Mechanism of Ventricular Fibrillation in Hypothermia

By Benjamin G. Covino, Ph.D., and Henry E. D'Amato, Ph.D.

Two general theories of cardiac fibrillation currently prevail: the circus movement theory of Garrey\textsuperscript{1} and Lewis,\textsuperscript{2} and the ectopic focus theory of Sherf\textsuperscript{3} and Prinzmetal.\textsuperscript{4} Surprisingly, little systematic work has been done to establish whether either of these theories applies to the cardiac fibrillation that occurs spontaneously when mammals are cooled.

The circus movement theory postulates repetitive re-excitation of cardiac tissue by a cardiac impulse re-entering an original area of excitation. As stated by Lewis,\textsuperscript{2} three factors are important to the development of circus movement fibrillation: (1) the length of the conduction pathway, (2) the conduction velocity, and (3) the duration of the refractory period. A relatively long conduction pathway, a slow conduction velocity, and a short refractory period would favor fibrillation. Any one or a combination of these events would allow re-entry of the cardiac impulse into the original area of excitation after it is no longer refractory. Myocardial threshold need not be altered.

By contrast, the ectopic focus theory postulates repetitive excitation arising spontaneously in hyperirritable foci. Thus, either a general or local decrease in myocardial threshold should be present prior to the onset of this type of fibrillation. Length of conduction path, conduction velocity, and duration of refractoriness would not affect ectopic focus fibrillation in a predictable way. Previous studies\textsuperscript{5} have indicated that during progressive hypothermia there is either no change or an increase in ventricular diastolic threshold, which would argue against the ectopic focus mechanism as the source of fibrillation.

The present study examines the relationship between the incidence of fibrillation in cooled animals and the parameters that favor circus movement fibrillation. The data afford direct evidence that the circus movement theory can account for this type of fibrillation.

Methods

GENERAL

Dogs, cats, rabbits, and rats were used during the course of this study. All animals except rats were anesthetized with pentobarbital sodium (30 mg/Kg., I.V. or I.P.). Electrocardiograms (standard limb lead II) were taken prior to and periodically during hypothermia and monitored continuously on an oscilloscope. Arterial blood pressure was recorded in dogs and cats by means of a mercury manometer. Rectal temperature was measured with a thermometer. Heart temperature was measured at the end of each experiment by a mercury thermometer placed in the left ventricle. All dogs, cats, and rabbits were ventilated artificially when rectal temperature reached 30°C. Body temperature was lowered by immersion in an ice water bath until either ventricular fibrillation occurred or no electrocardiographic activity was seen for a period of 10 consecutive minutes (asystole).

INTACT HEART

Conduction velocity, refractory period, and ventricular threshold were measured in closed-chest intact dogs using Ag-AgCl electrodes placed directly on the myocardium. One indifferent and two stimulating electrodes were attached to the base of the right ventricle for the measurement of ventricular threshold and refractory period as previously described.\textsuperscript{5} Duration of the test stimuli was 3 usec, and maximal current strength was 30 ma. Conduction time in ventricular muscle (MCT) was taken as the time interval between the stimulus artifact and action potential of an induced extrasystole recorded from a unipolar needle electrode inserted in the muscle at a distance of 6 mm. from the stimulating electrodes. The duration of the QRS on the electrocardiogram was used as a measure of the time required for conduction through the entire ventricle, which includes both Purkinje tissue and muscle. All
FIBRILLATION IN HYPOThERMIA

Conduction measurements were expressed in time units rather than velocity units so that the comparative changes in conduction and refractoriness (also a time measurement) could be evaluated more simply. Measurements were made at rectal temperatures of 37, 30, 25, and 20 C.

ISOLATED PAPILLARY MUSCLE

Ten experiments were performed on the isolated papillary muscle of cats anesthetized with pentobarbital sodium (30 mg./Kg., I. P.). The muscles, 7 to 8 mm. long and 1 mm. in diameter, were attached to a specially designed muscle holder and placed in Krebs-Henseleit solution aerated with 95 per cent O₂ and 5 per cent CO₂. The muscle holder contained two stimulating needle electrodes, two loop recording electrodes, and one indifferent electrode. Action potentials were recorded from the surface electrodes on a dual-channel oscilloscope and photographs were taken with a Polaroid camera. The time interval between the action potential recorded from the two surface electrodes, spaced 5 mm. apart, served as a measure of conduction time in papillary muscle. Refractory period and threshold were measured in the same fashion as in the intact dog except that the duration of test stimuli was 1 msec, and maximum current strength was 10 ma. Measurements were made at bath temperatures of 37, 30, 25, 20, and 15 C.

