Ventricular Conduction and Refractoriness During Hypothermia

By Joseph C. Torres, Ph.D.

With the technical assistance of Rachelle Warschaw and Patricia Chase

The effects of hypothermia on the electrophysiological properties of the heart have received considerable attention, but precise information regarding ventricular conduction during hypothermia is still lacking. Existing evidence has been derived largely from measurements of QRS duration and, because the exact limits of the QRS interval are difficult to define below 25°C, various estimates have ranged from an approximately twofold to a greater than fourfold increase of conduction time at 20°C. Measurements of ventricular conduction by more direct methods are relatively scarce and their interpretation is made difficult by basic differences in the experimental conditions employed. Furthermore, a question still to be answered is whether ventricular conduction measured in situ varies with electrode placement as previously reported for isolated epicardial strips.

The present studies were designed (1) to provide direct evidence of the effect of hypothermia on ventricular conduction and (2) to compare changes of ventricular conduction with those of refractoriness at similar temperatures.

Methods

Apparently healthy mongrel dogs, 19 in number and ranging in weight from 9 to 15.5 kg, were anesthetized with pentobarbital (33 mg/kg) administered intraperitoneally. Any additional anesthetic required during the induction of hypothermia was administered intravenously via an indwelling cannula. Left thoracotomy was done under artificial respiration and a multipolar electrode was sutured to the left ventricular surface near the apex. Subsequently the thorax was closed in two layers and spontaneous respiration allowed to resume before control measurements were made.

A modified version of the “compass electrode” of Schaefer and Haas was designed with nine recording terminals intersecting at 90 degrees and two other terminals utilized for bipolar stimulation. The terminals were 1 mm in diameter and 1 mm distant from each other. The electrode was attached with terminals S1 and S2 closest to the apex and aligned in parallel with the long axis of the ventricles so that the two rows of recording terminals maintained the same general orientation relative to the ventricular surface in all experiments.

The two bipolar potentials thus derived were amplified with Tektronix 53/54 E preamplifiers and displayed on a Tektronix 564 storage oscilloscope equipped with a type 3B3 time-base generator. Estimates of conduction time were derived from five separate determinations of the interval between the respective peaks of the stored complexes, at calibrated sweep rates of 10 to 2 msec/cm. After these measurements were made directly on the oscilloscope screen, a Polaroid camera was used to provide a permanent record of the stored tracing for further study.

Measurements of conduction time at each temperature were made only while driving the ventricle with an American Electronic Laboratory stimulator via an isolation unit at a frequency slightly faster than the existing spontaneous rate. In order to minimize the possible influence of threshold increases at low temperatures, the driving current was maintained at an arbitrary suprathreshold level of 2 ma, throughout each experiment.

Before and after these determinations of epicardial conduction time the heart was allowed to beat spontaneously except when the occasional presence of A-V block and/or S-A nodal arrest.
Diagram illustrating electrode design, its orientation on the ventricular surface and salient features of the recording system. Recording terminals employed in the present study (solid circles) form two perpendicular axes, R_5 to R_1 and R_3 to R_7, for directional comparisons of conduction velocity. Two additional terminals, S_1 and S_2, utilized for bipolar stimulation are also designated (x). For additional details, see text.

at low temperatures necessitated continuous driving.

In a separate series of animals the lengths of both the absolute and relatively refractory periods of ventricular excitability were determined over a temperature range of 37°C to 22 ± 1°C. In these experiments, as previously described,^1^ driving and testing cathodal pulses of 1 msec duration were delivered to a ventricular electrode from two stimulators connected in parallel.

In all experiments the dogs were wrapped in two cooling blankets and body temperature reduced gradually (1°C/15 min) with a “Thermorite” hypothermia unit. Esophageal temperature was measured with a Yellow Springs “Telethermometer” using a no. 401 thermistor probe positioned at heart level. Simultaneous measurements of ventricular surface temperature (no. 409 thermistor disc) served to verify that the esophageal temperature measured was truly representative of the epicardial electrode site. These comparisons were made over a temperature range of 37°C to 19°C under both open chest (normothermia) and closed chest (hypothermia) conditions.

