effective Refractory Period**

During this period no propagated activity (16, 17) could be produced with direct current pulses up to 7 mamp.

Its duration varied between 100 and 220 msec after the beginning of the QRS complex at the stimulating electrode. It was shortest for anodal break excitation (mean value 130 msec, range 100 to 160 msec). It was longest for anodal make excitation (mean 175, range 130 to 220 msec). The effective refractory periods of cathodal make and cathodal break excitations were contained in strongly variable positions in the interval between these two extremes. The mean values for the duration of the effective refractory period of cathodal break and cathodal make excitations were both 155 and 155 msec, with respective ranges of 115 to 185 and 105 to 205 msec.

**Relative Refractory Period**

Threshold curves for cathodal make and anodal make excitation fit into the traditional concept of a relative refractory period in which the threshold values fall rapidly and then gradually decrease from refractoriness to the end-diastolic level.

"Relative refractory period" would, however, be a misnomer for anodal break and cathodal break excitation. The threshold interval curves of both modes of activation show a dip during this episode, indicating a phase of hyperexcitability.

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Curves obtained from one particular electrode, a: most typical for the set of curves usually obtained. The remaining parts are selected to illustrate the variability in the results. Note the "primary dip" in the cathodal break curve in b and the similarity in general outline between anodal break and cathodal break curves for each individual electrode.

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Myocardial threshold interval curves are plotted for short rectangular anodal pulses of 0.5, 1, 5, and 10 msec duration. Superimposed are the threshold values for anodal make and anodal break for this same electrode. The dotted line indicates, for each particular interval, which of the two thresholds is lowest—anodal make or break. Note the similarity between the dotted line and the threshold interval curves for short rectangular pulses.

In anodal break excitation the descent from refractoriness is extremely steep and the dip is pronounced. Its width varies between 5 and 45 msec. Threshold in it reaches a mean minimum value of 0.7 mamp. The ascent later in the cycle is more gradual. The ascending limb often has a notch followed by a dome-shaped maximum before the final descent towards the end-diastolic level. There is considerable variability in this part of the curve in different electrodes.

The dip in the threshold interval curve for cathodal break excitation is less pronounced. It generally reaches its minimum later in the cycle. As illustrated by Figure 3 the morphology of the ascending limb of the cathodal break dip for a given electrode shows some similarity to that of the ascending limb of the anodal break dip.

In four instances this dip in the cathodal break curve was preceded by a primary dip high in the descending limb in a position comparable to that previously described (2, 4, 5, 18) in bipolar stimulation. Figure 3b shows an example. As this phenomenon occurred near the maximum current strength, it seems possible that more such dips might have been found if stronger currents would have been used.

EXPERIMENTS USING SHORTER RECTANGULAR PULSES

Figure 4 is representative of a series of eight experiments in which thresholds to shorter rectangular anodal pulses were determined. If the impulse duration is increased stepwise from 0.5 to 10 msec, it is observed that the end-diastolic threshold decreases. The decrease in early diastolic threshold is even...
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stronger, thus deepening and widening the diastolic dip. These observations confirm results of earlier workers (2, 4, 18).

A hypothesis explaining these observations is introduced at this point to give meaning to the description of the remaining experiments: The methods employed in this study do not allow us to explain our observation in terms of potentials at the membrane level. The threshold curves for make and break excitation which we obtained may, however, be used for the elucidation of threshold interval curves by the following hypothesis: a rectangular pulse has separate thresholds for its make and break and the lowest of these thresholds determines whether the heart is excited.

Figure 4 gives support to this hypothesis. Thresholds to make and break phenomena for this same electrode have been superimposed on the threshold interval curves for the rectangular pulses. The dotted line, indicating the lowest thresholds for make and break at each given interval, shows a remarkable similarity to the threshold interval curves of the rectangular pulses.

Figure 4 more specifically suggests that the end-diastolic threshold of a rectangular anodal pulse may be determined by its threshold of the make phenomenon. During the anodal dip it seems to be determined by the break phenomenon.

For impulses with a duration of 40 msec or more, this can be directly observed. If an anodal pulse with a duration of 50 msec is placed in the end-diastole of the preceding propagated beat, as in Figure 5D, the QRS response is seen to fall within the rectangular pulse before the break, thus indicating anodal make excitation.