DRUG REGIME

In those experiments in which sympathomimetic amines were used, the following dose regimen was employed: epinephrine, continuous intravenous drip of 0.5 μg./Kg./min.; norepinephrine, continuous intravenous drip of 1.0 μg./Kg./min.; mephentermine, 3 mg./Kg. (single injection); methoxamine, continuous intravenous drip of 50 μg./Kg./min.; metaraminol, 0.25 mg./Kg. (single injection); and isoprenaline, continuous intravenous drip of 0.25 mg./Kg./min. Administration of these agents was started at 30 to 27 C., except in the mephentermine- and norpinephrine-treated dogs in which conduction velocity and refractory period were measured. In these two groups the drugs were administered at 25 C.

Results

COMPARATIVE CHANGES IN CONDUCTION VELOCITY AND REFRACTORINESS

Intact Heart

QRS duration, myocardial conduction time (MCT), and absolute refractory period (ARP) were measured in 15 intact dogs prior to and during progressive hypothermia. As the rectal temperature was reduced from 37 to 25 C., all three parameters were prolonged to the same extent. When, however, the rectal

temperature fell to 20 C., the prolongation of the QRS duration and MCT was significantly greater than the prolongation of the ARP (P < 0.01) (table 1). As indicated in table 1, the average values for QRS duration and MCT at a rectal temperature of 20 C. were 195 and 130 msec., respectively, a greater than 400 per cent increase above the values obtained at 37 C. The average refractory period duration at 20 C. was 460 msec., a 228 per cent increase above the normothermic level.

When measurements of QRS, MCT, and ARP were completed at a rectal temperature of 20 C., the threshold for ventricular fibrillation was measured. Seven dogs fibrillated spontaneously before the fibrillary threshold could be measured. In six dogs a single stimulus of 0.4 to 2.0 ma. produced fibrillation (table 2). All six of these dogs had a QRS/ARP or MCT/ARP ratio of greater than one, which indicated that the QRS and MCT were prolonged to a greater degree than the ARP. Two dogs required stimuli of 6.8 and 8.0 ma. for the initiation of ventricular fibrillation.
and the conduction time/refractory period ratios in both cases were less than one.

**Isolated Papillary Muscle**

Papillary muscles were studied to obtain a more precise measurement of linear conduction velocity in cardiac muscle free of Purkinje fibers. All preparations were driven at a rate of 30 beats per minute at each temperature. As in the intact canine heart, conduction time and refractory period were prolonged in a linear fashion as bath temperature was lowered to 25°C. At temperatures of 20 and 15°C, the prolongation of conduction time again was significantly greater than that of refractory period (*P < 0.01*) (table 3). For example, the average conduction time at 15°C was 90.9 msec., an increase of 830 per cent from the control value of 9.7 msec. at 37°C. The average refractory period, on the other hand, was prolonged from 205 msec. at 37°C to 913 msec. at 15°C, an increase of 345 per cent (table 3).

**SHORTENING OF CONDUCTION PATHWAY**

If circus movement is responsible for ventricular fibrillation in hypothermia, then reduction of the length of the conduction

---

**TABLE 1**

Average QRS Duration, Conduction Time (MCT), and Absolute Refractory Period (ARP) of Intact Dog Heart during Progressive Hypothermia

<table>
<thead>
<tr>
<th>Rectal temperature (°C)</th>
<th>QRS duration (msec.)</th>
<th>Per cent change</th>
<th>MCT* (msec.)</th>
<th>Per cent change</th>
<th>ARP (msec.)</th>
<th>Per cent change</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>47</td>
<td>...</td>
<td>24</td>
<td>...</td>
<td>140</td>
<td>...</td>
</tr>
<tr>
<td>30</td>
<td>83</td>
<td>124</td>
<td>51</td>
<td>112</td>
<td>280</td>
<td>100</td>
</tr>
<tr>
<td>25</td>
<td>115</td>
<td>210</td>
<td>110</td>
<td>360</td>
<td>388</td>
<td>177</td>
</tr>
<tr>
<td>20</td>
<td>195</td>
<td>428</td>
<td>130</td>
<td>442</td>
<td>460</td>
<td>228</td>
</tr>
</tbody>
</table>

*MCT represents conduction time between two electrodes spaced 6 mm. apart.

