Br. J. Pharmac. (1979), **66**, 609–618

THE EFFECT OF THE AMINOSTEROID, ORG 6001, ON HYPOTHERMIA-INDUCED VENTRICULAR FIBRILLATION IN THE CAT

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1 The effect of the antidysrhythmic aminosteroid, ORG 6001, on hypothermia-induced ventricular fibrillation was investigated in cats anaesthetized with pentobarbitone.

2 ORG 6001 (total dose, 10 mg/kg, by intravenous injection) reduced both the incidence of fibrillation and the temperature at which it occurred. The number of animals that survived to 16°C was increased.

3 This protective effect of ORG 6001 could not be explained by changes in respiratory acidosis, plasma concentrations of sodium and potassium, or by changes in the action potential of excised hypothermic ventricular muscle. The hypothermia-induced elevation of blood lactate was less in cats treated with the aminosteroid.

4 Over a limited temperature range, ORG 6001 prolonged the P wave and QRS duration and shortened the QT_C interval. ST segment elevation was slightly reduced in the drug-treated group. J deflections were observed but were not correlated with the development of fibrillation.

5 The onset of fibrillation was not considered to be due to temperature differences between the myocardium and arterial blood or between localized areas of the left ventricular wall.

Introduction

ORG 6001 (3α-amino-5α-androstan-2β-ol-17-one hydrochloride) is a new orally-active antidysrhythmic agent which is at present undergoing clinical trials. It has been reported to be effective in reducing ventricular ectopic activity induced either by aconitine, ouabain or coronary artery ligation (Marshall & Parratt, 1975; Vargaftig, Sugrue, Buckett & Van Riezen, 1975) and to decrease the incidence of ventricular fibrillation following coronary artery occlusion in the dog and pig (Marshall & Parratt, 1975; Verdouw, Schamhardt, Remme & de Jong, 1978). The aim of the present work was to examine further the antifibrillatory activity of ORG 6001 in a model (hypothermic cat) in which ventricular fibrillation is usually the sole ventricular dysrhythmia.

The occurrence of fibrillation upon cooling is still a major drawback to the application of hypothermia in cardiac and neurosurgery, and is also thought to be the main cause of death in accidental hypothermia (Maclean & Emslie-Smith, 1977). The currently available antidysrhythmic drugs appear to be of little use against hypothermia-induced fibrillation in the clinical situation and indeed 'should not be given as they have little value in the hypothermic patient and may even precipitate ventricular fibrillation' (Golden, 1973). Procainamide and lignocaine have, for example, been shown to have adverse effects in experimental hypothermia by increasing the temperature at which fibrillation occurs (Covino, Wright & Charleston, 1955; Angelakos & Hegnauer, 1959).

The fact that there is no reliable antidysrhythmic drug for the treatment of hypothermic ventricular fibrillation reflects the lack of knowledge about both the mechanism underlying this dysrhythmia and the action of antidysrhythmic drugs in hypothermia. In this study, therefore, we also examined various factors, such as arterial pH and blood gases, arterial lactate and electrolyte levels and myocardial temperature to assess their importance in the initiation of hypothermic fibrillation. An electrophysiological study of ventricular muscle excised from the hypothermic animals was also carried out in an attempt to examine the effects on the action potential characteristics of cardiac cells.

Methods

In vivo

Experiments were carried out on 18 cats of either sex weighing 1.3 to 3.1 kg (mean = 2.0 kg), deprived of food overnight. Anaesthesia was induced with pen-

0007-1188/79/080609-10 $01.00

tobarbitone sodium (42 mg/kg intraperitoneally). Small additional amounts were administered intravenously as required. The animals were allowed to respire spontaneously until respiratory movements were judged to be inadequate; this occurred at a mean arterial blood temperature of 28.2 ± 0.8°C (range 22.1 to 32.2°C). At this point, positive-pressure artificial ventilation with room air was initiated at a rate of 18/min and a stroke volume of 20 ml/kg. This degree of hyperventilation has been found necessary to maintain a reasonable arterial oxygen tension.

Flexible direct recording thermocouples (Ellab, Copenhagen) of appropriate diameter were placed in the rectum, the mid-oesophagus and the aorta. Systemic arterial blood pressure was measured from the aorta, with a capacitance transducer (Elema-Schönander, type EMT35). The electrocardiogram was recorded from standard limb leads. Arterial blood pressure and the electrocardiogram were monitored continuously on an oscilloscope and recorded every 15 min down to an arterial blood temperature of 20°C, and thereafter continuously, with a Mingograf 81 ink-jet recorder (Elema-Schönander, Stockholm).

