Influence of Induced Hypothermia on Digitalis Toxicity

By E. T. Angelakos, M.D., Ph.D., and H. I. Hurwitz, B.S.

PREVIOUS studies on the effect of digitalis on the hypothermic heart have indicated that the arrhythmic effects of hypothermia and digitalis are antagonistic. Those experiments were primarily intended to study the effect of digitalization on hypothermia using pharmacological doses of digitalis. In the experiments reported herein, the procedure was reversed in that it was thought to be of value to investigate the possible use of hypothermia as an antagonist of digitalis toxicity.

For this purpose dogs injected with toxic doses of ouabain were subsequently cooled and stabilized in a state of moderate hypothermia at body temperatures of 28 to 31 C. where spontaneous fibrillation (due to hypothermia) does not occur.

The clinical problem of digitalis toxicity is too well known and needs no further comment. However, it should be emphasized at this point that digitalis-induced arrhythmias are only a prelude and warning of impending death due to ventricular fibrillation. Yet arrhythmias and ventricular fibrillation are not entirely dependent on the same mechanisms, so that protection from arrhythmias is not necessarily associated with protection from death due to ventricular fibrillation or possibly cardiac standstill. It is essential, therefore, to determine whether hypothermia could alter the lethal as well as the arrhythmic effects of digitalis.

From the Department of Physiology, Boston University School of Medicine, Boston, Massachusetts.

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Methods

Twenty-six apparently healthy mongrel dogs ranging in weight from 7.8 to 14.0 Kg. were used. Anesthesia was accomplished by intraperitoneal pentobarbital (35 mg./Kg.) supplemented as needed during cooling. Atropine sulfate (0.1 mg./Kg. I.V.) was injected to eliminate any vagal effects of digitalis glycosides. Ouabain (U.S.P.) was used for digitalization, and doses were freshly prepared from ouabain powder dissolved in saline. All drug injections were made intravenously.

Hypothermia was induced by immersion in iced water as previously described. Temperature measurements were made by means of a thermistor probe placed in the esophagus at the level of the atria. The temperature was lowered to approximately 33 C. before removing the animals from the iced bath so that temperature stabilization would occur at about 28 C. In the test group, hypothermia was applied 10 minutes after the injection of ouabain.

Electrocardiograms (usually lead II) were recorded on a Sanborn Viso-Cardiette and continuously monitored through a DuMont oscilloscope. Blood pressures were recorded with a mercury manometer attached to the left carotid artery.

Results

Arrhythmias

To evaluate the effect of cooling on the cardiac arrhythmias produced by ouabain toxicity, several animals were cooled 10 minutes after injection of toxic doses of ouabain (0.07 to 0.1 mg./Kg.).

Five to seven minutes following injection and prior to the onset of cooling, the electrocardiogram showed the characteristic digitalis arrhythmias. As the body temperature decreased during immersion hypothermia, cardiac arrhythmias had a tendency to decrease or disappear at body temperatures of 35 to 33 C. (fig. 1). In some animals, a regular sinus rhythm returned with only infrequent extrasystoles. However, as shown later, this improvement in the electrocardiographic picture did not result in any change in the overall
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Table 1
Mortality due to Digitalis Toxicity in Control and Cooled Animals

<table>
<thead>
<tr>
<th>Dose of ouabain (mg./Kg.)</th>
<th>Controls</th>
<th>Cooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
<td>0.07</td>
<td>0.07</td>
</tr>
<tr>
<td>Mortality (per cent)</td>
<td>66</td>
<td>50</td>
</tr>
<tr>
<td>Mean lethal time (min.)</td>
<td>20</td>
<td>54</td>
</tr>
<tr>
<td>Median lethal time, LT_{50} (min.)</td>
<td>21</td>
<td>46</td>
</tr>
</tbody>
</table>

survival. Several of these animals terminated abruptly in ventricular fibrillation, notwithstanding the apparent improvement of the electrocardiographic picture regarding arrhythmias (fig. 1).

Mortality

A total of 10 control and 10 cooled dogs was tested to determine the incidence of deaths following intravenous injections of 0.07 mg./Kg. ouabain. The cooled animals were subjected to hypothermia 10 minutes after injection at a time when the electrocardiographic tracings showed distinct signs of digitalis toxicity. The results are shown in table 1. The incidence of mortality in the two groups was identical, but there were distinct differences in times of survival. A more accurate picture of the latter can be obtained from the time cumulative mortality curves plotted on probit-log coordinates as shown in figure 2. The median lethal times (LT_{50}) obtained from these curves are included in table 1. However, a quantitative comparison of the two LT_{50} values cannot be made because the two lines are not parallel and actually show a statistically significant deviation from parallelism.

A similar effect of cooling on survival times was also manifested by comparing the body temperature and survival time in each of the cooled animals which died. A negative correlation was found, indicating that the longer survivals were associated with lower temperatures. Nevertheless, this correlation applies only within the group of animals that eventually die. When the mean temperature of these animals (29.7 C.) is compared to that of the survivors (28.2 C.) no significant difference is found.