**TABLE 2**

Per Cent Change in QRS Duration, Conduction Time (MCT), and Absolute Refractory Period (ARP), and Ventricular Fibrillary (VF) Threshold at 20°C.

<table>
<thead>
<tr>
<th>Dog number</th>
<th>QRS (msec.)</th>
<th>MCT (msec.)</th>
<th>ARP (msec.)</th>
<th>QRS/ARP</th>
<th>MCT/ARP</th>
<th>VF threshold (ma.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>133</td>
<td>67</td>
<td>56</td>
<td>2.38</td>
<td>1.20</td>
<td>1.2</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>100</td>
<td>67</td>
<td>1.49</td>
<td>1.49</td>
<td>1.2</td>
</tr>
<tr>
<td>3</td>
<td>250</td>
<td>200</td>
<td>111</td>
<td>2.26</td>
<td>1.50</td>
<td>0.4</td>
</tr>
<tr>
<td>4</td>
<td>740</td>
<td>435</td>
<td>384</td>
<td>1.93</td>
<td>1.13</td>
<td>0.9</td>
</tr>
<tr>
<td>5</td>
<td>500</td>
<td>220</td>
<td>1.98</td>
<td>4.63</td>
<td>2.04</td>
<td>1.2</td>
</tr>
<tr>
<td>6</td>
<td>466</td>
<td>200</td>
<td>143</td>
<td>3.25</td>
<td>1.40</td>
<td>0.9</td>
</tr>
<tr>
<td>7</td>
<td>100</td>
<td>110</td>
<td>118</td>
<td>0.85</td>
<td>0.93</td>
<td>3.3</td>
</tr>
<tr>
<td>8</td>
<td>167</td>
<td>84</td>
<td>200</td>
<td>0.84</td>
<td>0.42</td>
<td>7.0</td>
</tr>
</tbody>
</table>

**TABLE 3**

Average Conduction Velocity (CV), Conduction Time (MCT), and Absolute Refractory Period (ARP) of Cat Papillary Muscle at Various Temperatures

<table>
<thead>
<tr>
<th>Muscle temperature (°C)</th>
<th>CV (mm./sec.)</th>
<th>MCT* (msec.)</th>
<th>Per cent change</th>
<th>ARP (msec.)</th>
<th>Per cent change</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>514</td>
<td>9.7</td>
<td>...</td>
<td>205</td>
<td>...</td>
</tr>
<tr>
<td>30</td>
<td>300</td>
<td>16.6</td>
<td>...</td>
<td>379</td>
<td>...</td>
</tr>
<tr>
<td>25</td>
<td>247</td>
<td>26.2</td>
<td>105</td>
<td>520</td>
<td>153</td>
</tr>
<tr>
<td>20</td>
<td>89</td>
<td>56.2</td>
<td>481</td>
<td>800</td>
<td>292</td>
</tr>
<tr>
<td>15</td>
<td>55</td>
<td>90.9</td>
<td>830</td>
<td>913</td>
<td>345</td>
</tr>
</tbody>
</table>

*MCT represents conduction time between two electrodes spaced 5 mm. apart.
FIBRILLATION IN HYPOTHERMIA

Incidences of Ventricular Fibrillation (VF) in Various Mammals Rendered Hypothermic

<table>
<thead>
<tr>
<th>Species</th>
<th>Number of animals</th>
<th>Number term. in VF</th>
<th>Other arrhythmias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats</td>
<td>15</td>
<td>0</td>
<td>single extrasystoles</td>
</tr>
<tr>
<td>Rabbits</td>
<td>20</td>
<td>0</td>
<td>single extrasystoles</td>
</tr>
<tr>
<td>Cats</td>
<td>10</td>
<td>1</td>
<td>spontaneously reversible VF</td>
</tr>
<tr>
<td>Dogs</td>
<td>41</td>
<td>30</td>
<td>single and multiple extrasystoles</td>
</tr>
</tbody>
</table>

pathway should abolish or prevent the development of cardiac fibrillation.

Anatomical Shortening

Twelve fibrillating hearts were removed from the thorax of hypothermic dogs and placed in a beaker of oxygenated 0.9 per cent NaCl solution at room temperature. The fibrillating ventricles were bisected, and six of them stopped fibrillating within 15 seconds. In the remaining hearts, the apex became quiescent although the base continued to fibrillate. A second incision through the base stopped all fibrillation. In one instance, both halves of the ventricle resumed rhythmic organized contractions. In all other cases, mechanical stimulation of any portion of the dissected ventricular muscle produced an organized contraction with no further sign of fibrillation.

