The Excitability Cycle of the Dog's Left Ventricle Determined by Anodal, Cathodal, and Bipolar Stimulation

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Investigations are reported in which the excitability cycle of the dog's heart was tested successively by unipolar anodal and cathodal square wave shocks as well as by bipolar stimulation. The classical view that excitability decreases smoothly during the relative refractory phase was substantiated. The excitability for anodal stimulation reached its maximum of the cardiac cycle immediately after the absolute refractory period and exceeded cathodal excitability at that moment. Evidence is presented that the dip phenomenon described by Orias, Brooks and their associates is due to their arrangement of driving and testing electrodes. The coincidence of the dip phenomenon with the vulnerable period may be related to simultaneous spreading of two fronts of activation from cathode and anode of bipolar electrodes which would create favorable conditions for reentry.

Since Marey, in 1879, definitely demonstrated the refractory period of the heart, numerous investigations have been carried out upon the variations in excitability that occur during the cardiac cycle. Whereas, according to most investigators, excitability in the relative refractory period decreases continuously along a smooth curve to the diastolic level, Orias and his associates observed a constant irregularity in this curve which they described as a dip phenomenon. Within a short interval the threshold reached a lower level than was observed immediately before and after the dip. Furthermore, strong supraliminal stimuli, delivered during the dip, caused the appearance of multiple systoles or gave rise to ventricular fibrillation. Thus, the dip phenomenon coincided with the vulnerable period, originally observed by Wiggers and Wegria. In recent experiments by Sikand and associates, however, no dip was observed.

These contradictory findings, as well as the clinical interest attached to the reported coincidence of the dip phenomenon with the vulnerable period, led us to reinvestigate the changes of the excitability occurring during the cardiac cycle. Since investigators have employed different arrangements of the stimulating electrodes, experiments were designed to analyze the effects of unipolar cathodal and anodal, and of bipolar stimulation.

METHODS

Mongrel dogs (25) were anesthetized with Pernocton. During the determination of a continuous series of strength/interval curves no additional Pernocton was administered. It was, therefore, assumed that the level of anesthesia was constant during one run. After tracheal intubation, respiration was maintained by a respiratory pump, the heart was exposed by median sternotomy and suspended in a pericardial cradle. A small plastic block, containing a bipolar driving electrode, was sewed to the right atrial appendage. After insertion of the electrode needles into the wall of the left ventricle the thorax was closed with clamps, and moist cotton wool soaked in saline was placed on the heart to prevent cooling and drying. The temperature within the thorax was kept approximately at 37 C. by use of an electric heat pad.

Electrode needles: Two types of electrode needles, previously described by Durrer and van der Tweel, were used. Those, used only for recording, consisted of a shaft 20 mm. in length and 0.9 mm. in diameter, carrying to its surface 10 silver electrodes about 0.2 mm. diameter, placed at regular intervals. The needles used for stimulation were of a similar construction, but contained 7 platinum electrodes which proved less liable to electrolytic deterioration during prolonged stimulation than the silver ones.
The use of electrode needles has great advantages for the localization of the electrodes in the ventricular wall, as well as for determining the site of origin of systoles evoked by stimulation. As the needles were carefully polished, the small electrodes did not project beyond the surface of the shaft. Thus, after insertion into the ventricular wall, they caused no further damage to the myocardium during the contractions. This was proved by the complete disappearance of all injury potentials within 15 minutes. Furthermore, after every systole, the small electrodes came to occupy exactly the same position. This was demonstrated by the reproductibility of the observed complexes, during many hours. This constant localization can only be achieved by placing the plastic head of the needle upon the epicardial surface without exerting undue pressure, and allowing the tip of the needle to protrude through the endocardium into the ventricular cavity, during every phase of the cardiac cycle.

**Stimulating and recording equipment:** The general arrangement of the stimulating and recording plan is shown in figure 1.

