Influence of Prostigmine and Acetylcholine on Ventricular Fibrillation Elicited by Focal Cooling

By D. Scherf, M.D., R. Bussan, M.D., W. C. Gittinger, M.D. and S. Torin, M.D.

Focal cooling of the exposed ventricle of the dog, beating at high rates, elicits ventricular fibrillation within a few seconds. The effect of this mode of cooling on hearts pre-treated with prostigmine or acetylcholine is studied. These compounds do not prevent ventricular fibrillation, but on the contrary some observations show that they enhance its appearance.

Focal cooling of the exposed heart of the dog or cat, which is beating rapidly either regularly or irregularly, is followed within a few seconds by ventricular fibrillation. The higher the ventricular rate of the hearts of these animals is, the earlier ventricular fibrillation appears. By the administration of large doses of atropine this form of fibrillation, initiated by focal hypothermia, was prevented or delayed, provided the cardiac rate was not extremely rapid.

Recently it has been found that prostigmine given during general hypothermia of the dog, particularly if given by means of coronary perfusion, had a decided antifibrillatory effect. When the coronary sinuses of the hypothermic dogs were catheterized, ventricular fibrillation was elicited in 10 of 11 instances. However, ventricular fibrillation failed to occur in 10 experiments when the dogs were pretreated with prostigmine. Acetylcholine had a similar effect. On the other hand, it is known from previous experiments that under the influence of acetylcholine the inclination of the dog’s heart to fibrillate following light mechanical stimulation is enhanced. Therefore, we decided to investigate the influence of prostigmine and acetylcholine on the result of focal cooling of the exposed ventricles of the dog.

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Method

The dogs varied in weight from 6.5 to 13.5 Kg. and their hearts were exposed in the manner described in previous reports by the authors. The anesthesia employed was morphone given intramuscularly and Nembutal injected intraperitoneally. The trachea was intubated and controlled respiration was instituted. The dose of prostigmine (Hoffmann-LaRoche) was 1 to 2 ml. of a 1:2000 solution which was injected into the superior vena cava or the right auricle. Similarly, a freshly prepared solution of acetylcholine (Hoffmann-LaRoche) was used in other experiments. In most of the experiments, following the injection of prostigmine, a marked bradycardia resulted so that focal cooling could not be expected to induce ventricular fibrillation according to previous experience. Therefore, in order to increase the rate, aconitine was applied topically to the tip of the right auricle to produce auricular fibrillation. The ensuing ventricular rate was slower than it would have been without the inhibitory effect of prostigmine, but yet faster than during sinus rhythm.

The cooling was accomplished by applying the tip of a small test tube filled with ice to the center of the exposed right ventricle. The electrocardiograms were recorded in lead II.

Results

Prostigmine. Focal cooling after the administration of prostigmine was performed on 13 dogs and ventricular fibrillation appeared in all. As table 1 shows the dose of prostigmine varied between 0.036 and 0.125 mg. per kilogram. In three experiments ventricular fibrillation appeared when the cooling was carried out during sinus rhythm. Once it appeared after a cooling period of only eight and eight-tenths seconds; however, in this instance the heart
Table 1.—Data Obtained in 16 Experiments

