A Study of Defibrillating Agents on Perfused Rabbit Hearts


Cooling the myocardium is an effective method for abolishing ventricular fibrillation. Using this method as a reference a comparison between five other methods for cardiac resuscitation is made using the Langendorff preparation of the rabbit's heart.

In the isolated rabbit's heart perfused with oxygenated Tyrode's solution, we found the tendency for fibrillation to depend greatly on the temperature of the myocardium as measured by a thermocouple in the left ventricle. On raising the temperature to 39°C the heart of the rabbit can be made to fibrillate by an electric stimulus as readily as the dog's heart, and there is no tendency for spontaneous defibrillation. Lowering the temperature of the perfusion fluid causes the heart increasingly to resist the fibrillation stimulus until, at about 30°C, fibrillation can no longer be evoked.

Decreasing the temperature of a fibrillating heart causes the fibrillation to be replaced by undulations which become slower with further falls in temperature. At a temperature of 22–24°C all irregular movements disappear. However, the sinus-activity is not fully suppressed and the heart starts beating in a very slow rhythm. Increasing the temperature to 38°C then increases the frequency and force of the heart-beat and restores the rhythm to normal. This procedure for suppressing ventricular fibrillation proved itself completely dependable, even when other defibrillatory methods failed. Thus it became feasible to study the effect of different agents on the same heart under as similar conditions as possible.

Methods

All experiments were done on isolated hearts of rabbits. The animals were anesthetized with urethane (1.5 g/kg) and every precaution was taken against myocardial hypoxia by starting the perfusion with oxygenated Tyrode's solution as soon as the aorta was clamped. The heart was connected to a Langendorff cannula after being inverted in order to promote better drainage of the ventricular cavities. The heart was perfused with oxygenated Tyrode's solution at body-temperature and was fibrillated either by faradic stimuli or an alternating current of 10 V., 0.1 second in duration. The temperature of the heart was kept at 37–39°C to suppress the tendency to spontaneous defibrillation. One minute after the onset of fibrillation, the defibrillation method to be tested was applied. In case of success, the heart was allowed a recovery time of at least ten minutes before the trial was repeated. In case of failure to suppress fibrillation, or when fibrillation resumed before the return of a normal rhythm, the cooling method was used to restore normal cardiac activity.

Results

Arrest of coronary perfusion. According to Djourno, Langendorff suppressed fibrillation of the isolated heart by stopping the flow of perfusion fluid. De Boer stated that the same method has been successfully applied by Hering on the isolated human heart. Although rather obsolete and of little practical use, it was tried 24 times in our experiments by closing the cannula one minute after the onset of fibrillation. In 10 cases, defibrillation was attained and the normal beat was resumed. In the other instances, the fibrillatory movements lessened and the normal beat broke through, but defibrillation returned on restarting the perfusion. In some of these experiments the cannula was again clamped, but fibrillation was found to return every time, even when the closure was so prolonged as nearly to cause cardiac arrest. In some hearts no success at all...
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FIG. 1: 1. electrical fibrillation at 37.5°C; 2. injection of 5 mg. ATP; 3. perfusion with cold, oxygenated Tyrode’s; 4. defibrillation at 21°C; 5. perfusion with warm, oxygenated Tyrode’s solution.

Time in minutes.

could be obtained; in others, success and failure varied at random.

Acetylcholin. Fröhlicher advises the injection of acetylcholin (1–3 mg. for rabbits and 1–5 mg. for dogs) into the cardiac cavities or coronary vessels for defibrillating purposes.

We have tried acetylcholin in 5 rabbits. With doses of 2, 1 and 0.2 mg., injected in the cannula, fibrillation was completely suspended, but no trace of the beginning of normal contractions could be observed. In one case we injected 10 gamma epinephrine after acetylcholin and got fibrillation. This was suppressed by perfusion with cold Tyrode. Subsequent perfusion with warm fluid restored the normal rhythm. Very soon, however, the contractions weakened and the heart stopped beating. In two more cases we injected only 0.1 mg. acetylcholin, which did not suppress fibrillation. The cardiac rhythm was restored by cooling and then warming but in neither case was the resuscitation permanent: the contractions ceased very soon.

