Ventricular Excitability and Refractoriness in the Hypothermic Dog

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ABSTRACT

ANGELAKOS, E. T., E. G. LAFORET AND A. H. HEGNAUER. Ventricular excitability and refractoriness in the hypothermic dog. Am. J. Physiol. 189(3): 591-595. 1957.—Measurements of ventricular excitability through the entire cardiac cycle of the dog under progressive hypothermia show that the ventricular refractory period (measured as absolute, total or functional refractory period) is greatly prolonged. This effect is not secondary to the changes in heart rate since normothermic animals with surgical A-V block having heart rates similar to those obtained under hypothermia do not show any great prolongation in the ventricular refractory period. At heart temperatures ranging from 38° to 23°C there is no significant alteration in the diastolic excitability of the ventricle. The rate of recovery of diastolic excitability and the response latency were greatly prolonged as reflected in the marked increase in the duration of the relative and functional refractory periods. It is suggested that the increased susceptibility of the hypothermic myocardium to ventricular fibrillation may be related to the observed changes in the rate of recovery of excitability.

THE FUNDAMENTAL ALTERATIONS leading to the marked tendency for the development of ventricular fibrillation (VF) under hypothermia are still obscure. A study of the excitability and refractoriness of the hypothermic myocardium may be expected to provide some insight into the mechanism of hypothermic VF.

Following the report by Hegnauer and Covino (1) in which previously reported results regarding cardiac excitability under hypothermia were found to be complicated by technical artefacts, a re-evaluation of the problem became necessary.

In the experiments reported here the excitability and refractory period of the dog heart was measured at various temperatures using valid methods which were free of technical artefacts. In addition an experimental study of the influence of heart rate on the parameters measured was made in normothermic and hypothermic animals.

MATERIALS AND METHODS

All experiments were made in dogs anesthetized with pentobarbital 30-35 mg/kg. Hypothermia was induced by immersion in iced water as previously described (2). Under artificial respiration left thoracotomy was performed at the level of the fourth intercostal space and a bipolar electrode was attached to the left ventricular epicardial surface overlying an area relatively free of major blood vessels. The electrode consisted of a plastic disc 2 cm in diameter containing two Ag-AgCl electrodes approximately 0.5 cm long and 2 mm wide with an interelectrode distance of 0.5 cm. The plastic disc was attached to the myocardium with 4-6 stitches of nylon suture. Subsequently the chest was closed, the pneumothorax was reduced, and the animals were allowed to respire spontaneously for 15-30 minutes before any measurements were made.

The stimulation apparatus consisted of two Grass square wave stimulators connected in parallel. One of the stimulators delivered the driving pulses and was synchronized with the second stimulator which delivered the testing pulses. An adjustable delay on the second stimulator determined the time interval between a driving and a testing pulse. Thus the strength and duration of the driving and testing pulses could be varied independently. A specially constructed switch was interposed in the synchronizing circuit between the driving and testing stimulators. When this switch was closed a single pulse from the synchronizer of the driving stimulator fired the testing stimulator; thereafter the circuit remained open until the switch was manually reset. Thus single testing stimuli could be delivered at will during any part of the cardiac cycle. Both driving and testing square wave pulses were of 1 msec. duration. Since Grass stimulators are so con-
structed that the cathode is at ground potential, the only ground connection to the dog was through the cathode via a 100-ohm resistor. The voltage drop across this resistor was determined with an oscilloscope and served as a measure of the current passing between the stimulating electrodes. The effective resistance of the circuit was of the order of 1000–2000 ohms in most experiments. The electrocardiogram was monitored on a DuMont oscilloscope with a long persistence (P7) screen and was also recorded on a Sanborn Visocardieter.

In the majority of the experiments reported here both driving and testing stimuli were applied to the ventricle through the same pair of electrodes. In a few experiments (see table 1) the ventricular diastolic threshold was determined while driving stimuli were delivered to the left atrium through a bipolar electrode attached to the auricle. In this case testing stimuli were delivered through a separate pair of electrodes attached to the left ventricle, and threshold current was measured in the ventricular circuit.

In all cases measurements were made while the heart was driven at a constant rate slightly faster than its spontaneous rate. Thus it was not necessary to crush or otherwise inactivate the S-A node.

Temperature measurements were made thermo-electrically through a catheter thermocouple placed into the right atrium via the right jugular vein.

Surgical interruption of the A-V bundle was performed following the method described by Starzl and Gaertner (3). Following right auriculotomy the bundle was cut at the level of the coronary sinus. A slow heart rate followed immediately after a successful cut. Subsequently the atrium was sutured and a bipolar electrode was attached to the left ventricle before the chest was closed. The pneumothora was reduced and the animals were allowed to respire spontaneously before measurements were made.

Definitions. Ventricular threshold. The current intensity necessary to produce a propagated ventricular response when delivered through a bipolar electrode attached directly on the left ventricular myocardium. It is measured in milliamperes (ma) of monophasic square wave pulses. These pulses are of 1-msec. duration.