<table>
<thead>
<tr>
<th>Date</th>
<th>Weight Kg.</th>
<th>Dose of Nembutal ml.</th>
<th>Dose of Morphine mg.</th>
<th>Prostigmine mg./Kg.</th>
<th>Cooling Period prior to Fibrillation (Sec.)</th>
<th>Heart Rate at Onset of Cooling</th>
<th>Rhythm at Onset of Cooling</th>
<th>Result of Cooling</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/25/54</td>
<td>9</td>
<td>3.5</td>
<td>160</td>
<td>0.055</td>
<td>18.2</td>
<td>72</td>
<td>Sinus rhythm</td>
<td>Vent. fib.</td>
</tr>
<tr>
<td>6/1/54</td>
<td>9</td>
<td>4</td>
<td>160</td>
<td>0.083</td>
<td>36.0</td>
<td>83</td>
<td>Sinus rhythm</td>
<td>Vent. fib.</td>
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<tr>
<td>6/8/54</td>
<td>13.5</td>
<td>6</td>
<td>160</td>
<td>0.055</td>
<td>170.0</td>
<td>160</td>
<td>Aur. fib.</td>
<td>No effect</td>
</tr>
<tr>
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<td>4</td>
<td>160</td>
<td>0.091</td>
<td>32.0</td>
<td>136</td>
<td>Sinus rhythm</td>
<td>Vent. fib.</td>
</tr>
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<td>6/29/54</td>
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<td>4</td>
<td>160</td>
<td>0.040</td>
<td>240.0</td>
<td>110</td>
<td>Sinus rhythm</td>
<td>No effect</td>
</tr>
<tr>
<td>10/5/54</td>
<td>8</td>
<td>3</td>
<td>160</td>
<td>0.125</td>
<td>22.4</td>
<td>280</td>
<td>Sinus rhythm</td>
<td>No effect</td>
</tr>
<tr>
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<td>3</td>
<td>160</td>
<td>0.045</td>
<td>21.0</td>
<td>152</td>
<td>Aur. fib.</td>
<td>Vent. fib.</td>
</tr>
<tr>
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<td>160</td>
<td>0.118</td>
<td>26.8</td>
<td>80</td>
<td>Aur. fib.</td>
<td>Vent. fib.</td>
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<td>4</td>
<td>160</td>
<td>0.050</td>
<td>60.0</td>
<td>68</td>
<td>Aur. fib.</td>
<td>Vent. fib.</td>
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<td>3</td>
<td>200</td>
<td>0.071</td>
<td>20.8</td>
<td>18.0</td>
<td>Aur. fib.</td>
<td>Vent. fib.</td>
</tr>
<tr>
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<td>3</td>
<td>200</td>
<td>0.050</td>
<td>55.0</td>
<td>166</td>
<td>Aur. fib.</td>
<td>Vent. fib.</td>
</tr>
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<td>3</td>
<td>160</td>
<td>0.077</td>
<td>27.0</td>
<td>180</td>
<td>Aur. fib.</td>
<td>Vent. fib.</td>
</tr>
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<td>3</td>
<td>180</td>
<td>0.036</td>
<td>30.0</td>
<td>120</td>
<td>Aur. fib.</td>
<td>Vent. fib.</td>
</tr>
</tbody>
</table>

was electrically stimulated at a rate of 280 per minute.

Figure 1 shows the final few seconds of the electrocardiogram before ventricular fibrillation appeared. In the first tracing (experiment of Nov. 23, 1954) auricular fibrillation (induced by the topical application of aconitine) is present and it is seen that this fibrillation was followed by left ventricular ones and finally by ventricular fibrillation.

![Electrocardiogram](image)

Fig. 1. The three tracings show the terminal phase of topical cooling after the administration of prostigmine and immediately before the appearance of ventricular fibrillation. In figure 1A auricular fibrillation, caused by the topical application of aconitine to the appendix of the right auricle ends, and right as well as left ventricular extrasystoles appear with increasing rate; in figure 1B ventricular tachycardia and fibrillation suddenly appear during sinus rhythm; auricular fibrillation existed in figure 1C; the tracing shows clearly that a series of right ventricular extrasystoles is followed by left ventricular ones and finally by ventricular fibrillation.
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Fig. 2. This experiment (June 15, 1954) shows many right ventricular extrasystoles appearing during cooling after administration of prostigmine in the presence of sinus rhythm. Finally a bizarre electrocardiogram is seen presumably caused by simultaneous appearance of right and left ventricular extrasystoles; ventricular flutter follows and suddenly stops at the end of figure 2A. Ventricular fibrillation appears on the second attempt at cooling (fig. 2B).

disappears during the cooling of the right ventricle, a common but unexplained effect.6,7 Numerous extrasystoles appear from both the right and left ventricles, suddenly increasing in number and rate, and terminating in ventricular fibrillation.

The second tracing (experiment of June 1, 1954) reveals the sudden onset of ventricular fibrillation during focal cooling performed in the presence of sinus rhythm. In the lowermost tracing (experiment of Nov. 9, 1954) cooling the right ventricle during auricular fibrillation leads to the appearance of a series of right and left ventricular extrasystoles and finally ventricular fibrillation.