Adenosin triphosphoric acid. Fischer and Fröhlicher have proposed the use of adenosin triphosphoric acid (ATP) to resuscitate the heart from ventricular fibrillation. The experiments were done on the isolated hearts of rabbits, cats and dogs and were successful every time. Using the same dosage for the rabbit (0.4–5 mg. intracardially) we were unable to reproduce these results. In nine of 32 trials the injection of ATP suppressed fibrillation and, after a short pause, normal rhythm was initiated, but, in the remaining 23 trials, even the highest dose did not stop fibrillation. We then resorted to the cooling procedure (fig. 1). In most cases the ATP was injected into the coronary system via the cannula. Injection into the ventricular cavities, as proposed by Fischer and Fröhlicher was no more effective.

Potassium and calcium. The injection of these agents to combat ventricular fibrillation was inaugurated by d’Halluin and Hooker.

In our 63 trials with the K/Ca method full resuscitation was attained 38 times. In all cases, the warm Tyrode fluid was replaced by oxygenated K and Ca solution (0.5% KCl in 0.9% NaCl; 0.023% CaCl₂ in 0.9% NaCl) of the same temperature. In 23 cases, fibrillation returned upon injection of the calcium solution and in two cases cardiac arrest by potassium proved to be definitive. In most cases we omitted the injection of adrenalin as we feared its potent fibrillatory action. Sometimes, indeed, it may help the restoration of cardiac activity (fig. 2) but, more often, the resuscitation initiated by calcium was cut short by the reappearance of fibrillation. This was suppressed by the cooling method as in all other cases when the K/Ca method failed. In some experiments we tried the effect of potassium and calcium on ventricular fibrillation induced by the injection of 0.2 ml. 0.1 per cent adrenalin, which, after a short period of forceful contractions, led to the sudden development of fibrillation. This was fully arrested by the injection of potassium but reappeared.

FIG. 2: 1. electrical fibrillation at 38°C; 2. perfusion with warm, oxygenated 0.5 per cent KCl; 3. perfusion with warm, oxygenated 0.023 per cent CaCl₂ solution; 4. injection of 0.1 ml. 0.1 per cent adrenaline; 5. perfusion with warm, oxygenated Tyrode’s.

Time in minutes.
again after the application of calcium. Normal rhythm was restored later by the cooling procedure.

**Electric defibrillation.** This method of restoring normal activity of the heart has received the most wide-spread attention, both experimentally and clinically. We used an A.C. defibrillator as described by Mackay et al. Single and serial shocks of 0–270 Volts for 0.1 or 0.5 second were applied. The electrodes consisted of pads of 1 cm. diameter placed on the epicardium. Fibrillation was induced with one shock of 10 V. for 0.1 sec. For defibrillation much stronger shocks were needed (about 100 V. for 0.1 sec).

Sixty-one trials at electric defibrillation were made and in 39 cases direct success was attained, either with one or with a series of shocks. In six of the 22 failures, lasting cardiac arrest occurred. In the remaining 16 cases, the fibrillation could not be suppressed and the cooling method had to be resorted to. In successful cases the method is a very dramatic one and leaves the heart in good condition. But the effect is variable, even with the same heart. In one heart 12 trials were made. Of these the 1, 3, 5, 6, 9, 11 and 12th were successful, either after one or after a series of shocks. In the other cases we had to apply the cooling method. If one shock does not suffice a maximal series of seven may still be effective, but further stimulation was of no use. After a successful electrical defibrillation, fibrillation sometimes restarted spontaneously after some seconds. In this case it was often possible to defibrillate anew by a second series of shocks. Most experiments with repeated electric defibrillation ended with complete arrest of cardiac activity. After a series of electric defibrillations interspersed eventually with cooling defibrillations the application of a shock of the usual strength ended the fibrillation but at the same time stopped normal sinus rhythm and led to a final arrest of the heart.