Anodal make excitation remains the mode of the rectangular pulse activation up to point C in Figure 5. Shortening the delay 1 msec as in Figure 5B causes the QRS response to suddenly shift into a position behind the break phenomenon. This critical delay coincides with the peak following the anodal dip.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Left: threshold interval curve for a rectangular anodal pulse of 50-msec duration. Right: at four different intervals, A through D, the oscillographic image of the bipolar intramural complex (top trace) was photographed together with the amplitude of the stimulating current as measured over a 1000-ohm series resistor. The rapid deflections have been retouched. In C and D the ventricular complex occurs before the break, indicating make excitation (open squares). Between C and B there is a sudden "jump" of the complex to a position after the break transient. Break excitation is maintained throughout the anodal dip (solid squares).}
\end{figure}

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Duration of a unipolar cathodal rectangular direct current pulse is increased stepwise from 1 to 50 msec. A pronounced cathodal dip is seen to develop in early diastole. The effective refractory period for such stimuli can be reduced to virtually zero by increasing the pulse width. This is largely an artifact of the conventional plotting method whereby the interval is measured from the QRS to the make of the stimulating pulse. However, as shown in Figure 7, it is the break which causes the propagated beat.

The QRS response remains behind the break phenomenon during the anodal dip (Fig. 5A). The timing of the QRS response in this area moves with the timing of the break phenomenon, if the latter is slightly changed. The QRS response does not follow slight variations in the timing of the make phenomenon and thus our criteria for break excitation are met.

Similar phenomena are observed if rectangular pulses of cathodal polarity are applied. If the pulse width is increased from 1 to 50 msec, an early diastolic dip appears which gradually deepens and broadens (Fig. 6). By the same method as described above for anodal stimuli, it can be shown that during the cathodal dip break excitation prevails and during the remaining cycle make excitation (Fig. 7).

Figure 8 gives details of the comparison of excitation patterns produced by slightly supra-threshold anodal pulses of different duration during the end-diastolic period. Anodal pulses of 3 msec are shown to arrive at the exploring electrode with virtually the same delay and the same pattern as the 200-msec pulses. Excitation is largely independent of the timing.
Threshold interval curve for 70-msec rectangular unipolar cathodal pulses through the same electrode as in Figure 6. In the same manner as in Figure 5, it is shown that in late diastole this cathodal pulse activates by its make (open squares) and in early diastole by its break (solid squares). Note the plotting artifact, discussed in legend to Figure 6, which seemingly reduces the effective refractory period to 20 msec.

Discussion

Our experiments seem to have established that the heart is able to respond to all four modes of direct current activation, i.e., anodal make, anodal break, cathodal make, and cathodal break.

These conclusions, however, should only be extrapolated with caution from the experimental setting in which they were obtained, i.e., in unipolar stimulation through relatively large platinum epicardial disc electrodes on the left ventricle of the dog anesthetized with pentobarbital. Each of these factors may have influenced the results.

The type of electrode was chosen in the hope of giving our results possible relevance to the mechanisms of therapeutic use of electronic pacemakers. It seems prudent to stress at this point the risk of repeating similar measurements in man. Ventricular fibrillation frequently brought our measurements in dogs to a premature end.

There is a remarkable paucity of data in the literature on the threshold behavior to anodal and cathodal make and break excitation of the heart.

In the older literature, experiments are reported with direct current stimulation of the hearts of different species, mostly of lower vertebrates (19-27), molluscs (28) and arthropods (29). Most of these experiments were devised to demonstrate an analogy to Pfliiger's law (30) for the nerve-muscle preparation and to the rules laid down by von Bezold (31) for direct stimulation of frog skeletal muscle. In these experiments bipolar stimulation from atria and ventricles or from an intact and a damaged part of the ventricle was often used with currents "ascending" and "descending" with respect to the longitudinal axis of the heart or the whole body.
Comparison of the effects of short and very long anodal pulses on the activation time and pattern of the myocardial responses. The experimental situation was identical to that of Figure 2b. The sweep speed of the oscilloscope has been increased to show the high frequency components of the myocardial complexes. The records of the current pulses are placed in the same vertical order as their responses. Current make was fixed in the cardiac cycle. Current break was timed progressively later so as to produce pulses of 3, 6, 9, 12 and 200 msec (break not shown). All these pulses have approximately the same response. The deformation caused by the stimulus artifact is, of course, different.

The partially conflicting results of this work are difficult to interpret which is perhaps the reason why we were unable to find the topic discussed in 27 textbooks on physiology written between 1845 and 1964. Nevertheless from these studies emerged the conviction that the heart can be stimulated by breaking an anodal current but not by making it, and by making a cathodal current, but not by breaking it (27).

Through the classical texts of Biederman (32), Porter (33), and Schaefer (34) this concept found its way into modern texts of electrophysiology of the heart (13). Even in the older literature, however, anodal make excitation has been reported (20, 21, 23, 25) and evidence for its occurrence can be found in some additional illustrations (35) which for some reason did not draw any comment from the author.