The animals were injected with heparin sodium, 300 i.u./kg intravenously. Samples of arterial blood were taken before cooling and at intervals throughout the cooling procedure for the determination of pH, P_{O_2}, P_{CO_2}, lactate and plasma sodium (Na^+) and potassium (K^+). Arterial pH, P_{O_2} and P_{CO_2} were measured at 37°C and subsequently corrected for temperature using the nomograms given by Maclean & Emslie-Smith (1977). Lactate was determined enzymatically with a Boehringer test kit, and plasma Na^+ and K^+ were determined by standard flame photometry.

The cats were cooled by packing ice around the shaved abdomen. A uniform rate of cooling of approximately 0.12°C/min was achieved by this method of surface cooling. In all cases cooling was continued until death of the animal in ventricular fibrillation or asystolic arrest, or until arterial blood temperature fell below 16°C, at which point the experiment was terminated.

The animals were divided into three groups: Group (1): 7 control cats were subjected to the above cooling procedure after the establishment of baseline haemodynamic and metabolic parameters. Group (2): 7 cats were pretreated with ORG 6001 (Organon International); 5 mg/kg was given intravenously before cooling and a further 5 mg/kg when arterial blood temperature had reached 30°C. Group (3): in 4 cats, a left thoracotomy was performed and two thermocouples inserted directly into different regions of the left ventricular myocardium. The chest was then closed and the animals cooled as above. These animals were artificially ventilated throughout the entire course of the experiment.

Statistical significance of differences between means was calculated by Student's t test for Groups 1 and 2. Group 3 contained insufficient animals for such statistical analysis.

In vitro

Right ventricular papillary muscles, which were excised from Groups 1 and 2 cats at the end of the experiment, were pinned to the silastic base of the recording chamber and perfused at a rate of 10 ml/min with Krebs solution equilibrated with 95% O_2 and 5% CO_2. The composition of the Krebs solution was (mM): NaCl 119.6, $NaHCO_3$ 25, NaH_2PO_4 1.2, KCl 4.0, $MgCl_2$ 0.57, $CaCl_2$ 2.7 and glucose 5.5. The temperature of the bath was maintained at the final temperature of the cat for 1 h, then the muscle was rewarmed to 36°C. When spontaneous activity ceased the muscle was stimulated at a frequency of 1 Hz by rectangular pulses of 1 ms duration and twice threshold voltage delivered through a bipolar silver electrode. Transmembrane action potentials were recorded with conventional microelectrode techniques and recording began immediately after excision of the heart. The parameters measured were resting membrane potential (RMP), action potential height (AP), the maximum rate of rise of phase zero (MRD), and the action potential duration at both 50 and 90% repolarization (APD_{50} and APD_{90}).

Results

Incidence of ventricular fibrillation

In Figure 1 the percentage of cats which fibrillated, the temperature at which ventricular fibrillation first occurred and the percentage of survivors at 16°C are shown for each of the 3 groups. Of the 7 control cats (Group 1), 6 fibrillated at a mean arterial temperature of 19.54 ± 0.22°C. The fibrillation was terminal in 5 cats, but spontaneously reverted to sinus rhythm in one. Only 1 animal from the control group survived to 16°C. In the drug-treated group, fibrillation was observed in 4 of the 7 animals but the mean arterial temperature at which fibrillation first occurred, 17.9 ± 0.68°C, was significantly lower than in the control group ($P < 0.05$). Of these 4 animals, only one suffered terminal fibrillation and in this group there were 5 survivors at 16°C. In Group 3, all 4 cats fibrillated at a mean arterial temperature of 18.68 ± 0.45°C. As in Group 2, these animals showed spontaneous reversion to sinus rhythm and 3 cats survived to 16°C.

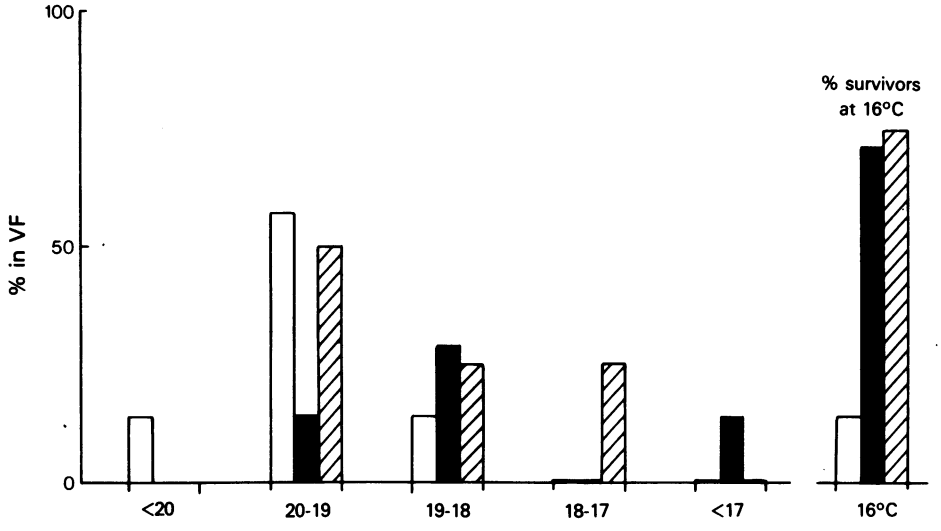

Figure 1 The arterial temperatures at which ventricular fibrillation (VF) occurred in cats subjected to hypothermia, together with the percentage of survivors at 16°C. Open columns: Group 1; solid columns: Group 2; hatched columns: Group 3.