As noted above, the electrocardiograms of the cooled animals showed fewer arrhythmias (fig. 1). Blood pressures had a tendency to drop in both groups. As might be anticipated, heart rates were generally slower in the cooled animals. The mean heart rate of the atropinized control group was near 180 beats per minute, while the mean heart rate of the atropinized and cooled group was approximately 90 beats per minute.

The control animals which survived over two hours, having nearly normal electrocardiographic records at that time, were subsequently cooled to body temperatures between 28 and 26 C. Of these animals, two out of five terminated in ventricular fibrillation while cooling, and the remaining three survived.

An additional control was provided by testing six normothermic animals with intravenous injections of 0.1 mg./Kg. ouabain. The cumulative per cent mortality, mean lethal temperature, and LT_{50} of this group are included in figure 2 and table 1.

Discussion

By comparing the two groups of control animals receiving 0.07 and 0.1 mg./Kg. ouabain (table 1 and fig. 2), it is clear that increasing the dose of ouabain results in higher mortality and a shorter survival time. The latter can be measured either from the mean lethal time or from the median lethal time (LT_{50}). In this type of experiment, the mean lethal time calculated only from the animals that succumbed is not so representative a measure as the median lethal time which indicates the time when 50 per cent of all animals tested have died. Therefore, the median lethal times and, preferably, the entire cumu-
Mortality times following toxic doses of ouabain in normothermic controls and in animals which were cooled 10 minutes after the administration of the drug.

Figure 2
Mortality times following toxic doses of ouabain in normothermic controls and in animals which were cooled 10 minutes after the administration of the drug.

Relative mortality curves are the best indices available for assessing changes in toxicity.

Both control groups showed the same distribution of mortality times, as can be judged from the similar slopes of the lines representing cumulative deaths in figure 2. By contrast, the cooled animals showed entirely different distribution of mortality times (fig. 2), even though the incidence of deaths was no different from that of similarly treated controls (table 1).

In short, animals which received toxic doses of ouabain and were subsequently cooled lived longer than the controls but met with eventual death in the same proportion as the normothermic control animals receiving the same dose.

The contribution of the difference in heart rates between the two groups in the increased survival of the latter cannot be fully evaluated. The slower heart rates of the cooled animals were apparently secondary to the effect of hypothermia on pacemaker automaticity.5

It has been previously reported that digitalization with nontoxic doses of ouabain does not increase the incidence of ventricular fibrillation under progressive hypothermia and that the hypothermic heart is more resistant to the arrhythmic effects of digitalis.4 The latter finding has recently been confirmed.6,7 From the present study, it appears that once digitalis toxicity is fully manifested through arrhythmias, subsequent cooling does not affect the overall mortality, even though it does prolong survival. Apparently, the protective effects of hypothermia on digitalis toxicity are manifested only when the drug is injected in animals which are already at low temperatures. By contrast, low body temperatures which are subsequently induced cannot reverse toxicity, notwithstanding the fact that lowering the body temperature seems to have a beneficial effect on ouabain-induced arrhythmias. This observation supports the previously proposed hypothesis that, in general, protection from other ventricular arrhythmias is not necessarily associated with protection from ventricular fibrillation.8

Considering the electrophysiology of the heart under the influence of digitalis9 or hypothermia,10,11 it appears that these two agents act antagonistically only in certain respects. Digitalis compounds decrease the refractory period and increase the automaticity of the ventricular myocardium, while hypothermia produces the opposite effect on these parameters. However, both hypothermia and toxic doses of digitalis tend to decrease conduction velocity through the A-V bundle and unspecialized ventricular tissue. In fact, this slow conduction has been implicated as playing a dominant role in the development of ventricular fibrillation by toxic doses of digitalis.9 A similar mechanism has been postulated for hypothermia.8,12 It would appear therefore, that the arrhythmic effects of digitalis are antagonized by hypothermia, probably as a result of the increased refractory period produced by cooling. However, the onset of ventricular fibrillation is apparently dependent on other mechanisms, such as changes in conduction velocity, and is only delayed by hypothermia.

The myocardial ionic changes which might be responsible for this complex relation between digitalis and hypothermia cannot be discussed at the present time since there seems to be no general agreement regarding the
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Effects of either hypothermia or digitalis alone on the ionic balance of the ventricular myocardium.7, 13-15

Summary

Toxic doses of ouabain were injected in animals which were subsequently cooled. The mortality in this group was compared to that of similarly treated controls. Lowering of body temperature by 8 to 12°C reduced the arrhythmias produced by the toxic doses of ouabain but did not alter the overall incidence of mortality from ventricular fibrillation when compared to the controls. However, cooled animals survived for considerably longer periods of time than the normothermic controls. It is concluded that subsequently induced hypothermia does not afford an effective protection from digitalis toxicity, even though arrhythmias are reduced and survival is prolonged. These results support the hypothesis that partial protection from ventricular arrhythmias is not necessarily associated with protection from lethal ventricular fibrillation.

References

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