**Results**

**Ventricular Conduction**

In a series of experiments involving a total of 19 dogs, one of the two sets of recording terminals, i.e., R_5 to R_1, or R_3 to R_7 (fig. 1), was selected to evaluate ventricular conduction at different temperatures. The selection was based on the premise that the particular lead axis which provided the smoother and larger potentials at 37°C was more closely aligned with the prevailing path of excitation.14

Figure 2 shows such bipolar potentials and illustrates the typical changes that occur with progressive reduction of temperature. In the experiment shown in figure 2, the epicardial conduction interval increased from 4.0 msec at 37°C to 7.0 msec at 21°C, representing a less than twofold increase. Mean data from 13 experiments (table 1) demonstrated that cooling to 22°C increased the conduction interval by an average of 95% of the control value. Seven of these 13 dogs survived cooling to 20°C and in this group the conduction interval increased by 148% at the latter temperature (table 1). The average conduction velocity at 37°C was 0.55 m/sec, with individual values ranging from 0.27 m/sec in one experiment to 0.80 m/sec in two instances.
In response to hypothermia the average conduction velocity for the entire series diminished to 0.29 m/sec at 22°C and (for the smaller group) to 0.19 m/sec at 20°C (fig. 3). The results suggested a generally exponential relationship between conduction velocity and the decrease of temperature. Values below 30°C, however, decreased almost linearly (fig. 3) and indicated a Q10 of 1.6 for the 13 experiments and 1.8 for the 7 experiments.

The preliminary comparisons made at 37°C failed to reveal a significant difference in the rate of conduction as derived from the two sets of electrode terminals, R3 to R1 vs. R5 to R6. Mean values (± standard deviation) for conduction time were 5.1 ± 2.5 msec and 5.6 ± 3.1 msec respectively for the two sets of leads; the difference was not statistically significant.

**TABLE 1**

<table>
<thead>
<tr>
<th>Temp °C</th>
<th>Number of dogs</th>
<th>Conduction Duration (msec)</th>
<th>Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>13 (7)</td>
<td>4.1 ± 1.6* (4.8 ± 1.8)†</td>
<td>— % —</td>
</tr>
<tr>
<td>30</td>
<td>13 (7)</td>
<td>4.0 ± 2.3 (5.7 ± 2.8)</td>
<td>19 (19)</td>
</tr>
<tr>
<td>27</td>
<td>13 (7)</td>
<td>5.7 ± 2.6 (6.6 ± 3.2)</td>
<td>39 (38)</td>
</tr>
<tr>
<td>25</td>
<td>13 (7)</td>
<td>6.6 ± 2.9 (7.3 ± 3.4)</td>
<td>61 (52)</td>
</tr>
<tr>
<td>23</td>
<td>13 (7)</td>
<td>7.2 ± 3.2 (8.2 ± 3.7)</td>
<td>76 (71)</td>
</tr>
<tr>
<td>22</td>
<td>13 (7)</td>
<td>8.0 ± 3.4 (9.3 ± 4.2)</td>
<td>95 (94)</td>
</tr>
<tr>
<td>21</td>
<td>13 (7)</td>
<td>10.0 ± 3.8 (10.8 ± 3.9)</td>
<td>108 (108)</td>
</tr>
<tr>
<td>20</td>
<td>13 (7)</td>
<td>11.9 ± 3.9 (11.9 ± 3.9)</td>
<td>148 (148)</td>
</tr>
</tbody>
</table>

*Mean ± sd.
†Values in parentheses are from the seven animals in the series that survived to 20°C.
significant. In each experiment slightly different rates of conduction were measured along the two lead axes but within the entire group, the direction of relatively faster conduction varied inconsistently between the two. Since magnitude of conduction slowing in response to hypothermia might depend on the electrode axis used, placement of electrodes was duplicated as precisely as possible in six of the animals, and determinations of conduction time were obtained from both sets of leads at corresponding temperatures.

As illustrated in figure 4, the average conduction velocity determined for each of the two electrode axes and expressed as per cent of control (at 37°C) diminished in parallel to almost identical levels of 42 and 40% respectively at 20°C. This similarity in changes of conduction velocity, when obtained by two sets of leads, characterized the results from individual experiments as well as from the entire group. Furthermore, in each individual experiment the particular electrode axis which provided the relatively faster conduction at 37°C continued to do so at all temperatures.