In order to avoid any possible influence of natural irregularities in cardiac rhythm upon the excitability cycle, the heart was driven at a constant frequency. A simple stimulator delivered square wave pulses of slightly supraliminal strength to the right auricular appendage. This resulted in a normal activation of the ventricles, which would not have been the case if the heart had been driven on the ventricles. With a driving frequency of about 120 per cent of the original sinus rhythm, crushing of the sinus node proved unnecessary. To insure accurate control of the intervals between excitation and the delivery of the test shock a synchronizer with a variable delay circuit was employed. The activating signal was the depolarization spike led off from a point near the site of the electrodes that delivered the test stimuli. This arrangement eliminated errors of interval that might have resulted from conduction variations, A-V or intraventricular, if activating signals from other sites had been used. The synchronizer rejected incoming signals which arrived at any interval shorter than that which had been selected. The delay interval could be set for any duration between 50 and 1000 mense. The number of normal beats after which a test shock was given, could be chosen from 1 to 15.

The testing stimulator delivered a test shock at a certain interval in the cardiac cycle, which could be chosen with a reproductibility of less than one-third per cent of the selected interval. Without the use of transformers, the square wave impulses varied in strength from 0.03 to 30 ma and in duration from 0.1 to 100 mense. Since the internal resistance of the stimulator was very high (more than 10 megohms), the resistance of the tissue and the electrodes had only a negligible influence upon the strength of the testing stimulus.

All stimuli were separated from ground by means of special 1:1 transformers with a low spreading inductance (30 mh) and a high self-inductance (500 h). Prevention of the current flow to the ground electrode ensured true bipolar stimulation of the heart, because the stimulating current was then concentrated in the tissue between the electrodes. Also, the stimulus artifact in the recorded complexes was minimized. Since the deformation of the current impulse in such transformers depends on the L/R time of the circuit, it is mainly governed by the ration of the self-inductance of the transformer and the resistance of the stimulating electrodes. With our transformers, this deformation was negligible when stimuli less than 2 mense, duration and 5 ma strength were used. This was verified by inserting a small resistance in series with the stimulating electrodes and feeding the voltage over the terminals into a calibrated oscilloscope. By means of a double selector switch, connected to the secondary terminals of the transformer, the testing stimuli could be delivered between any chosen pair of electrodes. Also, stimulation could quickly be changed from bipolar, using two small terminals of the needle, to unipolar using one of the small needle terminals and a large electrode under the skin of the left fore-leg.

All electrical phenomena were observed with the cathode-ray oscillograph previously described by Durrer and van der Tweel.6

**Experimental procedure:** After the insertion of the electrode needles into the wall of the left ventricle, their position was verified by taking leads from all electrodes. As soon as all evidence of injury had disappeared from the complexes, the diastolic threshold for unipolar cathodal stimulation was determined at every electrode of the stimulation needle. Constant differences in threshold between the various electrodes were generally observed, which probably were due to small differences of their
contact area with the myocardium or to the local anatomic situation (interposition of blood vessels, etc.).

All thresholds were determined by gradually increasing the current strength, until a premature systole occurred. In this way, the heart was beating in a regular rhythm until the threshold was reached; the threshold was not affected by the aftereffect of a previous premature systole, which sometimes may lower the threshold, as was observed in preliminary experiments. Furthermore, as a rule the thresholds were determined at progressively shorter intervals after the beginning of the cardiac cycle, starting from the end of the diastole; in this way the strongest stimuli were delivered at the end of a series of determinations.

In order to minimize changes in excitability during the delivery of the square wave test-shock, we used a duration of 0.5 msec.

For several reasons the maximal strength of the stimuli was limited to 2 ma; stronger stimuli were considered to be outside the physiological range. Since in most of our experiments 2 ma. was nearly the 20 times of the cathodal diastolic threshold, the intensity of the strongest stimuli employed largely exceeded the safety margin described by Rosenblueth and by Tasaki. These authors state, that in nerve fibers the size of the fully developed action potential is approximately 7 to 10 times that of the resting threshold. Strong stimuli spread far from the electrodes, as was shown in similar experiments on cats, when stimuli of 2.4 ma, delivered to the ventricle of the heart sometimes caused general convulsions. Thus, the local thresholds cannot be exactly determined with strong stimuli. Furthermore, stimuli of excessive strength can damage the heart, as follows from the observation that after a test shock of 5 ma, the myocardium close to the stimulating electrodes showed no electrical activity during the next 5 to 8 beats.