Physiological Shortening

In order to shorten the conduction pathway without cutting the heart, mammals of various sizes were cooled, and the incidence of ventricular fibrillation was determined. No fibrillation occurred in 15 rats and 20 rabbits, although extrasystoles were observed at low body temperatures. Four of five cats exhibited a spontaneously reversible type of ventricular fibrillation, i.e., the heart commenced fibrillating, judged by electrocardiographic irregularity and reduction of blood pressure to zero, then suddenly resumed normal rhythmic activity with a concomitant elevation in blood pressure. This pattern was repeated several times, but eventually all cats showed gradual bradycardia and, ultimately, asystole. Five isolated cat hearts perfused via the aorta were studied also. One heart commenced fibrillating at 14°C, and no reversal to a normal rhythm occurred. Three hearts showed brief bouts of spontaneously reversible fibrillation and ultimately became asystolic at 15 to 10°C. The fifth heart failed to develop ventricular fibrillation. Finally, during the course of this study, 41 dogs were cooled to low body temperatures. Thirty of these animals developed ventricular fibrillation, while the remaining 11 dogs went into asystole. The incidence of ventricular fibrillation during hypothermia in these various species of mammals is summarized in table 4.

Pharmacological Shortening

Although it is not actually possible to reduce the length of the conduction pathway...
by the use of drugs, the conduction velocity can be increased pharmacologically. Such an increase in conduction velocity would be comparable to shortening of the conduction pathway. The sympathomimetic amines are capable of increasing conduction velocity in normothermia, and a number of these drugs were tested as possible antifibrillatory agents in hypothermia. Norepinephrine, mephentermine, and methoxamine significantly reduced the incidence of ventricular fibrillation in hypothermic dogs (table 5). Epinephrine, isoproterenol, and metaraminol possessed no antifibrillary activity in the doses used. Below a rectal temperature of 25 C, a correlation existed between the duration of the QRS and the incidence of fibrillation in the control and drug-treated dogs. The QRS duration was shortest in those groups which had the lowest incidence of ventricular fibrillation (fig. 1).

This relationship between the QRS duration and frequency of fibrillation suggested that the antifibrillary activity of norepinephrine, mephentermine, and methoxamine was related to an increase in conduction velocity. To obtain more definitive evidence on this point, myocardial conduction time, refractory period, and QRS duration were measured in 10 dogs in which either norepinephrine or mephentermine was administered when rectal temperature fell to 25 C. An immediate reduction in conduction time (increase in conduction velocity) was produced by both agents with little or no change in refractory period (fig. 2). The prolongation of QRS duration which occurs during hypothermia also was reversed by the administration of these drugs (figs. 2 and 3).

Ventricular fibrillary threshold was also measured in eight drug-treated dogs. The threshold was greater than 6.8 ma. in 80 per cent of these animals. These dogs showed little change or an actual decrease in the conduction velocity/refractory period ratio (table 6). Two dogs with fibrillary thresholds
TABLE 5
Effect of Sympathomimetic Amines on Incidence of Ventricular Fibrillation in Hypothermic Dogs

<table>
<thead>
<tr>
<th></th>
<th>Fibrillation Asystole</th>
<th>Term. rectal temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>30</td>
<td>17.7 ± 3.9</td>
</tr>
<tr>
<td>Saline</td>
<td>18</td>
<td>17.8 ± 3.4</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>10</td>
<td>13.5 ± 5.0*</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>8</td>
<td>12.8 ± 4.1*</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>10</td>
<td>18.9 ± 5.4</td>
</tr>
<tr>
<td>Mephenetermine</td>
<td>7</td>
<td>13.8 ± 3.7*</td>
</tr>
<tr>
<td>Methoxamine</td>
<td>8</td>
<td>14.4 ± 3.2*</td>
</tr>
<tr>
<td>Metaraminol</td>
<td>8</td>
<td>15.3 ± 3.7</td>
</tr>
</tbody>
</table>

*Significant difference from controls at 0.01 level (Student’s t-test).
†Significant difference from controls at 0.05 level (chi-square).

of 2 and 5 ma. showed a prior increase in the QRS/ARP ratio. With the exception of dog M-5, the QRS/ARP and MCT/ARP ratios always changed in the same direction both in the control and drug-treated dogs.

