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THE EFFECT OF SYMPATHOMIMETIC AMINES ON THE VENTRICULAR FIBRILLATION THRESHOLD IN THE RABBIT ISOLATED HEART

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1 The ventricular fibrillation threshold (VFT) was measured in the isolated heart of the rabbit perfused via the aorta with McEwen's solution at 37°C by applying a single 10 ms pulse of current during the vulnerable period of late systole. The arrhythmia induced was either fibrillation or a rapid tachycardia.

2 The catecholamines adrenaline, noradrenaline and isoprenaline, but not dopamine, when infused at rates which produced similar moderate effects on cardiac rate and force, significantly lowered the VFT; it was reduced slightly more by adrenaline than by the other two. Phenylephrine and methoxamine were ineffective. Only those sympathomimetic amines which lowered the VFT also shortened the vulnerable time, i.e. minimal time after the R-wave of the ECG at which the pulse had to be applied to induce the arrhythmia.

3 The lowering effect of adrenaline on the VFT was not influenced by phentolamine but was blocked by propranolol and pindolol.

4 Chloroform potentiated the lowering effect of adrenaline, but not that of isoprenaline, on the VFT. Carbachol did not alter the effect of adrenaline on the VFT.

5 The results indicate that adrenaline, noradrenaline and isoprenaline lower the VFT by a direct action on the cardiac musculature and that this effect is mediated via β-adrenoceptors.

Introduction

It has been well authenticated that catecholamines may induce cardiac arrhythmias and occasionally ventricular fibrillation. Some workers have suggested that an increased vagal discharge to the heart may play a significant role in the induction of ventricular arrhythmias and fibrillation by adrenaline (Riker, Depierre, Roberts, Roy & Reilly, 1955). Depression of sino-atrial node activity (Roberts & Baer, 1960) and of atrio-ventricular nodal conduction (Dresel, 1962) are believed to permit the emergence of ventricular pacemakers due to the loss of driving dominance by the higher pacemaker. On the other hand acetylcholine (MacLeod & Reynolds, 1964) and methacholine (Hoff & Nahum, 1934) have been shown to suppress or reduce ventricular adrenaline-induced arrhythmias and vagal stimulation to increase the ventricular fibrillation threshold (Kent, Smith, Redwood & Epstein, 1973). Various anaesthetics, e.g. chloroform (Oliver & Schäfer, 1895; Levy & Lewis, 1911-12), cyclopropane (Meek, Hathaway & Orth, 1937), halothane (Andersen & Johansen, 1963) and other agents, e.g. benzol (Wégria & Nickerson, 1943) sensitize the dog and cat heart muscle so that an intravenous injection of adrenaline or noradrenaline induces ventricular fibrillation in a high proportion of trials. However, isoprenaline, invariably failed to induce ventricular fibrillation under similar circumstances (Garb & Chenoweth, 1948) but did induce a ventricular tachycardia (Katz, 1965).

In the studies quoted where the anaesthetic agent sensitized the heart to the sympathomimetic amine, the experiments were carried out on the anaesthetized animal where merely the incidence of a ventricular tachycardia and/or fibrillation was recorded after a chosen dose of the sympathomimetic amine which gave an all-or-none response. In all these studies the whole animal was used and it was not possible to know whether the sympathomimetic amine was acting directly on the heart or whether the latter was being largely influenced by secondary factors, e.g. reflex autonomic nerve activity, increased plasma potassium and free fatty acids etc.

Consequently it appeared desirable to investigate the arrhythmic effect of the sympathomimetic amines directly on the isolated Ringer-perfused heart (Langendorff preparation) and to measure on a quantitative basis the change produced on a selected parameter which could

account for the induction of the arrhythmia. The parameter chosen for study was the ventricular fibrillation threshold (VFT), i.e. the minimal value of a single pulse of current applied during the vulnerable period of late systole which was required to induce ventricular fibrillation or a rapid tachycardia in the isolated perfused heart of the rabbit; Han, de Jalon & Moe (1964) had shown in the dog anaesthetized with pentobarbitone that an intravenous infusion of adrenaline or noradrenaline initially lowered the VFT.

The purpose of the present investigation was four-fold in its approach: (1) to compare the effect of four catecholamines (adrenaline, noradrenaline, isoprenaline and dopamine) and two other sympathomimetic amines on the VFT in the rabbit isolated perfused heart, (2) to demonstrate whether this effect was mediated via α- or β-adrenoceptors, (3) to determine whether chloroform sensitizes the ventricular muscle to catecholamines by potentiating the lowering effect of the latter on the VFT, and (4) to study whether carbachol, used to simulate increased parasympathetic activity, influences the effect of adrenaline on the VFT. The results indicate that the catecholamines, with the exception of dopamine, significantly lower the VFT but that the α-agonists phenylephrine and methoxamine are ineffective; that this lowering of the VFT is abolished by β-adrenoceptor blockade but not by α-blockade; that adrenaline, but not isoprenaline, lowers the VFT significantly more in the presence of chloroform; and that the lowering effect of adrenaline on the VFT is not significantly increased by carbachol.