To allow for possible influence of subliminal shocks, the testing stimuli were delivered only after every tenth beat.

A series of strength/interval curves was made by determining at a selected interval in the cardiac cycle the thresholds for various combinations of electrode terminals with both unipolar and bipolar stimuli. Subsequently the same determinations were made at the next interval chosen, until the entire cardiac cycle had been scanned.

Whenever the testing stimulus reached threshold, premature systoles were observed in bipolar leads, taken from the stimulating or leading-off needle. From these complexes the site of origin of the premature systoles could be determined, as will be described hereafter.

RESULTS

The conventional terms absolute and relative refractory period have been used for the sole purpose of describing the changes in threshold occurring under controlled conditions during the cardiac cycle. The durations of the absolute and relative refractory periods so determined depend on the duration and the maximal strength of the stimuli used. From a theoretical point of view the best approach to refactoriness is offered by the concept of a functional refractory period as developed by Rosenblueth and associates. This functional refractory period extends up to the moment when an action potential sufficient in amplitude to exceed the progressively decreasing threshold develops and thereby initiates a propagated impulse. However, in previous studies, it has not been possible to check the relationship of the return of myocardial conduction to the changes in excitability during the refractory period of a heart, driven at a constant frequency.

In this report the absolute refractory period (ARP) covers the interval between the local beginning of the cardiac cycle and the first moment (sometimes obtained by extrapolation) at which a stimulus having a 0.5 msec. duration and a strength of 2 ma was followed by a premature systole. The relative refractory period (RRP) covers the next part of the cycle and ends upon recovery of threshold diastolic level. Since this occurs asymptotically, the end of the RRP is also rather arbitrary.

Effects of unipolar cathodal stimulation: With different driving frequencies in different experiments, the duration of the ARP varied between 120 and 180 msec. During the RRP the threshold at first dropped abruptly, then declined progressively less steeply until the diastolic level was reached. The duration of the RRP varied between 20 and 40 msec. For the remaining part of the cycle the electrical diastolic threshold was found to be constant. In none of the experiments was a supernormality of cathodal excitability observed (fig. 2).

These results agree entirely with the classical view of the excitability cycle. In some cases the threshold was less reproducible during the first part of the RRP. Owing to the time sequence of the determinations, these variations could suggest the presence of a dip, but
in control observations they appeared not to be constant, even within a very short time.

Effects of unipolar anodal stimulation: During the first part of the cardiac cycle all stimuli of a strength up to 2 ma failed to produce premature systoles. In simultaneous determinations of anodal and cathodal strength/interval curves, the ARP for anodal stimuli was 2 to 5 msec. shorter than for cathodal stimuli. In one experiment this difference was 15 msec. The remaining part of the anodal strength/interval curves is mostly very different from those obtained with cathodal stimulation (fig. 2).

Immediately after the end of the ARP in these cases, the anodal threshold drops even more abruptly than the cathodal threshold to values approximately twice that of the cathodal diastolic threshold. After this sudden drop, the threshold rises gradually until the end of the cardiac cycle. This rising of the anodal strength/interval curves shows a great variability in different experiments. In about one-half of the experiments there was (fig. 2) a marked oscillation; the threshold at first rose steeply, to decline afterwards. Thereafter the diastolic threshold rose very gradually again. The rate of rise of the anodal threshold in the latter part of the cardiac cycle displayed a marked variability in different experiments. In three experiments a second, slow and small oscillation in threshold appeared to exist.

Although the anodal strength/interval curves presented great individual differences, they were frequently characterized by an "anodal dip", corresponding to the maximum of anodal excitability immediately after the end of the ARP, whereas at the same moment the ventricles were still relatively refractory to cathodal stimuli.

Effects of bipolar stimulation: The results obtained by bipolar stimulation are entirely consistent with the findings for unipolar anodal and cathodal stimulation. They can be discussed most clearly by describing a typical experiment designed as illustrated (fig. 3).

The electrodes 1 and 7 of the stimulation needle served alternately as an anode (+) and as a cathode (—). As the cathodal diastolic thresholds determined at each point did not differ greatly, the threshold changes at both points were reasonably comparable. In leading from either electrode, the activation during normal beats occurred some 30 msec. earlier at electrode 1 than at electrode 7.