Hoffman and Cranefield (13) observed that in end-diastole, excitation may arise at the anode after an anodal stimulus which lasts 30 msec or longer. In stimuli of shorter duration, i.e., up to 20 msec, excitation at the anode was ascribed to anodal break, apparently on the ground that excitation occurred after cessation of current flow. This conclusion, however, deserves further discussion. Evidently ventricular excitation cannot be caused by a current break which follows it. If, on the other hand, current make and break both precede excitation, conclusions become more difficult, especially when stimulating and exploring electrodes are spatially separated, as in our experiments. As shown in Figures 2 and 8, excitation occurring after anodal break need not be caused by the break but may be due to anodal make with a suitable delay, because of latency and conduction time. Even in anodal make pulses, however, the break is important as it determines the pulse width. And pulse width is intimately related to current threshold.

This brings us to another observation which likewise seems to have been overlooked. The curves of pulse width versus current threshold, for rectangular end-diastolic anodal pulses, both in dogs (36) and man (37), show an asymptotic approach to the rheobase and then continue to run parallel to the abscissa. This also means that beyond a certain pulse duration, the threshold for anodal stimuli is independent of the further delay of the break phenomenon. It follows logically that this response cannot be due to the break of the anodal current. In fact the "decision" of the heart to respond to the anodal stimulus is made after the utilization time, which we found to be in the order of 4 to 12 msec in a small series of experiments with rectangular pulses. Shorter pulses will require a stronger current. In the experiment illustrated in Figure 8, a 3-msec pulse gave a propagated response. When the current break was moved further to the left, so as to limit pulse width to 2 msec, the pulse fell below threshold. This
MYOCARDIAL RESPONSE TO CURRENT MAKE AND BREAK elucidates the meaning of make and break excitation as used in this paper. Current make and break transients determine the timing of excitation, but they are, of course, meaningless without a following or preceding charge transport of at least a certain magnitude. The minimum quantity of charge that must pass after direct current make to give an effective stimulus is obviously transported within a few milliseconds. This finding suggests similarity in mechanism between stimulation with short pulses, as used in therapeutic application to the human heart, and long pulses.

The gradual transition of the threshold interval curves in Figures 4 and 6 likewise suggests that the threshold interval behavior of short, intermediate, and long pulses may be closely related, although this is admittedly only indirect evidence. The work of Van Dam et al. (7, 9, 12) has shown that Orias and co-workers (2) were correct in suggesting that previous bipolar threshold interval curves for electrical stimulation of the canine heart with such short pulses were composite curves corresponding to the most effective portions of the anodal and cathodal unipolar curves. Our findings suggest that these anodal and cathodal unipolar curves are again composite curves corresponding to the most effective portions of the threshold interval curves to make and break.

We could find no prior study of threshold interval relations for all four modes of excitation by extracellular electrodes in the mammalian heart. In the frog, however, recent studies on isolated strips of ventricular muscle by Goto and Brooks (38) led to results very similar to ours obtained with the dog ventricle in situ. Using the same method for isolating make and break pulses, these authors found that the frog ventricular muscle, the classical object of earlier physiology, does respond to anodal make and cathodal break stimulation so that four threshold interval curves were obtained which show considerable similarity to our observations in dogs. This conformity is the more remarkable because of the great differences in electrophysiologically important ultrastructure between these species (39, 40). As might be expected, there were differences in detail. Thus, end-diastolic thresholds in the frog were found to increase in a slightly different order, i.e., cathodal make, anodal make, and anodal break and cathodal break. The order in which the duration of the respective absolute refractory periods increases also seemed to differ in detail with our observations. Furthermore, the dip in the anodal break response curves in the frog was found to be less pronounced, and the dip in the cathodal break curve seemed to be absent.

It should be noted that our results, obtained with large epicardial electrodes, cannot be taken as proof that the same four threshold interval relationships we found on a macroscopic scale also exist at the membrane level. In fact Hoshi and Matsuda (41) concluded from their experiments with intracellular stimulation that intact terminal Purkinje fibers in the dog are unresponsive to anodal stimulation in end-diastole. The discussion on virtual anodes and virtual cathodes has constantly accompanied investigation in this field (13, 32-34, 41-44).

It seems indeed possible that current entering a chain of cells at a certain location leaves the cell interior at some other site which would result in transmembrane polarities of opposite sign at these two locations (45). Hoshi and Matsuda (41) have actually registered both depolarizing and hyperpolarizing transmembrane potentials in different cells in the vicinity of an extracellular electrode. Goto and Brooks (38) confirmed this finding. Thus anodal make and cathodal make phenomena would be almost identical processes at different sites. The dip in the cathodal break curve might be similarly related to the dip in the anodal break curve. The delay in the dip in the cathodal break curve may be due to the anodal direct current which precedes the break, shortening the plateau phase of the transmembrane potentials, whereas a preceding cathodal current lengthens it (46, 47).
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