Methods

Ventricular fibrillation or a rapid tachycardia was induced in rabbit hearts perfused via the aorta with McEwen's (1956) solution at 37°C by the method described previously (MacConaill & Murnaghan, 1967; Murnaghan, 1971; 1973). The fibrillation threshold was determined by measuring the minimal strength needed to produce arrhythmia of a 10 ms square-wave pulse of current applied after each 8th heart beat during the vulnerable period of late systole. It was achieved by testing at 5 ms steps during the latter half of the R-T interval. The minimal acceptable duration of the induced arrhythmia was set at 1 s because of difficulty in differentiating it from groups of 3 or 4 multiple extrasystoles.

The type of arrythmia induced, monitored on a large oscilloscope screen (Airmec), was recorded as fibrillation or tachycardia. The duration of the arrhythmia was listed as persistent ($>$ 60 s) or non-persistent. If a normal rhythm had not returned after 60 s, defibrillation was effected by manually infusing 0.3 M KCl (usually 0.5 ml sufficed) into the aortic cannula. The term ventricular fibrillation threshold (VFT) was used to indicate the minimal current required to induce either fibrillation or tachycardia. In order to indicate the magnitude of change produced by the sympathomimetic amine on the VFT despite the variation in magnitude of the latter among hearts, the VFT change ratio was calculated, i.e. the VFT in the presence of the sympathomimetic amine/VFT of the control. If the sympathomimetic amine was combined with another drug then the latter alone acted as control. The minimal time after the R wave of the ECG at which the 10 ms pulse had to be applied to induce the arrhythmia was called the vulnerable time.

The perfusion apparatus consisted of three heat-exchange glass columns connected to a perspex block fitted with a tap so that the fluid from any one column could be selected. Each column was fed from a reservoir bottle; the perfusion fluid was gassed with 5% CO_2 in O_2 within each column. At the front of the block an opening, with tap, permitted the injection of KCl into the perfusion fluid just above the aortic cannula; at the back of the block was an opening with tap for removal of air bubbles from the cannula when required. All drugs with the exception of the catecholamines were incorporated in the perfusion fluid. To avoid oxidative destruction of the catecholamine it was dissolved in 160 mM sodium chloride acidified with HCl to pH 5 and infused by a syringe pump at a constant rate into the aortic cannula via an opening on the side of the perspex block. Infusion of the acidic saline solution alone failed to influence the VFT. While the infusion rates for a catecholamine were very similar in the different hearts, its concentration in the perfusion fluid unavoidably varied because of the variable coronary perfusion flow rates. However, the mean concentrations did not differ significantly between the groups under comparison.

The results are usually expressed by the arithmetic mean with its standard error. Significance of difference was determined by Student's t test or the Chi-square test where appropriate.

Drugs used were: adrenaline hydrogen tartrate (Farbwerke Hoechst AG.), noradrenaline bitartrate (Winthrop), isoprenaline hydrochloride (Winthrop), dopamine hydrochloride (Calbiochem.), phenylephrine hydrochloride (Winthrop), methoxamine hydrochloride (Burroughs Wellcome & Co.), propranolol (ICI), pindolol (Sandoz Products Ltd.), phentolamine (Ciba), carbachol (Koch-Light) and chloroform (B.D.H.).

Results

All four catecholamines adrenaline, noradrenaline, isoprenaline and dopamine when infused for 2-15 min at rates indicated in Table 1 caused in most trials an increase in the diastolic tension of the heart, a positive inotropic and chronotropic response and an increase in coronary flow of approximately similar magnitudes. This increase in coronary flow induced by the catecholamine largely disappeared after several hours of perfusion by which time the heart had become oedematous. Propranolol 0.3 μM and pindolol 1 μM completely inhibited the chronotropic but not the inotropic response of the catecholamine.

Phenylephrine and methoxamine, which are considered to be 5-10 times less potent than adrenaline as pressor agents, were added to the perfusion fluid to give a concentration which was an equivalent number of times greater than that attained by adrenaline during its infusion. Both drugs increased the diastolic tension but had little or no effect on the systolic force or coronary flow; phenylephrine, however, increased the heart rate in three out of five trials.

In two experiments the Q-T interval was measured during the infusion of adrenaline. It shortened more than could be accounted for by the increase in heart rate suggesting a direct shortening in the duration of the ventricular action potential.

