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MECHANISM OF INCREASED SUSCEPTIBILITY TO FIBRILLATION OF THE HYPOTHERMIC MAMMALIAN HEART IN SITU

BY

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The susceptibility of auricles and ventricles to fibrillation during hypothermia of isolated hearts, and of hearts *in situ* in anaesthetized cats, was estimated by measuring the threshold for the production of fibrillation by electrical stimulation. Hypothermia reduced the threshold of *in situ* hearts, but increased the threshold of isolated perfused hearts and of heart-lung preparations. The increased sensitivity of *in situ* hearts to fibrillation could be induced by cooling the head only, and was abolished by cutting the vagi. At normal body temperature, section of the vagi had no influence on the fibrillation threshold. In contrast, cutting the sympathetic increased the fibrillation threshold of *in situ* hearts at normal temperature, but had no influence on the threshold during hypothermia. It was concluded that the increased susceptibility of anaesthetized animals to fibrillation could be attributed to changes in the central nervous control of the heart induced by the cooling of the head.

It is well known that one of the major limiting factors in the therapeutic application of artificial hypothermia is an increased susceptibility of the heart, especially of the ventricles, to fibrillation. Owing to the enhanced sensitivity to external stimuli, manipulation of the heart, which is unavoidable in heart surgery, can precipitate fibrillation (Hegnauer, D'Amato & Flynn, 1951; Bigelow, Lindsay & Greenwood, 1950). On the other hand, it has been shown by Szekeres & Lénárd (1960) that, in the isolated Langendorff preparation of cats and rabbits, susceptibility of the auricles and ventricles to fibrillation, evoked by electrical stimuli, was depressed to some extent by hypothermia. In these experiments the susceptibility to fibrillation was expressed by the fibrillation threshold, that is, by the minimal strength of current needed to produce fibrillation of the ventricles and auricles respectively. There is other evidence of a reduced susceptibility to fibrillation of the isolated heart during hypothermia. Indeed, cooling was found to be the most effective method for abolishing ventricular fibrillation produced by strong faradic stimuli or A.C. impulses in the Langendorff preparation of the rabbit heart (Dirken, Gevers, Heemstra & Huizing, 1955; Baumgartner, 1959). Prolonged fibrillation of Langendorff preparations, provoked by electrical stimulation in the presence of a reduced potassium concentration in the perfusion fluid, could not be induced in the hypothermic heart (Goodford, 1958), and the proportion of hearts fibrillating on a given calcium concentration of the perfusion fluid was reduced by cooling (Milton, 1959). Thus four independent investigations have shown a reduced susceptibility to fibrillation of the isolated Langendorff heart preparation during hypothermia.

It would be an advantage if the reason for this reduction in susceptibility to fibrillation of the isolated heart could be elucidated, for it might lead to a better understanding of the basic mechanism underlying the susceptibility to fibrillation in general, and might help towards an understanding why the mammalian heart *in situ* shows increased susceptibility during hypothermia, which would be of clinical value as well as of theoretical interest. The difference between the heart *in vivo* and *in vitro* might be occasioned by myocardial hypoxia or other metabolic deficiencies in the isolated preparation, or to extracardiac influences *in vivo*. Our present work is devoted to the investigation of differences between the behaviour of the mammalian heart in isolation and *in situ* during hypothermia. As in our earlier work, the reactions of both auricles and ventricles were considered separately in all experiments.

METHODS

Experiments were performed on 32 cats of both sexes with an average weight of 3.5 kg. The animals were anaesthetized with 1.5 ml./kg Dial-urethane solution (4% (w/v) Diallyl-barbiturate and 16% (w/v) ethyl-urethane) administered intraperitoneally. When artificial respiration just sufficient to prevent spontaneous respiration had been established, the thorax was opened by a midsternal approach. Two pairs of silver electrodes were introduced through small apertures made in the pericardium, and stitched to the ventral surface of the right ventricle and auricle respectively. The electrocardiogram was recorded by an oscillograph.