**Epinephrine.** Use of this agent has been proposed to support the K/Ca method and also electrical defibrillation. In the Langendorff heart epinephrine proved a powerful fibrillatory agent. The untreated heart could be made to fibrillate by injection of 0.2 ml. 0.1% epinephrine solution into the inflow cannula at an intracardiac temperature above 34–35 C. Below this temperature the contractions increased slightly, but the normal rhythm remained undisturbed. The fibrillation induced by adrenaline may also be abolished by cooling and subsequent warming.

**DISCUSSION**

The degree of success with any procedure for ventricular defibrillation seems to depend a great deal upon the technical details observed by individual investigators. Some of these have been defined clearly by Wiggers who points out that fibrillation should cease completely in every part of the myocardium before attempts to encourage coordinated beats should be made. Adequate pacemakers—preferably only one—must survive to inaugurate excitation of the defibrillated ventricles.

Our study allows a comparison of a number of methods for defibrillation in the hands of the same investigator. Several different procedures could be tested on the same heart because in case of failure the method of cooling and subsequent heating was always successful in resuscitating the isolated rabbit’s heart. The divergent effects of cooling, mentioned by others, must be ascribed to imperfect methods of cooling the whole heart muscle.

In the present series of experiments the figures given in table 1 for the cooling method are mostly from experiments in which one of the other methods had failed. A cooling experiment was done at the beginning of a series of trials on a fresh heart to ascertain the effective-

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**Table 1**

<table>
<thead>
<tr>
<th>Method of Defibrillation</th>
<th>Number of Preparations</th>
<th>Total Number of Trials</th>
<th>Effect in % of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfusion stopped...</td>
<td>6</td>
<td>24</td>
<td>42</td>
</tr>
<tr>
<td>Acetylcholine...........</td>
<td>5</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>A.T.P...................</td>
<td>6</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>K/Ca perfusion...........</td>
<td>10</td>
<td>63</td>
<td>60</td>
</tr>
<tr>
<td>Electrical...............</td>
<td>7</td>
<td>61</td>
<td>64</td>
</tr>
<tr>
<td>Cooling..................</td>
<td>42</td>
<td>88</td>
<td>100</td>
</tr>
</tbody>
</table>
ness of this procedure which might have to be called upon at any moment. These trials are incorporated in the total number.

The positive defibrillatory effect of arresting the perfusion through the Langendorff heart might be caused by the resulting fall in temperature. We have measured the temperature in the ventricular cavity and have observed the reappearance of normal beats at temperatures between 28 and 33°C. Although these were much higher than those at which normal cardiac activity restarted in the cooling experiments (21–25°C), we should remember that we did not measure the temperature of the myocardium, which must have been lower.

If we count only the first ATP-treatments on a fresh preparation, resuscitation was achieved only in 2 of 19 tries (10 per cent). Our impression was that in spite of the continued perfusion with Tyrode’s, the heart’s action was definitely altered by one or more injections of ATP. Spontaneous arrhythmias and partial heart block occurred and in these cases it was difficult to induce fibrillation and relatively easy to defibrillate.

Compared to the excellent results obtained by others with electrical defibrillation our data are somewhat disappointing. Both the strength of current and the rate of stimulation were the same as those commonly used, and other modes of stimulation did not improve the results.

SUMMARY

Six different methods for cardiac resuscitation from ventricular fibrillation have been compared on the isolated heart of the rabbit. Injection of acetylcholine was uniformly unsuccessful. Four other methods: a) arrest of coronary perfusion; b) ATP injection; c) K/Ca perfusion; and d) electrical stimulation produced variable results, ranging from 28 per cent success for ATP injection to 64 per cent success for the electrical method. Cooling the isolated heart by coronary perfusion and subsequent rewarming gave consistently good results where other methods failed.

REFERENCES

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