During the experiment bipolar complexes were led off from electrodes 3 and 4, and 5 and 6, situated on the same needle as shown (fig. 3). Prior to the actual threshold determinations, these bipolar complexes 3–4 and 5–6 were recorded during unipolar stimulation at electrodes 1 and 7. An example is shown in figure 4. The premature systole starting at electrode 1 causes complexes at 3–4 and at 5–6 of the same polarity (record A). During stimulation at electrode 7 the polarity was inverted in both leads (record B). Thus, during bipolar stimulation at electrodes 1 and 7, the site of origin of the evoked systoles can be deduced from the polarity of the bipolar complexes 3–4 and 5–6.

The results obtained with bipolar stimulation between electrode 1 as an anode, and electrode 7 as a cathode were as follows: after an ARP with a duration of 150 msec., the strength/interval curve shows a marked dip and consists of two parts. Between 150 and 180 msec. after the onset of the cardiac cycle all premature systoles originate at the anode, whereas, from 180 msec. on, their origin is at the cathode. The reason for this shift of origin
appears from the separate strength/interval curves determined for the anode and cathode. During diastole the cathodal threshold is generally much lower than the anodal. Therefore, when with a delay of 220 msec., the strength of the testing stimulus was gradually increased above the cathodal threshold of 0.09 ma, it eventually also reached threshold intensity at the anode, which, in this case, was 0.21 ma (fig. 4 C). This caused two complexes of opposite polarity indicating simultaneous spread of two excitations from both electrodes 1 and 7 (fig. 3 C). Aided by visual observation of bipolar complexes 3–4 and 5–6, the thresholds at both electrodes could be easily determined at every interval of the cardiac cycle.

The results of such tests are shown (fig. 5). At the anode (1+) the ARP lasted for 150 msec. after the onset of depolarization of the synchronizing electrodes. From 160 to 170 msec. the threshold has a low value of 0.12 ma, rises to 0.25 ma at 180 msec., declines afterwards until the slowly rising level is attained at 190 msec. delay. At 300 msec. the maximal anodal threshold during diastole, 0.22 ma, was observed, just before the next beat occurred. On the other hand, at the cathode (7–) the strength/interval curve presents an ARP of
180 msec; the threshold declines between 180 and 200 msec. to the constant diastolic threshold of 0.09 ma. Both strength/interval curves intersect at 190 msec. delay. The intersection marks the end of the interval during which excitability at the anode exceeds cathodal excitability. The bipolar strength/interval curve that would merely represent the lowest threshold at every interval of the cardiac cycle, consists of an anodal and a cathodal part; there is a marked dip, corresponding to the interval of maximal anodal excitability. (See inset, fig. 5.)

Simultaneously with the foregoing curves, a series of strength/interval curves was determined for opposite polarity of the testing stimulus; electrode 1 now served as a cathode and electrode 7 as an anode. Now, the AEP ends first at the cathode and some 25 msec. later at the anode. The cathodal strength/interval curve represents the lowest threshold at every interval of the cardiac cycle and is not intersected by the anodal curve. As a consequence, the bipolar curve entirely follows the cathodal threshold and a dip is lacking.

**Discussion**

The findings of Sikand and co-workers who tested the recovery of excitability with unipolar cathodal stimulation in the dog and failed to demonstrate a dip, are entirely confirmed by our results.

The determination of a threshold with cathodal stimuli is considered to be the most satisfactory approach to measurement of excitability. However, during the RRP, determined with cathodal stimuli, anodal stimuli are often more effective.

The cause of the greater effectiveness of the anode during recovery is obscure. However, it may be recalled that cathodal stimuli have mainly a depolarizing action whereas anodal stimuli enhance repolarization and shorten the refractory period. Acceleration of repolarization can not be the only effect of an anodal stimulus, however, since a new impulse is started. Much more information about repolarization, and the mode of action of anodal stimuli will be needed before a satisfactory explanation can be attempted.