Fibrillation in both auricles and ventricles was induced by rectangular pulses of 1 msec duration and 30/sec frequency. The strength of the current passing through the heart could

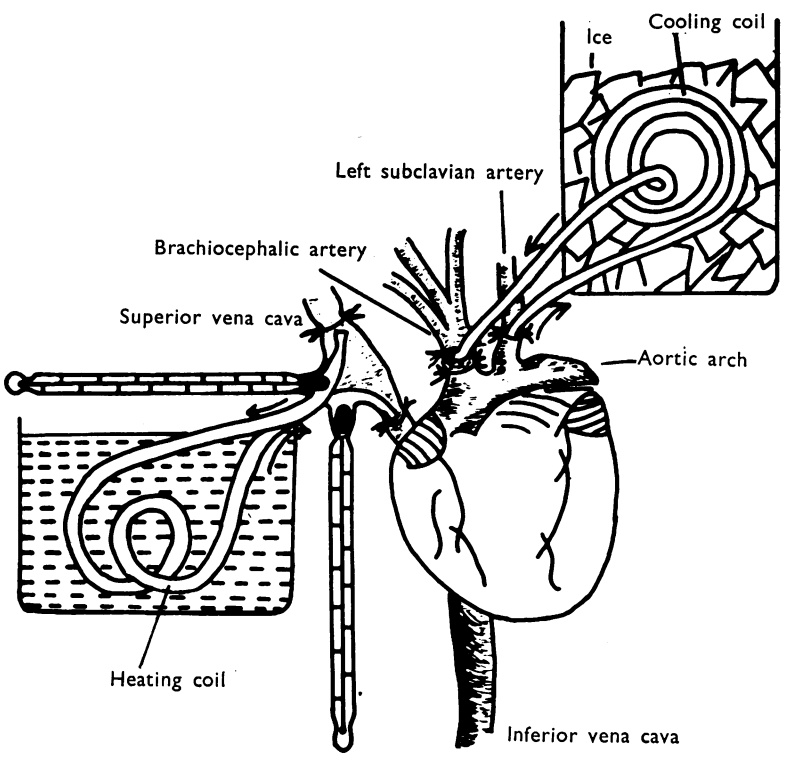

Fig. 1. Diagram of arrangement for cooling the head only.

be read directly in milliamps from a specially built oscilloscope (calibrations 1.0, 0.1, 0.05 and 0.01 mA/cm). This method was found to give reliable results in evaluating antifibrillatory drugs by DiPalma, Lambert, Reiss & Schults (1950), and had the advantage of requiring less complex equipment than techniques requiring the delivery of a stimulus during the "vulnerable period."

The temperature of the blood in the heart was measured by a thermocouple introduced into the right atrium. Hypothermia was produced either by extracorporeal cooling of the blood of the femoral artery by passing it through a polythene coil placed in ice, or in some of the experiments simply by placing ice bags into the abdominal cavity. The procedure used for isolated cooling of the head is summarized by the schematic diagram given in Fig. 1. The arterial blood flowing to the head was cooled by interrupting the brachiocephalic artery with a polythene tube immersed in ice. The venous blood returning from the head was rewarmed to body temperature similarly by a polythene rewarming coil inserted into the superior vena cava. Heart-lung preparations as described by Szegi and Rausch (1958).

RESULTS

Effect of hypothermia on the auricular and ventricular fibrillation threshold of hearts in situ *in normal anaesthetized cats.* Our first experiments were designed to investigate whether the well-known increased susceptibility to fibrillation of the hypothermic heart *in situ* could be demonstrated also by the quantitative method of determining the threshold for fibrillation by electrical stimuli. As the strength of the stimuli was increased, multiple extrasystoles, flutter and finally fibrillation appeared. The appearance of fibrillation was established (a) by direct observation of the cardiac activity, (b) by the electrocardiogram, (c) by the record of the blood pressure. Fibrillation stopped as soon as electrical stimulation was interrupted or immediately after it, as was expected in a heart as small as that of the cat. Fibrillation appeared at a well-defined and reproducible threshold. In normal anaesthetized cats the threshold for fibrillation diminished with cooling in both auricles and ventricles (Table 1). This finding, therefore, was in accord with the increased

TABLE 1

AURICULAR AND VENTRICULAR FIBRILLATION THRESHOLDS OF *IN SITU* HEARTS OF NORMAL ANAESTHETIZED CATS AT DIFFERENT BODY TEMPERATURES EXPRESSED AS A % OF THE VALUE AT 38° C

Figures represent means ± standard errors

	No. of experiments	Body temperature					
		38° C	35° C	31° C	28° C	25° C	21° C
Auricular fibrillation	7	100·0	76·6±8·9	75·8±0·9	70·3±11·5	66·6±6·6	44·5±10·7
Ventricular threshold	7	100·0	73·0±8·3	76·0±9·4	71·6±8·1	58·5±7·5	60·1±6·7

susceptibility to fibrillation of the hypothermic heart manipulated during cardiac surgery.