Heart rate, blood pressure and electrocardiographic changes induced by cooling and ORG 6001

Table 1 shows the decreases in arterial pressure and heart rate observed during cooling. There was no significant difference in blood pressure or heart rate between the groups at any point during the course of cooling.

Examples of the electrocardiographic changes induced by cooling are shown in Figure 2. All the components of the electrocardiogram were progressively lengthened during cooling. ST segment elevation was observed as the temperature fell, and ultimately J deflections and inverted T waves appeared. These changes occurred in all 3 groups. In the control group, sinus rhythm usually persisted until the sudden onset of fibrillation, whereas in the other groups ventricular extrasystoles were often observed before fibrillation. Figure 3 summarizes the effect of decreasing temperature on the P, QRS and QT_C (QT corrected for heart rate) intervals. In the control group (Group 1) the lengthening of the P and QRS intervals was more pronounced at arterial temperatures below 25° and 23°C respectively. In the Group 2 cats, following administration of the second dose of ORG 6001, P and QRS durations were increased compared to control, down to the temperature at which the more marked prolongation occurred. However, the QT_C interval was significantly shortened in the ORG 6001-treated animals at arterial temperatures below 22°C. ST segment changes, which occurred in all 3 groups during cooling, are shown in Figure 4. It can be seen that the maximum ST segment elevation occurred at approximately the same temperature in all 3 groups and that it was greatest and least in Groups 1 and 3 respectively. As temperature de-

Table 1 The effects of cooling on heart rate and systolic arterial blood pressure in anaesthetized cats

	Heart rate (beats/min)			*Arterial blood pressure (mmHg)*		
Arterial temp. (°C)	*Group 1*	*2*	*3*	*1*	*2*	*3*
Pre-cooling value	196 ± 10	188 ± 9	145 ± 16	137 ± 11	154 ± 14	117 ± 10
30	142 ± 5	145 ± 5	125 ± 14	130 ± 10	115 ± 16	107 ± 5
25	79 ± 3	74 ± 7	59 ± 13	90 ± 11	72 ± 9	72 ± 5
20	46 ± 4	42 ± 3	33 ± 7	63 ± 10	51 ± 3	47 ± 4

Values are means ± s.e. of 3–7 observations.

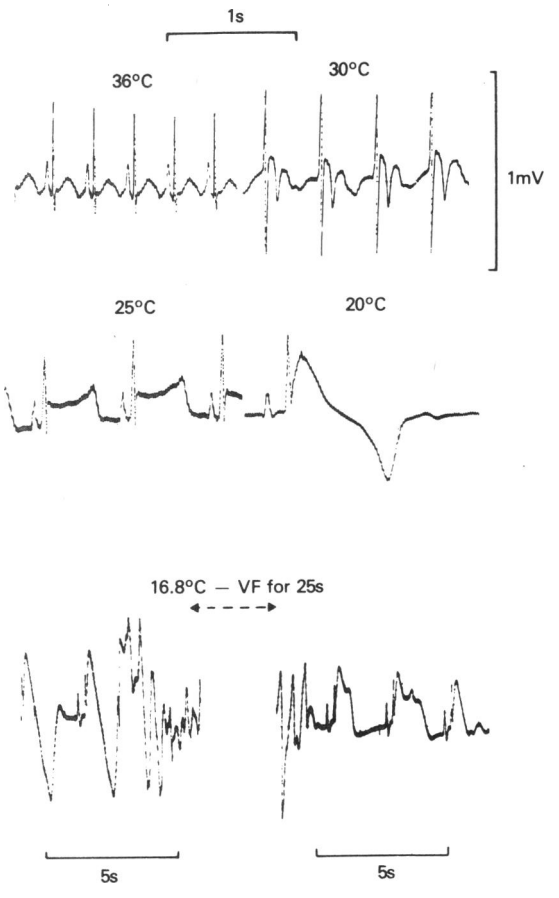

Figure 2 Electrocardiographic changes induced by cooling in a cat pretreated with ORG 6001. Note the spontaneous reversion to sinus rhythm after 25 s of ventricular fibrillation (VF).

creased below 22°C, a decline in ST segment elevation occurred in Groups 2 and 3. In Group 1 most of the animals had undergone terminal fibrillation before reaching such temperatures.