The conduction velocity/refractory period ratio was plotted against the ventricular fibrillary threshold for the 18 control and drug-treated dogs in which these measurements were made. An exponential relationship exists, yielding a linear relationship between the QRS/ARP and the logarithm of the fibrillary threshold (fig. 4).

Discussion
As indicated by Lewis2 in 1920, three factors must be considered in any theory of circus movement, namely, the length of the conduction pathway (P), the conduction velocity (V), and the duration of the refractory period (R). The relationship between these three entities can be expressed simply in the following fashion:

\[ \frac{P}{V} = K \cdot R \text{ or } P = K \cdot VR. \]

K provides an index of whether a conducted impulse can re-enter an area of previously excited tissue. Thus, we can describe K as the "re-entry factor." Normally conduction terminates prior to the completion of refractoriness. Thus, in normothermia K is less than one, since R must be greater than P/V.

When, however, P/V becomes equal to R, then K = 1 and circus movement theoretically can occur. In other words, a K value of one or less than one indicates that absolute refractoriness has been completed while an impulse is still being conducted. Under these conditions, the conducted impulse can re-enter an area of previously refractory tissue and so initiate circus movement. Therefore, any situation in which P is increased or VR is decreased will allow K to approach or exceed one.

In hypothermia the following progression of events occurs: (1) reduction of body tem-
Table 6
Per Cent Change in QRS Duration, Conduction Time (MCT), and Absolute Refractory Period (ARP), and Ventricular Fibrillation (VF) Threshold at 20 C. in Mephentermine- and Norepinephrine-treated Dogs

<table>
<thead>
<tr>
<th>Dog number</th>
<th>QRS (msec.)</th>
<th>MCT (msec.)</th>
<th>ARP (msec.)</th>
<th>QRS/ARP</th>
<th>MCT/ARP</th>
<th>VF threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-1</td>
<td>150</td>
<td>150</td>
<td>172</td>
<td>0.87</td>
<td>0.87</td>
<td>7.0</td>
</tr>
<tr>
<td>M-2</td>
<td>200</td>
<td>266</td>
<td>400</td>
<td>0.50</td>
<td>0.66</td>
<td>8.0</td>
</tr>
<tr>
<td>M-3</td>
<td>100</td>
<td>152</td>
<td>218</td>
<td>0.46</td>
<td>0.69</td>
<td>10.0</td>
</tr>
<tr>
<td>M-4</td>
<td>143</td>
<td>266</td>
<td>606</td>
<td>0.29</td>
<td>0.38</td>
<td>25.0</td>
</tr>
<tr>
<td>M-5</td>
<td>539</td>
<td>114</td>
<td>320</td>
<td>1.63</td>
<td>0.36</td>
<td>3.6</td>
</tr>
<tr>
<td>NE-1</td>
<td>100</td>
<td>200</td>
<td>264</td>
<td>0.38</td>
<td>0.76</td>
<td>8.3</td>
</tr>
<tr>
<td>NE-2</td>
<td>200</td>
<td>200</td>
<td>100</td>
<td>2.00</td>
<td>2.00</td>
<td>5.0</td>
</tr>
<tr>
<td>NE-3</td>
<td>67</td>
<td>133</td>
<td>233</td>
<td>0.29</td>
<td>0.57</td>
<td>16.6</td>
</tr>
<tr>
<td>NE-4</td>
<td>40</td>
<td>100</td>
<td>125</td>
<td>0.32</td>
<td>0.80</td>
<td>6.7</td>
</tr>
<tr>
<td>NE-5</td>
<td>133</td>
<td>153</td>
<td>189</td>
<td>0.71</td>
<td>0.71</td>
<td>6.8</td>
</tr>
</tbody>
</table>

*M = mephentermine = treated dogs; NE = norepinephrine = treated dogs.

per temperature from 37 to 25 C. decreases V but increases R proportionally, with P presumably remaining constant. Thus, the re-entry factor, K, remains less than one and circus movement is not possible. This is consistent with the absence of spontaneous fibrillation in dogs above a temperature of 25 C. (fig. 5).