Effect of cooling on the thresholds for fibrillation of the heart-lung preparation of cats. In further experiments the Starling heart-lung preparation was used for estimation of the thresholds for fibrillation. In this preparation the heart is isolated from central influences, but is performing work under more physiological circumstances than the Langendorff preparation, and its oxygen supply is adequate for a 4 to 5 hr experiment even at 37° C. Nevertheless it reacted to cooling in the same

TABLE 2

AURICULAR AND VENTRICULAR FIBRILLATION THRESHOLDS OF THE STARLING HEART-LUNG PREPARATION OF CATS AT DIFFERENT BLOOD TEMPERATURES EXPRESSED AS % OF THE VALUE AT 38° C

Figures represent means±standard errors

	No. of experiments	Blood temperature 38° C	35° C	31° C	28° C	25° C	21° C
Auricular fibrillation	5	100·0	144·2±24·7	143·5±10·8	154·5±11·1	213·2±19·7	254·5±35·9
Ventricular threshold	5	100·0	138·1±36·2	140·4±14·7	165·5±16·1	193·0±18·2	209·0±2·13

way as did the Langendorff heart, namely, the threshold for fibrillation of both auricles and ventricles was not reduced but considerably raised by cooling (Table 2).

The influence of cooling on the threshold for fibrillation in the auricles and ventricles of the denervated heart in situ *in cats.* Hearts *in situ* in anaesthetized cats were denervated acutely, that is, both cervical vagi were cut and the stellate ganglion and the first five thoracic sympathetic ganglia on both sides were extirpated. As seen in Fig. 2, after eliminating the nervous control of the heart, the fibrillation threshold, particularly that of ventricles, increased suddenly and was no longer reduced but somewhat elevated by subsequent cooling. The susceptibility to

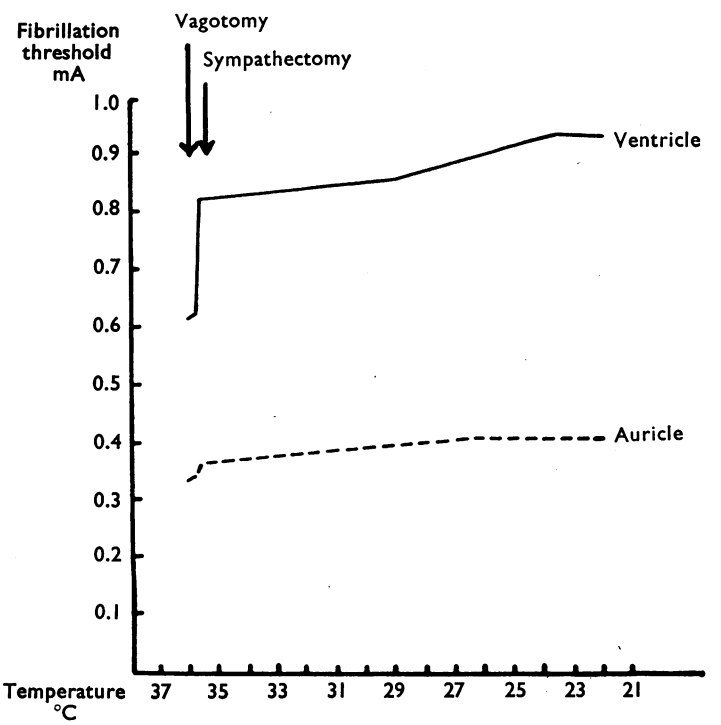

Fig. 2. The effect of cooling on the fibrillation threshold of the auricles and ventricles of the denervated *in situ* hearts of cats. Ordinate: fibrillation threshold. Abscissa: temperature.

fibrillation of the denervated heart *in situ* was thus changed by hypothermia in the same way as that of the isolated heart.