Changes in arterial pH, P_{CO_2}, P_{O_2}, lactate and electrolytes

Table 2 shows the changes in pH and P_{CO_2} during cooling in all 3 groups. In Groups 1 and 2, arterial blood pH fell and P_{CO_2} remained unchanged during the period of spontaneous respiration. After the start of artificial ventilation there was a significant rise in pH and fall in P_{CO_2} in both groups when compared with pre-cooling values. During artificial ventilation, the arterial blood pH of the animals treated with the aminosteroid became significantly greater than that of the control, untreated cats ($P < 0.02$), whereas

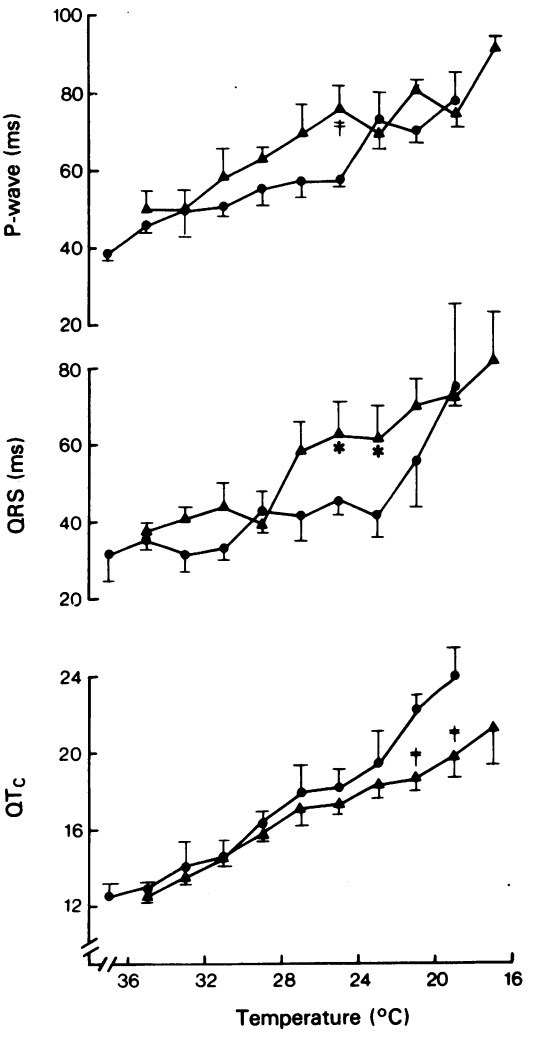

Figure 3 The effect of decreasing arterial temperature on the P, QRS and QT_C intervals in control (●) and drug-treated cats (▲). Each point is the mean of (usually) seven observations; vertical lines indicate s.e. * $P < 0.05$; † $P < 0.01$. The interval changes in the artificially ventilated cats (Group 3) were similar to those of the controls.

there was no significant difference in P_{CO_2} between the groups at any point. In the cats subjected to thoracotomy (Group 3) pH remained unchanged and P_{CO_2} fell during the course of each experiment. The arterial oxygen tension decreased gradually during the course of each experiment; this decline was neither arrested nor reversed by the initiation of artificial ventilation.

In Figure 5 the changes in arterial lactate have been plotted over certain temperature ranges. The arterial

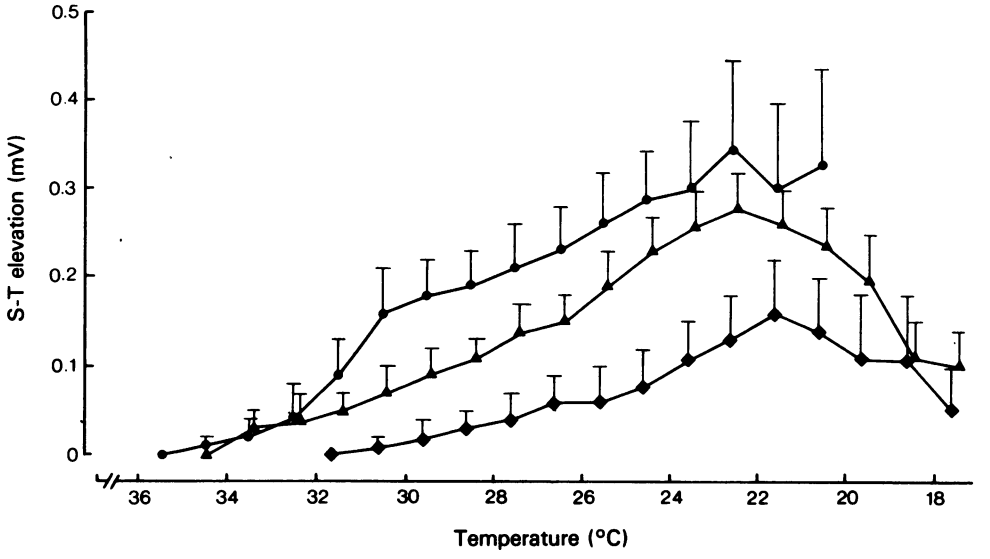

Figure 4 The effect of decreasing arterial temperature on the mean ST segment elevation; vertical lines indicate s.e. Group 1 (●), Group 2 (▲) and Group 3 cats (◆).