During the diastole internal sodium ions are exchanged for external potassium ions. Apparently this does not influence the stable cathodal diastolic threshold. But, in its slow rise, the anodal threshold may possibly reflect these ion-exchanges of which the temporal course is as yet unknown.

According to our results, the refractory period ends at different moments at various points of the ventricles. These time-differences are not necessarily due to local variations in the duration of the refractory period, but perhaps are caused at least in part by the different moment of activation. A statistical variation in the duration of the depolarized state of the different myocardial fibers probably exists. Woodbury and associates observed variations in the durations of the membrane-action potentials of different fibers.
in the frog’s heart. In unpublished experiments on isolated cat papillary muscles, notched spikes have been recorded by us as a result of stimulation immediately after the end of the ARP, whereas, the electrical complexes of premature systoles occurring at a later moment in the cardiac cycle had a smooth appearance. Thus, during the last part of the refractory period all myocardial fibers are not in the same condition. This means that a strength/interval curve in this part of the cycle represents the threshold of fibers momentarily most excitable. About the fibers which recover more slowly, no information is available.

It appears from the experimental findings that the following criteria for experiments measuring the excitability cycle are essential in any experiment of this kind.

Summarized, they are: 1. The excitability must be tested locally. This requires at least synchronization with the local depolarization, the use of small stimulating electrodes, and limitation of the intensity of the test shocks. 2. The site of origin of the resulting premature systoles has to be known.

With bipolar stimulation as employed by Orias and co-workers,1 the second point is especially important since the threshold at the anode reaches a lower value than at the cathode during a portion of the recovery period in typical experiments giving rise to the dip as follows from their arrangement of driving and testing electrodes. We did not observe a primary high-intensity dip for cathodal stimulation, as did Orias and co-workers. This negative result may be due to the excessive strength of the stimuli required for its determination. These were outside our range of 2 ma. As mentioned, however, in some experiments the presence of a slight dip was simulated in determinations with unipolar cathode stimuli, probably due to variations in the rapid phase of the recovery process.

A clue to the origin of the vulnerable period is found in the observation by Orias and associates that the dip coincides with a period of vulnerability for the onset of ventricular fibrillation. This suggests that the anode plays a role in the genesis of the vulnerable period. It appears probable that the simultaneous spreading of two fronts of activation from both cathode and anode, results in an erratic spread of excitation thus offering favorable conditions for the occurrence of reentry. Harris and Moe2 stressed the importance of the anode in this respect, since in their experiments most fibrillation started at the anode.

SUMMARY

With an accurate method (employing electrode needles, an especially designed testing stimulator and a cathode-ray oscillograph), the changes in excitability of the dog’s left ventricle, occurring during the cardiac cycle, were studied with unipolar cathodal and anodal and with bipolar stimulation, by means of short square wave test shocks.

The experiments established two essential requirements for a reliable determination of the excitability cycle: the excitability must be determined locally, and the site of origin of the premature systoles must be known.

Cathodal threshold was found to follow a course which, for descriptive purposes, can be divided into an absolute and a relative refractory period, followed by a diastolic interval of a constant excitability. During the relative refractory period, the threshold declines along a smooth curve.

For anodal stimuli an absolute refractory period was also observed; its duration was generally a few milliseconds shorter than for cathodal stimuli. Immediately after the absolute refractory period, in most experiments, the anodal threshold dropped to a minimal value and increased afterwards until the next systole. In this rising part of the anodal strength/interval curve, oscillations were present, varying from experiment to experiment.

With bipolar stimulation the resulting strength/interval curves at every interval of the cardiac cycle followed the lowest threshold of both electrodes. The bipolar curve represented solely the cathodal threshold changes, when the refractory period ended first at the cathode. If the refractory period ended first at the anode, a complex bipolar strength/interval curve was obtained, consisting of a first, anodal
part and a second, cathodal part. Depending on the time-difference in activation at the two electrodes, the cathodal part of the curve began after the excitability at the anode had passed through its maximal value. In this case, a dip was present in the resulting bipolar strength/interval curve.

The dip phenomenon, as has been described by Orias and others, is attributable to their arrangement of driving and testing electrodes. It cannot be regarded as a fundamental characteristic of the recovery of excitability.