The effect of cooling of only the head on the fibrillation threshold of auricles and ventricles of the heart in situ *in anaesthetized cats.* In these experiments, the temperature of the heart and trunk was held constant throughout the experiments, but the head, whose nervous connexions with the heart were intact, was cooled gradually by the method described. As shown in Fig. 3, in spite of the unaltered

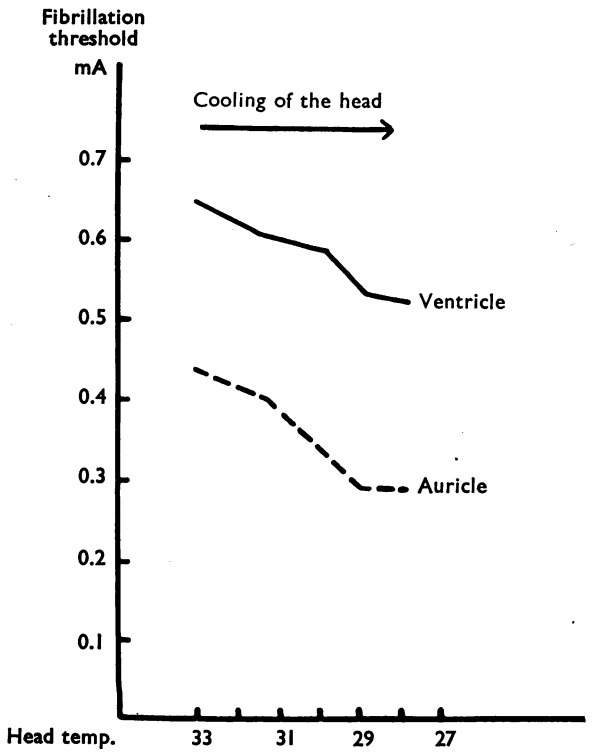

Fig. 3. The effect of cooling of the head only on fibrillation threshold of auricles and ventricles of the *in situ* heart of anaesthetized cats. Body temp., 34.5° C. Ordinate: fibrillation threshold. Abscissa: head temperature in ° C.

body and heart temperature the fibrillation threshold of both auricles and ventricles was now reduced by isolated cooling of the head, as it was when the whole animal was cooled.

Influence of the vagi on the hypothermic changes of auricular and ventricular fibrillation threshold of anaesthetized cats. When both vagi were cut in the neck (sympathetic left intact) cooling did not reduce fibrillation threshold, but both auricular and ventricular fibrillation thresholds increased (Table 3). Fibrillation appearing spontaneously in hypothermic animals could be occasionally restored to normal rhythm simply by eliminating vagal influence. Further, in the experiments

TABLE 3

THE EFFECT OF VAGOTOMY ON AURICULAR AND VENTRICULAR FIBRILLATION THRESHOLDS OF HEART *IN SITU* OF ANAESTHETIZED CATS AT DIFFERENT TEMPERATURES

Fibrillation thresholds expressed as % of the value at 38° C. Figures represent means±standard errors

	No. of experiments	Body temperature				
		38° C	35° C	31° C	28° C	25° C
Auricular fibrillation	7	100·0	108·6±4·0	106·5±8·8	114·6±7·1	149·9±8·2
Ventricular threshold	7	100·0	107·8±2·0	119·5±2·7	126·1±7·1	145·0±26·1

in which the head alone was cooled, the fall of the fibrillation threshold could be prevented by previous vagotomy, and when the vagi were cut during hypothermia the threshold for fibrillation suddenly increased above the control values (Fig. 4). When the vagi were cut at normal body temperature, the thresholds for fibrillation were not significantly changed (Table 4). The thresholds were much raised if the sympathetic nerves were cut and the vagi left intact. Sympathectomy had no effect during hypothermia (Fig. 5).