Absolute refractory period (ARP). For purposes of uniformity the ARP is defined here as that period, starting at the beginning of the ventricular depolarization, during which the ventricular threshold is more than 10 times that which obtains in late diastole in the same cardiac cycle. In the majority of the experiments however this period corresponds with much higher ventricular thresholds usually greater than 15 ma. In general the choice of the 10X factor as an end point is not critical, since in this region of the cycle the strength interval curve is so steep that choosing a factor of 10X, 20X, or 40X, will make a difference of but a few milliseconds in the value of the ARP.

Total refractory period (TRP). The time interval between the beginning of the ventricular depolarization and the moment at which the threshold assumes a steady level later in the same cardiac cycle. Diastolic threshold. The ventricular threshold following the end of the TRP, when the threshold assumes a steady level which is maintained for the remainder of the cardiac cycle.

The ARP, TRP and diastolic threshold are obtained from measurements of the ventricular threshold at 5-10-msec. intervals through the entire cardiac cycle.

Functional refractory period (FRP). The measurement of this period is based on the well known finding that as testing stimuli are moved from diastole towards the ARP, the response follows the stimulus earlier in the cycle until a point is reached beyond which the response does not follow the stimulus when the latter is delivered at still earlier points of the cycle. The time interval between the response to the driving stimulus and the earliest obtainable response to a testing stimulus has been called: 'period of irresponsiveness,' 'period of prolonged latency' or 'functional refractory period' (4).

Relative refractory period (RRP). RRP = TRP - ARP. When FRP is used in place of TRP then RRP is defined as: RRP = FRP - ARP.

RESULTS

Strength-Interval Curves. Strength-interval curves were determined in each case before and at various temperatures during cooling. A total of 64 successful determinations of the entire curve were made before and during hypothermia. Examples are shown in figure 1. While only a few critical points are shown in the figure, threshold measurements were made every 5-10 msec. through the cardiac cycle.
VENTRICULAR EXCITABILITY IN HYPOTHERMIA

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TABLE 1. VENTRICULAR EXCITABILITY AND
REFRACTORINESS DURING PROGRESSIVE
HYPOTHERMIA*

<table>
<thead>
<tr>
<th>Heart Temperature ± 1°C</th>
<th>38°C</th>
<th>30°C</th>
<th>25°C</th>
<th>20°C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Auricular Driving</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of dogs</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Diastolic threshold, ma</td>
<td>0.5±0.1</td>
<td>0.5±0.2</td>
<td>0.5±0.1</td>
<td>0.6±0.2</td>
</tr>
<tr>
<td><strong>Ventricular Driving</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of dogs</td>
<td>30</td>
<td>26</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Diastolic threshold, ma</td>
<td>0.4±0.2</td>
<td>0.4±0.2</td>
<td>0.5±0.2</td>
<td>0.8±0.3</td>
</tr>
<tr>
<td>Heart cycle, msec</td>
<td>345±40</td>
<td>510±80</td>
<td>925±95</td>
<td>1800±160</td>
</tr>
<tr>
<td>ARP, msec</td>
<td>140±20</td>
<td>220±40</td>
<td>365±45</td>
<td>550±75</td>
</tr>
<tr>
<td>TRP, msec</td>
<td>165±20</td>
<td>205±50</td>
<td>490±85</td>
<td>920±140</td>
</tr>
<tr>
<td>FRP, msec</td>
<td>170±15</td>
<td>205±30</td>
<td>460±50</td>
<td>730±55</td>
</tr>
<tr>
<td>RRP = TRP - ARP</td>
<td>25</td>
<td>75</td>
<td>125</td>
<td>370</td>
</tr>
<tr>
<td>RRP = FRP - ARP</td>
<td>30</td>
<td>75</td>
<td>95</td>
<td>180</td>
</tr>
</tbody>
</table>

* Values of diastolic excitability are rounded to the nearest 0.1 ma. Values of refractory periods are rounded to the nearest 5 msec.

The most characteristic alteration in the shape of the curve during progressive hypothermia was manifested by a small and stepwise decrease in threshold before a steady minimum level was reached in the late part of the cardiac cycle. While these changes in threshold were very small (seemingly absent when plotted on the scale of fig. 1) they were nevertheless very consistent in individual experiments. Each (step) might last as long as 50-100 msec. In the type of strength-interval curve obtained under hypothermia the outer limits of the relative refractory period (RRP) are therefore indistinct, and it becomes difficult to measure with any degree of confidence the length of the total refractory period (TRP). By contrast measurements of the absolute refractory period (ARP) can be made with equal facility in either normothermic or hypothermic animals.

The strength-interval curves show the irregularities described by Orias et al. (5). Most often these irregularities were not manifested in the form of ‘dips’ but appeared as ‘breaks’ in the curve (fig. 1). It will be noted that there is little alteration in the relative position or magnitude of these irregularities with cold. It is noteworthy that a supernormal period such as described by Hoff and Nahum (6) was not detectable in either normothermic or hypothermic animals. This is in agreement with the main findings of Brooks et al. (4).