lactate levels in the control group became significantly greater than the pre-cooling value when the arterial temperature fell to 28°C or less ($P < 0.05$). However, in the ORG 6001-treated cats arterial lactate did not increase significantly until the arterial temperature fell to less than 22°C. In the Group 3 animals, arterial lactate showed little change from pre-cooling values at any time.

During the course of hypothermia there was no change in plasma Na^+ levels in the animals of either Group 1 or Group 2 from the pre-cooling values of 172 ± 5 and 181 ± 2 mEq/l respectively. Plasma Na^+ was not measured in the Group 3 cats. The pre-cooling values of plasma K^+ were 4.0 ± 0.2, 4.2 ± 0.2 and 3.6 ± 0.3 mEq/l for Groups 1, 2 and 3 respectively. All 3 groups showed a small, nonsignificant fall in plasma K^+ at 15 to 30 min after the start of cooling. The levels then rose again to around pre-cooling levels as hypothermia developed.

Changes in myocardial temperature

In all 4 cats the temperature of the left ventricular myocardium which was initially similar to that of aortic blood, became higher than the arterial temperature as cooling progressed. This effect is illustrated in Figure 6, in which the results obtained in 2 of the cats are shown. The mean myocardial–arterial temperature difference when ventricular fibrillation first occurred was 0.46 ± 0.7°C. Figure 6 also reveals that there were no consistent variations in temperature between the epicardium and the deep muscle layers at the time of fibrillation. In only 2 of the cats slight differences in the temperature recorded at these two different sites in the heart, of 0.3 and 0.32°C, were observed.

Electrophysiology

The RMP of the ventricular muscle was measured within 15 min of excision and was found to be 56 ± 1.5 mV ($n = 29$; 4 preparations of Group 1) and 51.5 ± 1.7 mV ($n = 35$; 5 preparations of Group 2).

However, 20 to 30 min after excision the RMP increased and the muscles became spontaneously active. An example of the first action potential recorded following excision is shown in Figure 7(a). The mean RMP and amplitude of such action potentials was respectively, 89.4 ± 4.9, 116.6 ± 6.4 mV (Group 1 cats; $n = 4$), and 77.8 ± 3.5, 100.4 ± 5.1 mV (Group 2 cats; $n = 5$). Although these action potentials were of normal amplitude, their configuration was quite different from that of normal ventricular muscle. As can be seen more clearly in Figure 7(b), repolarization often occurred in two distinct phases, an initial spike being followed by a second depolarization before the onset of repolarization. The APD of these action potentials was markedly prolonged; the mean APD_{50} and APD_{90} of the control muscles being 634 ± 161 and 1076 ± 33 ms respectively. The APD_{50} and APD_{90} of the drug-treated muscles was considerably shorter than those of the control group (545 ± 118 and 767 ± 83 ms respectively). Thereafter the action potentials were difficult to characterize as various

Table 2 The effects of cooling and of artificial ventilation on arterial blood pH and Pco_2

	Group 1		*Group 2*		*Group 3*	
	pH	*Pco_2 (mmHg)*	*pH*	*Pco_2 (mmHg)*	*pH*	*Pco_2 (mmHg)*
Pre-cooling value	7.370 ± 0.030 (5)	26.1 ± 4.4 (5)	7.419 ± 0.005 (6)	31.6 ± 5.0 (5)	7.567 ± 0.003 (4)	22.9 ± 2.3 (4)
Before artificial ventilation	7.340 ± 0.030 (5)	27.3 ± 4.7 (5)	7.396 ± 0.014 (5)	30.8 ± 4.9 (5)		
After start of artificial ventilation	7.595 ± 0.031 (7)*	14.6 ± 2.2 (6)**	7.772 ± 0.056 (4)*	14.7 ± 0.8 (4)**	7.776 ± 0.005 (3)	11.0 ± 0.9 (3)

Values are expressed as mean ± s.e. with the number of observations in parentheses.
Significantly difference from the pre-cooling value: * $P < 0.001$; ** $P < 0.005$.