Figure 2 shows a phenomenon which was not observed in previous experiments in which focal cooling was done.6,7 Cooling for 32 seconds after the administration of prostigmine led to ventricular extrasystoles and finally to ventricular fibrillation and flutter with a rate of 500 beats per minute. This suddenly stopped. Renewed cooling for 12 seconds caused permanent ventricular fibrillation.

Thus, prostigmine does not prevent the appearance of ventricular fibrillation during focal cooling, but some modifications of the usual effects of focal cooling can be seen: 1) Prefibrillatory groups of extrasystoles were common (fig. 1a); 2) fibrillation appeared

Fig. 3. In this experiment acetylcholine caused auricular fibrillation and marked bradycardia. Cooling elicited extrasystoles with increasing frequency and finally ventricular fibrillation appears.

Fig. 4. In this experiment the cooling abolished auricular fibrillation which had appeared after acetylcholine. Suddenly, during sinus rhythm, left ventricular extrasystoles appear, followed by right ventricular ones and by fibrillation.
more readily in the presence of slower rates (fig. 1b); 3) the ventricular flutter encountered disappeared and allowed sinus rhythm to return (fig. 2), a behavior observed very rarely in dogs under any experimental conditions.

Acetylcholine. After pretreatment with acetylcholine focal cooling caused ventricular fibrillation within 17.4 to 31 seconds. Here, too, fibrillation appeared in the presence of a relatively slow rate and regular rhythm which is rare in the dog. Figure 3 shows ventricular fibrillation appearing during cooling after administration of acetylcholine in the presence of auricular fibrillation and figure 4 exhibits the same phenomenon occurring during sinus rhythm. The cooling periods, necessary to initiate fibrillation were short.

**DISCUSSION**

It must be emphasized that the present experiments do not contradict those obtained with general hypothermia in which it was demonstrated that prostigmine and acetylcholine prevented ventricular fibrillation induced by general cooling. Although topical cooling also leads to ventricular fibrillation, the mechanism need not be the same as that of general cooling. Some effects may be common to both, while there are additional factors peculiar only to focal cooling, i.e., gradients of polarization between the cooled and the noncooled muscle and the fact that lower temperatures are obtained in a circumscribed area of ventricular myocardium than with general hypothermia. The ventricular fibrillation as a result of focal cooling cannot be explained by the release of adrenaline or overloading the heart as it has been postulated in general hypothermia.

In the present experiments topical cooling repeatedly abolished auricular fibrillation as demonstrated in figure 1a. A satisfactory explanation for this phenomenon cannot be given.

The experiments distinctly show the increasing rates of the ectopic ventricular centers before ventricular fibrillation sets in, confirming the studies of Wiggers and his pupils. The experiments with prostigmine as well as those with acetylcholine clearly demonstrate the appearance of extrasystoles of the other, non-cooled, ventricle before ventricular fibrillation occurs (fig. 1c, figs. 3 and 4). We are unable to explain these isolated extrasystoles appearing from the noncooled ventricle, but if they occur in conjunction with the extrasystoles originating from the area of the cooled ventricle, we assume that distant centers are awakened by rapid impulses. It is known that rapid electrical stimulation of preganglionic nerve fibers entering a sympathetic ganglion elicits repetitive discharges of the ganglion cells after the initial artificial electrical stimulus has ceased.1 Similarly, the specific myocardial tissue fibers, if stimulated rapidly beyond a certain critical rate, begin to fire repetitive impulses after the initiating stimulus has been abolished. The importance of this phenomenon for the explanation of ventricular fibrillation is discussed elsewhere.9

**Conclusions**

Pretreatment of the dog’s heart with prostigmine or acetylcholine does not delay or prevent the appearance of ventricular fibrillation initiated by focal cooling of the ventricular surface. The results of the cooling are, however, slightly modified in certain aspects which are discussed.

**Summario in Interlingua**

In experimentos con canes le pre-tractamento del corde con prostigmina o acetylcholina non preveniva e non retardava le fibrillation ventricular initiate per frigidation focal del superficie ventricular. Tamen certe aspectos del effectos producece per le frigidation focal esseva levemente modificate per le pre-tractamento mentionate. Iste modificationes es discutite.

**References**


2 Harris, A. S. and Moe, G. K.: Idioventricular rhythms and fibrillation induced at the anode or the cathode by direct currents of long duration. Am. J. Physiol. 136: 318, 1942.

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