(2) Below 25 C., V decreases without a proportional increase in R. The end result is a decrease in VR so that K approaches a value of one and now circus movement can occur. This agrees with the temperature range (25 to 15 C.) at which fibrillation was observed (fig. 5). If the decrease in VR is counterbalanced by a reduction in P, then the K value again will be less than 1.0 and circus movement should be inhibited. The conduction pathway (P) was shortened by the use of small mammals and by cutting the heart. These procedures were successful in preventing the onset of fibrillation and terminating an existing state of fibrillation. The sympathomimetic amines, on the other hand, increased conduction velocity (V) and in this way prevented K from approaching a value of one. Thus, all of the results reported herein are compatible with a circus movement mechanism as the basis for ventricular fibrillation in hypothermia.

The only other report concerning the nature of fibrillation in hypothermia was presented by Garcia Ramos7 who also concluded that his results favored the circus movement theory as the mechanism for ventricular fibrillation. Using the latency of response to electrical stimuli as a measure of conduction time in rat hearts, Garcia Ramos reported that at low temperatures the latency of responses to trains of stimuli was markedly increased. This was interpreted as being indicative of a pronounced reduction in conduction velocity. In addition, Garcia Ramos believed that at low temperatures the individual muscle fibers become more heterogeneous, which would indicate that the conduction pathway is enlarged because the path pursued by the wave of excitation becomes irregular.

The linearity of the conduction velocity curve at and below a temperature of 20 C. is related, undoubtedly, to a change in the rate constant of some cellular enzyme system at this temperature. In this regard, Hannon9 has reported that in the rat heart a definite break occurs at 20 to 21 C. in the Arrhenius-van't Hoff plot of several different tricarboxylic acid cycle oxidations. If, indeed, a correlation exists between Hannon’s results and those reported here, it would mean that the enzyme systems involved in the metabolism of the tricarboxylic acid cycle intermediates also regulate the speed of conduction in cardiac tissue. The enzymatic regulations of conduction velocity may occur indirectly via the resting potential, level of which is dependent on metabolic rate. A decrease in the resting potential of cardiac cells does produce a decrease in conduction velocity, and again the resting potential of hypothermic cardiac tissue...
fibers is found to decrease abruptly at and below 20°C. On the basis of these varied observations, it may be possible to describe the cellular events which lead to ventricular fibrillation in hypothermia. (1) Cold decreases the rate of oxidation of tricarboxylic acid cycle intermediates which results in decreased production of ATP and other high energy compounds. A reduction in the ATP level of the hypothermic rabbit ventricle has been described. (2) Reduced level of ATP results in decrease of cellular resting potential. The reduction in resting potential may be due to a failure in complete extrusion of intracellular sodium, which is an energy-requiring process. (3) Reduction in resting potential decreases the conduction velocity. (4) Decrease in conduction velocity leads to development of circus movement and ventricular fibrillation.

Elucidation of the mechanism for ventricular fibrillation in hypothermia now makes it possible to specify the properties of an ideal antifibrillatory agent. It should (1) increase conduction velocity and (2) prolong refractory period. Unfortunately, no such drug is presently available. The sympathomimetic amines are capable of increasing conduction velocity, although they may also shorten refractory period in normothermia. In this study, norepinephrine and mephentermine did increase conduction velocity while affecting the refractory period only minimally and did reduce the incidence of ventricular fibrillation. Presumably, methoxamine behaves in a similar fashion. The failure of the other sympathomimetic amines to prevent fibrillation may be related to an inadequate dose regimen since no attempt was made to determine optimal dose or frequency of administration. The QRS duration measurements indicate that those agents which exerted no antifibrillatory activity also failed to increase conduction velocity.

Summary
The mechanism of ventricular fibrillation in hypothermia is best explained by the circus movement theory. The main factor responsible for the initiation of a circus movement type of fibrillation is the marked reduction in conduction velocity which is not counterbalanced by a proportional prolongation of the refractory period, in other words, an increase in the conduction time/refractory period ratio occurs. Maintenance of a fibrillary state in hypothermia is dependent also on the size of the heart. Small hearts either fail to fibrillate or show a spontaneously reversible type of fibrillation. Moreover, shortening the conduction pathway by cutting a fibrillating heart will abolish the arrhythmia. Sympathomimetic amines which increase conduction velocity and so reduce the conduction time/refractory period ratio are also capable of decreasing the incidence of fibrillation. The sequence of events which may lead to development of ventricular fibrillation in hypothermia is discussed.

References
Mechanism of Ventricular Fibrillation in Hypothermia
Benjamin G. Covino and Henry E. D'Amato

doi: 10.1161/01.RES.10.2.148

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1962 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/10/2/148

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/