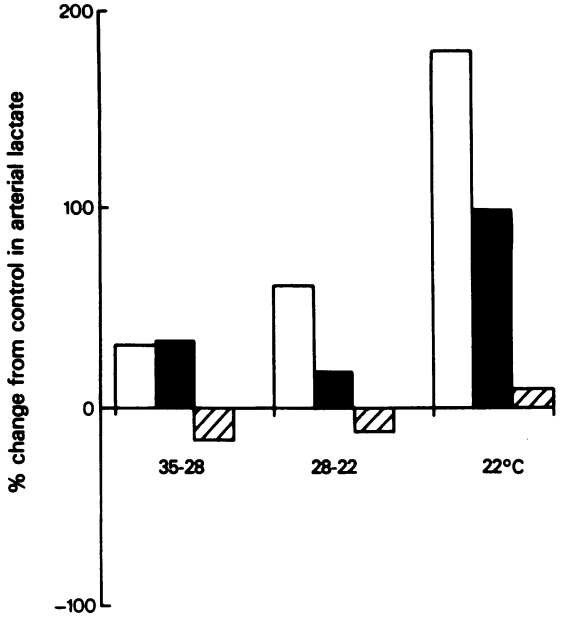

Figure 5 The effect of cooling on arterial lactate, expressed as percentage changes from initial resting levels (3.4 ± 0.8, 4.2 ± 0.9, 6.9 ± 2.3 mg/100 ml for Groups 1 to 3 respectively); open columns: Group 1; solid columns: Group 2; hatched columns: Group 3.

abnormal configurations were observed. For example, action potentials often arose during the course of repolarization and this was usually associated with uncoordinated muscle contractions. In most preparations it was also noted that action potentials, which arose just before complete repolarization, were considerably shorter in duration than the preceding action potential. Representative action potentials showing these characteristics are illustrated in Figure 7(c) and (d). Another feature which was commonly observed during spontaneous activity was oscillations of the membrane potential which, as can be seen in Figure 7(e), could give rise to action potentials. No difference was observed in either the occurrence or frequency of the features mentioned between Groups 1 and 2 muscle. Upon rewarming, the configuration of the action potentials became more normal as the APD decreased and the MRD increased, although in both groups spontaneous activity still presisted in some of the preparations. The spontaneous activity which occurred at 36°C was sometimes associated with the occurrence of after depolarizations (Figure 7f).

Discussion

From the results obtained in this study it is clear

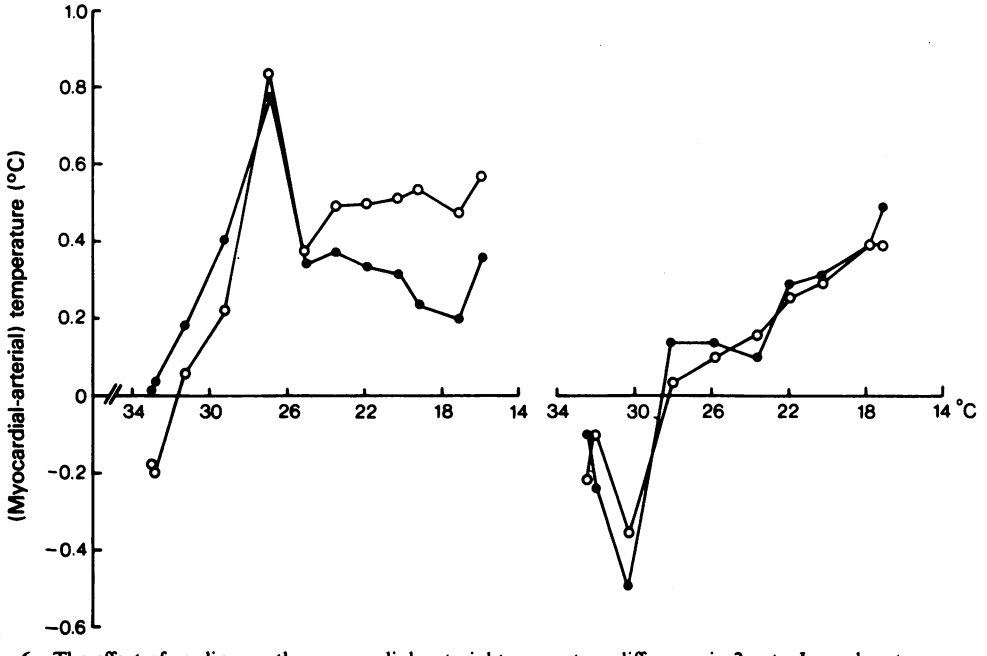

Figure 6 The effect of cooling on the myocardial–arterial temperature difference in 2 cats. In each cat, myocardial temperature was measured at two sites, one epicardial (●) and the other endocardial (○).