The occurrence of two simultaneous fronts of activation, which is supraliminal at both electrodes, is demonstrated. The possible meaning of this occurrence for the onset of ventricular fibrillation and for the genesis of the "vulnerable period" is discussed.

**SUMMARIO IN INTERLINGUA**

Per medio de un exacte methodo—empleante electrodos agulias, un stimulator experimentative de construction special, e un oscillographo a radios cathodic—le alterationes del excitabilitate que occurre in le ventriculo sinistre de canes durante le cyclo cardiac esseva studiate in stimulation unipolar cathodal e anodal e in stimulation bipolar, effectuate per medio de breve pulsos experimental a undas rectangular.

Le experimentos establiva duo requerimentos essential pro le solide determination del cyclo de excitabilitate: Le excitabilitate debe esser determinate localmente, e le sito de origine del systoles prematur debe esser cognoscite. Il esseva trovate que le limine cathodic seque un curso que nos pote divider, pro objectivos descriptivo, in un absolute e un relative periodo refractori, sequite per un intervallo a excitabilitate constante. Durante le relative periodo refractori le limine se abassa seundo un curva lisie.

Un absolute periodo refractori esseva etiam observate pro stimulos anodal. Su duration esseva generalmente alcun milliseccadas plus breve que in le caso de stimulos cathodal. In le majoritate del experimentos, le limine anodal se abassava a valores minimal immediatamente post le absolute periodo refractori; postea illo accresseva usque al proxime systole. In le parte ascendante del curva anodal de fortia/intervallo, oscillationes se manifestava que variava ab un experimento al altere.

In stimulation bipolar, le resultante curvas de fortia/intervallo sequeva, a omne punto del cyclo cardiac, le limine minimal de ambe electrodos. Le curva bipolar representava exclusivamente le alterationes de limine cathodal quando le periodo refractori se terminava primo al cathodo. Si le periodo refractori se terminava primo al anodo, il resultava un complexe curva bipolar de fortia/intervallo que consisteva de un prime parte anodal e un seconde parte cathodal. Determinate per le differentia temporal in le activation al duo electrodos, le parte cathodal del curva comenciava post que le excitabilitate al anodo habeva passate su valor maximal. In iste caso un depression appareva in le resultante curva bipolar de fortia/intervallo.

Le depression, un phenomeno describite per Orias e alteres, es attribuibile al arrangiamento del electrodos e non pote esser considerate como un caracteristica fundamental del restabilimento de excitabilitate.

Es demonstrate le occurrentia de duo simultanee frontes de activation supraliminal a ambe electrodos. Nos discute le possibile signification de iste occurrentia pro le declaration del fibrillation ventricular e del genese del "periodo vulnerabile."

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The Dawn of Plethysmography

"In 1846, Piégue enclosed a limb in a vessel of tepid water . . . connected to a narrow tube of liquid. . . . With each systole of the heart the water rose in the tube, with each diastole it descended. . . . Chelius (1850) proposed measurement of the volume of the blood wave penetrating an organ with each systole; he properly called it 'volumetric sphygmography'. He constructed two forms of apparatus . . . in which augmentation of volume of a hand or forearm displaced a certain volume of water; the rate of displacement . . . was recorded by a U manometer recorder. . . . Fick, unaware of Chelius' work, described similar apparatus in 1869. . . . Buisson (1862) had the idea of inscribing the movements of expansion and recoil of a limb by inserting a ventouse de Jounod (actually a glass bulb filled with water below and air above) and connecting the air chamber to a tambour with a writing lever. . . . The apparatus was again used by François Franch (1879) with great care. . . . Figure 100 shows a specimen record; the oscillations are in rhythm with the heart beat. . . . One can obtain a considerable swelling of the hand by compressing the veins of the forearm by means of a ligature (Fig. 101)."

(Editor's note: This is obviously a precursor of the method later quantitated by Brodie and Ruesell for study of kidney flow and adapted to venous occlusion plethysmography by Hewlett and van Zwalenburg in 1909.)

"In this experiment, the great variations of limb volume are not caused by changes in calibers of arteries alone, but include those of capillaries and veins. However, the variable cardiac wave necessarily applies solely to arteries and arterioles".

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