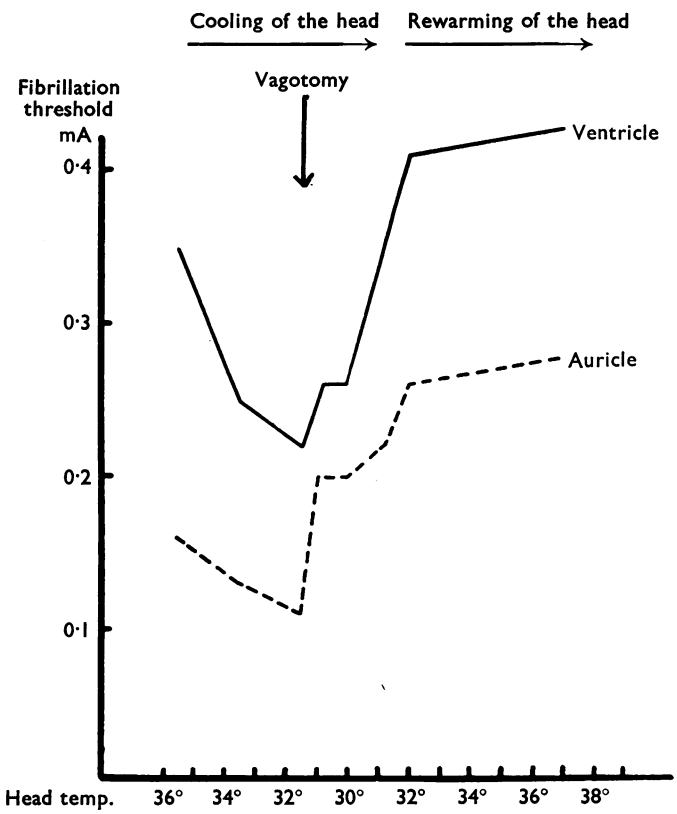

Fig. 4. Effect of vagotomy on fibrillation threshold of auricles and ventricles of the *in situ* heart if only the head is cooled. Body temp., 37° C. Ordinate: fibrillation threshold. Abscissa: head temperature.

TABLE 4

THE EFFECT OF SECTIONING OF THE VAGI AT DIFFERENT BODY TEMPERATURES ON FIBRILLATION THRESHOLD OF AURICLES AND VENTRICLES OF *IN SITU* HEARTS OF CATS

Figures represent fibrillation threshold in milliamps

			Fibrillation threshold				
		No. of experiments	Before vagotomy	After vagotomy	Difference	% difference	*P*
Auricles	37–38° C	7	0·454	0·498	0·443±0·053	+9·7	>0·50
	20–25° C	9	0·268	0·443	0·175±0·055	+65·1	>0·01 <0·02
Ventricles	37–38° C	7	0·724	0·690	0·034±0·06	−4·9	>0·50
	20–25° C	9	0·432	0·530	0·098±0·038	+22·7	>0·02 <0·05

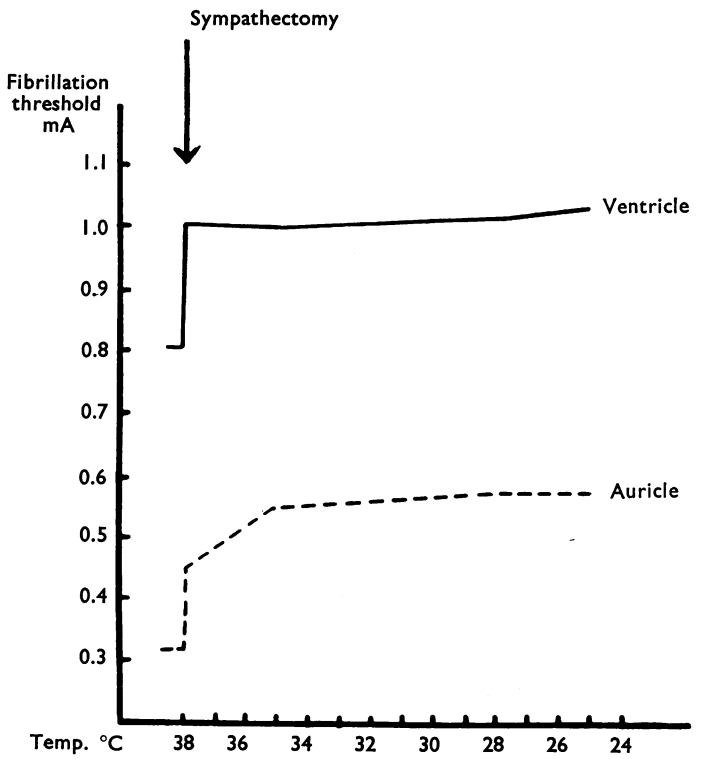

Fig. 5. Influence of sympathectomy on the auricular and ventricular fibrillation threshold of anaesthetized cats. Ordinate: fibrillation threshold. Abscissa: temperature.