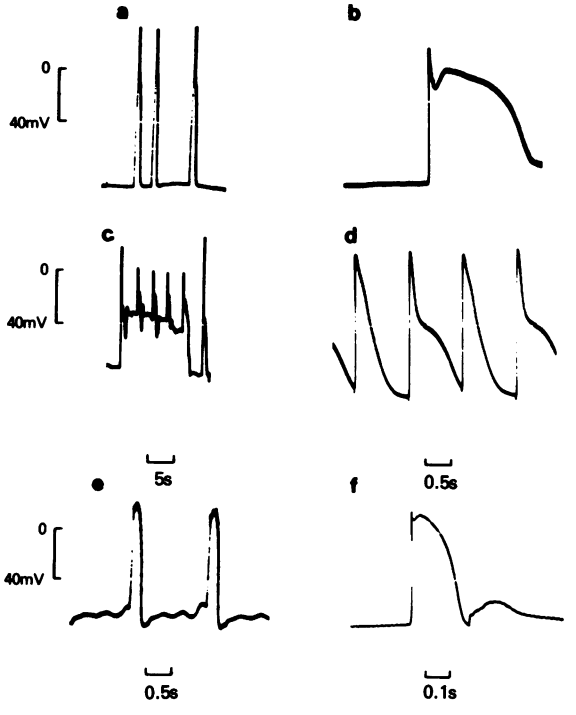

Figure 7 Action potentials recorded from excised hypothermic papillary muscles from control and drug-treated animals. Details in the text.

that a dose of 10 mg/kg of ORG 6001, although not completely effective in preventing the occurrence of hypothermic ventricular fibrillation, markedly reduced its incidence (from 86 to 57%) and significantly reduced the temperature at which it first occurred. Moreover, the number of survivors at 16°C was considerably increased in the drug-treated group as the pattern of fibrillation had been changed from a terminal event to a series of intermittent eposodes. ORG 6001 is, therefore, similar in its action in this model to quinidine which has also been shown to reduce both the lethal temperature and the incidence of fibrillation (Angelakos & Hegnauer, 1959). Very few of the other currently available antidysrhythmic drugs have been shown to be effective against hypothermic ventricular fibrillation and some, such as procainamide and lignocaine, have a positively adverse effect (Covino *et al.*, 1955; Angelakos & Hegnauer, 1959). It is not understood why only some antidysrhythmic drugs appear to be effective in experimental hypothermia and the mechanisms underlying this type of dysrhythmia have not been elucidated.

Several mechanisms have been postulated to explain the occurrence of hypothermic ventricular fibrillation. For example, Lloyd & Mitchell (1974) have proposed that it is due to selective cooling of the subendocardial Purkinje system by cold blood in the chambers of the heart, and hence preferential conduction through the muscle which might precipitate fibrillation. However, in our experiments, the myocardial–arterial temperature difference at the time of fibrillation was only 0.46°C. There was also no consistent relationship between changes in temperature, recorded from different regions of the myocardium (e.g. between epicardium and endocardium, Figure 6) and the onset of fibrillation. These results are in agreement with those of Mouritzen & Andersen (1965) who showed that, at temperatures above 25°C, fibrillation did not occur with temperature gradients less than 2°C and that below 20°C fibrillation could occur with no measurable gradient.

The development of acidosis has also been put forward as an underlying cause of hypothermic fibrillation (Covino & Hegnauer, 1955; Astrup & Engel, 1965). In the present study, the initial fall in arterial pH observed in the closed-chest cats (Groups 1 and 2) was reversed by the initiation of artificial ventilation, so that there was no evidence of acidosis in any of the groups at the temperatures at which fibrillation occurred. However, there were considerable differences between the groups with regard to changes in arterial lactate concentrations. In the control group the arterial lactate concentration markedly increased as cooling progressed. Similar findings have previously been reported in both animals and man (Brewin, Gould, Nashat & Neil, 1955; Ballinger, Vollenweider, Templeton & Pierucci, 1961). It has been postulated that increases in arterial lactate levels are due either to anaerobic metabolism caused by tissue hypoxia, a decreased hepatic extraction of lactate or to shivering-induced production of lactic acid. It would seem that in these experiments some degree of tissue hypoxia may have been the cause of the increase in the lactate levels, since this increase was totally prevented in the Group 3 cats, which had been artificially ventilated throughout the entire course of the experiment. In the aminosteroid-treated group, changes in lactate levels were less marked than in the controls and, in particular, the rise in lactate was delayed until the arterial temperature was less than 22°C. A similar ability of ORG 6001 to reduce the production of lactate has been observed in the ischaemic myocardium by Marshall & Parratt (1975). It is not possible to localize the mechanism of this action on lactate production in these experiments as arterial samples only were taken; nor is it known if this effect is a direct metabolic one or is due to a general membrane stabilization.