**VENTRICULAR REFRACTORINESS**

A comparative evaluation of changes in the respective durations of left ventricular absolute and relatively refractory periods (table 2) during hypothermia, indicated an approximately equal increase in both phases amounting to more than 200% at 22°C. This prolongation of ventricular refractoriness to more than three times control values was considerably greater than the increases noted in ventricular conduction interval at temperatures of 22°C and even 20°C (table 1).

**TABLE 2**

Changes in Ventricular Refractoriness During Hypothermia

<table>
<thead>
<tr>
<th>Temp°C</th>
<th>Cycle duration</th>
<th>Refractory period</th>
<th>Absolute</th>
<th>Increase</th>
<th>Relative</th>
<th>Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>msec</td>
<td>Total</td>
<td>Duration</td>
<td>,%</td>
<td>Duration</td>
<td>%</td>
</tr>
<tr>
<td>37</td>
<td>324 ± 50</td>
<td>172 ± 24</td>
<td>140 ± 20</td>
<td>—</td>
<td>32</td>
<td>—</td>
</tr>
<tr>
<td>30</td>
<td>398 ± 39</td>
<td>244 ± 41</td>
<td>207 ± 31</td>
<td>48</td>
<td>37</td>
<td>16</td>
</tr>
<tr>
<td>25</td>
<td>648 ± 143</td>
<td>398 ± 56</td>
<td>331 ± 48</td>
<td>89</td>
<td>67</td>
<td>108</td>
</tr>
<tr>
<td>22</td>
<td>960 ± 152</td>
<td>532 ± 56</td>
<td>430 ± 40</td>
<td>207</td>
<td>102</td>
<td>218</td>
</tr>
</tbody>
</table>

*Mean ± SD for five dogs.
Discussion

It has been pointed out that two major problems complicate the validity of conduction velocity measurement in ventricular muscle, a) the syncytial orientation of the myocardial fibers which makes the exact path of excitation uncertain, \(10, 14-16\) and b) the separation of myocardial conduction from that of the specialized Purkinje system. \(10, 12, 17\) In the present study, considerable justification existed for assuming that these difficulties, if not actually eliminated, were at least adequately minimized. Schaefer and Haas \(14\) emphasized that the complicated arrangement of the myocardial fibers limits the distance of uniform propagation to a few mm, and that reliable estimates of myocardial conduction require, therefore, at least three different but closely placed recording terminals, a procedure followed in the present study. According to Moe and Mendez \(17\) when the distance from stimulating to recording terminals does not exceed one cm, the conduction time measured results principally from spread along muscle fibers rather than along the underlying Purkinje system. The results reported here, were obtained only during ventricular pacing, with stimulating and recording sites separated by a distance considerably less than the maximum indicated above. Furthermore, the rate of conduction in dog Purkinje fibers has been established to be between 2.0 and 2.5 m/sec, \(15\) values which were never approached in the present experiments in which a mean conduction velocity of 0.55 m/sec with a range of 0.27 to 0.8 m/sec was observed. These values are consistent with previous estimates of myocardial conduction \(9, 10, 12, 13\) in which a similar variability was also observed.

With decreasing temperature, the average conduction velocity diminished to 0.29 m/sec at 22°C (13 dogs) and 0.19 m/sec at 20°C (7 dogs). The minor decrease which marked the transition from 37 to 30°C and the roughly linear changes in conduction velocity with lower temperatures have been reported previously for various other preparations and types of cardiac muscle. \(15, 16\) Both the roughly linear conduction velocity relationship at lower temperatures and the leveling off above 35°C have been ascribed to the effect of temperature on the rate of membrane depolarization. \(15\) Temperature coefficients of 1.8 and 1.6 derived from the present data likewise are in accord with \(Q_{10}\) values cited by others (1.5 to 2.0). \(10\)