DISCUSSION

There is at present no reliable method for stopping the fibrillation which may occur during hypothermia other than the rather drastic one of electrical countershock, which can be used only under suitable circumstances. It is to be hoped, therefore, that a detailed study of factors which increase or decrease the susceptibility

of the heart to fibrillation may lead to control by pharmacological means. To quote Angelakos, Laforet & Hegnauer (1957), " Experimental hypothermia, in addition to providing fundamental information needed for its successful application in surgery, can serve as an excellent experimental technique for the study of those factors which establish a condition rendering the ventricle highly susceptible to fibrillation. . . . "

The investigations reported here, carried out on the hearts of anaesthetized cats *in situ* by the fibrillation threshold method, agree with the observations made on patients, by heart surgeons, that at subnormal body temperatures manipulation of the ventricles leads much more easily to fibrillation. They also confirm the results of Covino & Beavers (1957), who found, using strong single shocks applied during the " vulnerable period " of the heart cycle, that the threshold current required to produce fibrillation of dog ventricles was lower during hypothermia. In addition our experiments have indicated that not only the ventricles but also the auricles of the heart *in situ* become more susceptible to fibrillation at lower temperatures. This observation may explain, at least in part, the arrhythmia which often precedes the onset of ventricular fibrillation.

As the threshold to fibrillation during hypothermia was raised not only in Langendorff hearts, but also in heart-lung preparations (in which there would be no reason to suppose that the myocardium was anoxic), it was unlikely that anoxia could account for the different responses to hypothermia of the isolated and *in situ* preparations.

When the head alone was cooled, the heart and trunk being maintained at normal body temperature, the fibrillation threshold was decreased, that is, the same result was obtained as when the whole animal was cooled. This suggested that impulses from the central nervous system were responsible for the difference in behaviour of *in situ* and isolated hearts. If the vagi were cut before or during hypothermia, the *in situ* heart then immediately resembled the isolated preparation, and the threshold was no longer diminished but higher than the control at body temperature. The importance of the vagi was underlined also by the observation that occasional spontaneous self-sustaining fibrillation due to cooling was often reverted to normal rhythm by section of the vagi.

The role of vagal stimulation (Winterberg, 1907) and of acetylcholine (Burn, 1960) in production of atrial flutter and fibrillation is well known, and the observations of Vaughan Williams (1958), who showed that acetylcholine increases the rate of both repolarization and depolarization of the intracellularly recorded action potential, as well as accelerating conduction velocity, provide an explanation for the action of the vagus shown here in decreasing the threshold for fibrillation.

There is, however, conflicting evidence concerning the role of cholinergic mechanisms in fibrillation. Armitage, Burn & Gunning (1957) found that in contrast to its effect on auricles, carbamylcholine failed to alter the response of the ventricles of the Langendorff preparation to stimulation and did not provoke long continued fibrillation. Moreover, Montgomery, Prevedel & Swan (1954) found that intracoronary perfusion of prostigmine to hypothermic dogs actually reduced the susceptibility of ventricles to fibrillation, but in contrast to this Scherf, Bussan, Gittinger & Torin (1955) could show no protective action by acetylcholine and

prostigmine against ventricular fibrillation elicited by focal cooling, and Malinow, Battle & Malamud (1954) found that *atropine* could prevent ventricular arrhythmias in rats.

Since cutting the vagi at normal body temperature did not influence susceptibility to fibrillation, it is probable that the difference between the behaviour of *in situ* and isolated hearts is due to an increased output of vagal impulses induced by hypothermia of the brain, though the possibility of an increased sensitivity of the heart to vagal impulses as an additional factor was not excluded. The abolition of the increased susceptibility to fibrillation during hypothermia by vagal section made it unlikely that hormonal influences were of much significance.

Section of the sympathetic increased the threshold to fibrillation in hearts at normal temperature, but had no influence during hypothermia. It is possible that the metabolic effects of adrenaline become less important on biochemical reactions already slowed down by cooling.

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