It should also be noted that in the Group 3 cats, which were artificially respired, fibrillation was not a terminal event and 75% of the cats survived to 16°C. Thus it would seem that either the high lactate level itself, or possibly some other metabolic change associated with it, may be involved in the maintenance of fibrillation rather than its initiation. It is not known to what extent the increased survival in the Group 2 cats is dependent upon the antidysrhythmic action of ORG 6001 or to its effect on arterial lactate.

Changes in myocardial and plasma electrolyte concentrations have also been postulated as a possible factor important to the initiation of hypothermic ventricular fibrillation. We could find no evidence to support the hypothesis that changes in plasma Na^+ and K^+ levels play an important role. During cooling, the plasma Na^+ level was unchanged and there was a small transient fall in plasma K^+. These results are similar to those previously obtained by Covino & Hegnauer (1955) and Axelrod & Bass (1956). It seems unlikely that such small changes in plasma K^+ might give rise to the electrocardiographic abnormalities observed although it remains a possibility that bigger changes in myocardial K^+ levels may have been taking place, which were not reflected in the arterial levels.

Finally, because the electrophysiological basis of hypothermia-induced ventricular fibrillation is poorly understood, we attempted to examine the electrophysiological characteristics of cardiac cells excised from the hypothermic animals. The results obtained with the isolated ventricular muscle are difficult to interpret because the processes of isolation and perfusion with normal Krebs solution, probably eliminated the special conditions which occurred *in vivo*. For example, it is difficult to assess whether or not the initially very low RMP recorded in the bath existed *in vivo* purely as a result of hypothermia or as a consequence of fibrillation. Moreover, the RMPs of the control group recovered more rapidly towards normal values than those of the drug-treated group; this is probably due to the fact that the latter animals were exposed to a much lower temperature for a longer time. In both groups spontaneous activity, membrane oscillations, after depolarizations and second upstrokes (i.e. action potentials arising during the course of repolarization) were observed and there was no difference between the groups with regard to their frequency and occurrence. Some of these features have previously been reported in cooled cardiac tissue (Trautwein & Dudel, 1954; Sleator & De Gubareff, 1964) and all are thought to play a role in the initiation of cardiac dysrhythmias (Cranefield, 1975). It is not possible from these results to say that these abnormal action potentials definitely played a role in the initiation of hypothermic ventricular fibrillation, nor is it clear what the electrophysiological basis of the antidysrhythmic effect of ORG 6001 might be in this model. According to Salako, Vaughan Williams & Wittig (1976) the antidysrhythmic effect of this compound can be explained by an ability to reduce the maximum rate of rise of the cardiac action potential and hence to reduce conduction velocity *in vitro* (i.e. a 'class I' effect). In these *in vivo* experiments ORG 6001 also appeared to have a class I action, as evidenced by the prolongation of the P and QRS duration of the electrocardiogram over a limited temperature range (Figure 3). However, at the temperature at which fibrillation occurred, the only significant effect of ORG 6001 was a shortening of the QT_C interval. Although it was also observed that the action potential duration of the isolated drug-treated muscle was considerably shorter than in the control muscle, it is not known if this effect of ORG 6001 is relevant to the drug's antifibrillatory action in this hypothermic model.

The other characteristic electrocardiographic features in hypothermia which were observed in these experiments were J deflections and ST segment elevation. It was originally thought that J deflections were correlated with the development of fibrillation (Boba, 1959) but Emslie-Smith, Sladden & Stirling (1959) showed that J deflections are invariably found in hypothermia whether or not fibrillation ensued. This is supported by our own findings; J waves were observed in all 3 groups, including those animals which did not fibrillate. It has been postulated by MacLean & Emslie-Smith (1974) that the appearance of J deflections in the ECG are related to changes in action potential configuration during hypothermia, and in particular to the characteristic second peak of the action potential, which was also observed in the isolated ventricular muscle (Figure 7b).

Hypothermia also resulted in a marked ST segment elevation of the electrocardiogram in the control cats. These changes are thought to correlate with the extent of anaerobic metabolism (Karlsson, Templeton & Willerson, 1973) and we did in fact find that the ST segment changes were least marked in the artificially ventilated (Group 3) cats, in which there was also no change in the arterial lactate levels during cooling. ORG 6001 appeared to cause a small decrease in the ST segment elevation perhaps related to the ability of this drug to reduce lactate production in hypothermia.

In conclusion, although the dose of ORG 6001 used in this study (10 mg/kg) was not sufficient to abolish completely the occurrence of hypothermia-induced ventricular fibrillation, it did greatly reduce its incidence and severity and consequently increased the survival. The basis of this protective effect is not known but may be related either to the drug's class I antidysrhythmic properties and/or to an effect on lactate handling.

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(*Received December 11, 1978*)