Sano et al., \(12\) employing micro-electrodes inserted 5 mm apart in epicardial strips, reported marked differences in conduction velocity when the recording axis was varied relative to the longitudinal axis of the fiber, the conduction velocity parallel to fiber orientation being two to ten times greater than that perpendicular to the fibers. In the present study, although different rates of conduction were also observed along the two sets of leads aligned at right angles, the differences were insignificant and for the entire group the comparatively faster conduction occurred with equal frequency in both lead axes. Regardless of the relationship between the rate of conduction and direction of recording during normothermia of an individual animal, cooling produced similar amounts of slowing along both recording axes. These findings differ from those of Sano et al. \(12\) and may be attributed presumably to basic differences in experimental conditions and procedures. In the intact ventricle it was possible to duplicate electrode placement only approximately in different dogs. Hence, the orientation of the respective lead axes relative to fiber axis remained not only uncertain but also variable. However, these results do indicate that under the conditions of the present study, the relative depression of epicardial conduction by hypothermia was independent of the lead axis selected for recording.

In terms of the conduction interval, hypothermia produced an average increase of 98% at 22°C and 148% at 20°C, as compared to the increase in excess of 400% reported by Covino and D'Amato \(8\) at 20°C. The discrepancy may be explained by differences of procedure because in the latter study, conduction time was taken as the interval between stimulus artifact and extrasystolic activity recorded at a unipolar electrode, 6 mm distant from the site.
of stimulation. The reliability of such measurements (which include the latency between stimulus and excitation) to indicate conduction velocity appears doubtful, particularly since the latent period is affected by the strength of stimulus. Furthermore, several investigators have been unable to relate the instant of arrival of excitation beneath an electrode to the peak of the corresponding unipolar electrogram.

In contrast to the observed increase of conduction time (98%) the durations of both the absolute and relatively refractory periods were prolonged by more than 200% during cooling to 22°C. Similar increases of ventricular refractoriness have been reported also by Angelakos et al. and by Covino and D’Amato. The former, moreover, by means of surgically produced heart block were able to compare normothermic and hypothermic animals at similar heart rates and thus eliminated the possibility that refractory period changes observed during hypothermia were secondary to the concurrent bradycardia. The comparatively greater increases of refractoriness at corresponding temperatures do not support the view that the occurrence of hypothermic ventricular fibrillation can be explained adequately by a greater slowing of conduction relative to prolongation of the refractory period.

The suggestion that hypothermia produces localized areas of conduction block remains an important possibility still to be explored. In this connection, Han and Moe have reported recently that hypothermia increases the nonuniformity of recovery following excitation, thus leading to a fractionation of propagated activity together with opportunity for re-entry and fibrillation.

Summary

The effect of hypothermia on ventricular conduction was determined with a multi-terminal electrode sutured to the epicardial surface. Measurements of conduction intervals revealed average increases of 95% at 22°C in 13 dogs and 148% at 20°C in seven dogs that survived to this temperature. The mean conduction velocity estimated at 0.55 m/sec at 37°C diminished to 0.29 m/sec and 0.19 m/sec respectively at 22° and 20°C. An apparent overall exponential relationship between conduction velocity and temperature was observed, although below 30°C the rate of conduction decreased almost linearly with a Q10 of 1.6 to 1.8.

Individual measurements along both rows of intersecting electrode terminals revealed slightly different rates of conduction. However, within the entire group the direction of relatively faster conduction was inconsistent and, furthermore, the changes of conduction velocity with hypothermia were practically identical for the two recording alignments in all instances.

During cooling to 22°C the absolute and the relative phases of ventricular refractoriness both increased by more than 200% of the control values observed at 37°C. This three-fold effect on recovery of excitability was in contrast to the twofold slowing of conduction at the same temperature.

It is concluded that the occurrence of ventricular fibrillation during hypothermia cannot be explained adequately by assuming a greater slowing of conduction relative to prolongation of refractoriness.

References

HYPOTHERMIA AND VENTRICULAR CONDUCTION

Ventricular Conduction and Refractoriness During Hypothermia
Joseph C. Torres, Rachelle Warschaw and Patricia Chase

Circ Res. 1966;18:323-329
doi: 10.1161/01.RES.18.3.323

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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/18/3/323

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/