Diastolic Thresholds. The ventricular thresholds in the late part of the cardiac cycle were measured in a large number of dogs before cooling and at various hypothermic temperatures. The results are given in table 1. The majority of the measurements were made with driving and testing stimuli delivered to the same pair of ventricular electrodes. To eliminate the possibility that the driving stimuli may alter the excitability of the myocardium, measurements of diastolic threshold were made in six dogs in which the driving stimuli were delivered through a separate set of electrodes attached to the auricle as described under methods. The results of this latter group of experiments are incorporated in table 1.

In other experiments in which the diastolic threshold of the ventricle was determined alternatively during auricular or ventricular driving in the same dog, the same diastolic threshold was obtained regardless of the method of driving.

In general, the threshold values showed a tendency to increase at temperatures below 25°C. This is more evident in the data from individual experiments than in the average values because the critical temperature is not the same for all animals.

Refractory Periods. Changes in the ventricular refractory period and its subdivisions as measured in a large group of animals before and during hypothermia are given in table 1. It must be emphasized that due to the uncertainties in the determination of the TRP under hypothermia, the tabulated values should be taken as conservative estimates. In arriving at these values the outer limit of the TRP was taken at a point where the ventricular threshold was distinctly above its steady diastolic level. Thus the magnitude of the tabulated values of the TRP under hypothermia may be underestimated by as much as 20-50 msec.

It has been claimed that in normothermic animals the TRP and the FRP are numerically equal (4) as would be expected if the period of prolonged latency between stimuli...
and response coincided with the end of the TRP. Data from a large number of measurements in over 50 normothermic dogs in the present studies suggested that the values for TRP and FRP in individual dogs correspond closely but not absolutely. The data given in table 1 show that the discrepancy is exaggerated under hypothermia.

**Heart Rate and Refractoriness.** To eliminate the possibility that the changes in the refractory periods seen under hypothermia were secondary to the concurrent changes in heart rate, measurements were made in normothermic animals with heart rates comparable to those which obtain in hypothermia. In order to produce very slow heart rates in normothermic animals surgical A-V interruption was successfully produced in six animals as described under METHODS. Strength-interval curves were thus obtained for a wide range of spontaneous and induced heart rates in both normal and blocked dogs. Measurements of the FRP were made at the same time as those of ARP and TRP.

A comparison of the ARPs and FRPs at the same heart rates in: a) dogs with A-V block, b) selected normothermic animals with spontaneously slow heart rates, and c) hypothermic animals, is shown in fig. 2.

**DISCUSSION**

Experimental hypothermia, in addition to providing fundamental information needed for its successful application in surgery, can serve as an excellent experimental technique for the study of those factors which: a) establish a condition rendering the ventricle highly susceptible to fibrillation and b) eventually lead to spontaneous ventricular fibrillation (VF) at certain critical temperatures (2, 7).

Following the now classical demonstration by Wiggers and associates of a 'vulnerable period' to fibrillation during a certain portion of the excitability cycle of the heart (8), there have been several speculations regarding a possible relationship between susceptibility to VF and measurable changes in the excitability cycle.

The investigations reported here were intended as an inquiry into any alterations in the ventricular excitability cycle which may account for the well known susceptibility of the hypothermic myocardium to VF. It was found that the refractory period (RP) is greatly prolonged as the body temperature is lowered. This marked increase is evident whether the RP is measured as ARP, TRP or FRP. Furthermore the comparison between normothermic and hypothermic animals at the same heart rates (fig. 2) reveals that the observed prolongation of the RP under hypothermia is not secondary to the prevailing slow heart rates.

In general our results on the diastolic excitability and ARP of the hypothermic dog agree well with those given in a brief report by Brooks and associates (9, 4). Similar changes in the ventricular RP have been reported for the hypothermic rat (10) and for the isolated perfused and cooled rabbit heart (11).

It is apparent that the increased susceptibility of the hypothermic heart to VF cannot be attributed to any changes in either diastolic excitability or RP. The former remains essentially unaltered at first and then shows a tendency to decrease while the latter increases throughout the period of cooling. In all current hypotheses regarding the development of VF, an increase in the RP and/or a decrease in the diastolic excitability would be expected to protect rather than predispose the ventricle to fibrillation. Similarly there are no apparent changes in the irregularities 'dips' of the excitability recovery curve, nor is there a distinct period of hyperexcitability. Such irregularities then cannot be implicated in the development of hypothermic VF (1).

These considerations emphasize the limi-
tations of the conventional measurements of excitability and refractoriness in demonstrating alterations in the cardiac susceptibility to VF. Nevertheless the rate of recovery of excitability is qualitatively and quantitatively altered during hypothermia, as is clearly manifested in measurements of the RRP and analysis of the recovery curves. It is of particular interest to note that under hypothermia 'responsiveness' (measured by the length of the FRP) recovers earlier in the cycle than excitability (measured by the length of the TRP). Since the end of the FRP has been taken to reflect the completion of repolarization, it appears that under hypothermia recovery of repolarization occurs faster than recovery of excitability. A similar conclusion was reached by Schütz (12).

The relationship between these subtle quantitative and qualitative changes in the recovery of excitability and responsiveness to the susceptibility of the ventricle to fibrillation is currently under investigation.

REFERENCES