Effect of sympathomimetic amines on the ventricular fibrillation threshold

Adrenaline when infused at a rate of 8-32 nmol/min lowered the VFT in 22 out of 24 trials. The mean infusion rate of 24 ± 2.5 nmol/min corresponded to a concentration of 2.44 ± 0.44 μM in the perfusion fluid and the mean duration of the infusion was 6 ± 0.58 minutes. This lowering of the VFT could be produced at least 2-3 times in the same heart and had passed off 15-30 min after termination of the infusion. The preceding control values for the VFT varied between 3.2-20 mA in the 24 trials on 11 rabbit hearts; the range during the adrenaline infusion was 0.9-9 mA. The mean VFT change ratio (VFT of test/VFT of control) of 0.56 ± 0.05 was significantly different from unity at the 0.1% level (Table 1). It did not differ significantly among the three subgroups at infusion rates of 8, 16 and 32 nmol/minute. Noradrenaline at a mean infusion rate of 23.3 ± 2.5 nmol/min (concentration 2.15 ± 0.35 μM) lowered the VFT in 8 out of 11 trials on 3 hearts while isoprenaline at approximately one-fifth the infusion rate (and concentration) of the other two lowered it in 7 out of 12 trials in 6 hearts. Their respective VFT change ratios of 0.72 ± 0.08 and 0.79 ± 0.06 were significantly different from unity but not from each other. However the value for isoprenaline, but not of noradrenaline, was significantly different ($P < 0.01$) from that for adrenaline. Both dopamine, when infused at a rate approximately 100 times greater than that of adrenaline, and phenylephrine and methoxamine, when perfused in a concentration approximately 9 times greater than that attained by adrenaline failed to alter significantly the VFT change ratio (Table 1).

In order to determine whether the sensitization produced by chloroform of the ventricle to

Table 1 Effect of sympathomimetic amines on induced ventricular fibrillation

Amines	*Drug*	*Infusion rate (nmol/min)*	*Concentration (μM) Drug or Amine*	*Proportion of trials VFT was reduced*	*VFT change ratio (Mean ± s.e. mean)*	*Value P*
Adrenaline	–	24 ± 2.5	–	22/24	0.56 ± 0.05	0.001
Adrenaline	Chloroform	32	1 mM	8/8	0.24 ± 0.01	0.001*
Adrenaline	Carbachol	28 ± 4.0	0.4	4/4	0.60 ± 0.05	NS*
Adrenaline	Phentolamine	32	1.0	3/3	0.49 ± 0.17	NS*
Adrenaline	Beta-blockade	32	P – 0.3 L – 1.0	0/2	1.14 ± 0.15	0.01*
Noradrenaline	–	23 ± 2.5	–	8/11	0.72 ± 0.08	0.02
Noradrenaline	Propranolol	16	0.3	0/1	1.22	NS*
Isoprenaline	–	5.1 ± 1.2	–	7/12	0.79 ± 0.06	0.01
Isoprenaline	Chloroform	3.7 ± 1.2	1 mM	3/6	0.82 ± 0.18	NS*
Dopamine	–	2460 ± 530	–	3/8	0.95 ± 0.06	NS
Phenylephrine	–	–	23.2 ± 4.8	2/5	0.97 ± 0.15	NS
Methoxamine	–	–	20.0 ± 5.8	1/4	1.26 ± 0.32	NS

* Comparison with catecholamine alone in same hearts.
P—propranolol, L—pindolol, in column 4.

develop arrhythmias and even ventricular fibrillation when exposed to adrenaline could be related to an increased lowering of the VFT, chloroform was incorporated in the McEwen's solution in a concentration of 1 mM which is approximately equivalent to the blood concentration achieved during anaesthesia with this agent. The chloroform caused a temporary depression in cardiac contractility and an insignificant increase in the VFT. When adrenaline was now infused the VFT was markedly reduced; the mean VFT change ratio of 0.24 ± 0.01 in 8 trials on three hearts was significantly lower ($P < 0.001$) than that produced by adrenaline in the absence of chloroform (0.53 ± 0.05) in a similar number of trials on the same hearts (Table 1). When, however, isoprenaline was infused in the presence of chloroform it failed to lower the VFT more than that of isoprenaline alone. This result confirms the work of Garb & Chenoweth (1948) who showed that chloroform sensitized the ventricles of the cat *in situ* to fibrillate to adrenaline but not to isoprenaline.

In order to determine whether parasympathetic activity could increase the predisposition to ventricular fibrillation produced by adrenaline, carbachol was incorporated in the McEwen's solution in a concentration of 0.25-1 μM. During the perfusion with carbachol the heart rate fell so markedly that the atria had to be driven by a second stimulator at a rate of 60-80% that of the control spontaneous rate. More rapid driving could not be used as it resulted in a 2/1 A-V block. The carbachol alone did not significantly alter the VFT and when adrenaline was now infused it caused a reduction in the mean VFT change ratio to 0.60 ± 0.05 which was not significantly different from that with adrenaline alone (Table 1).

In order to determine whether the lowering effect by the catecholamines on the VFT was mediated via α- or β-adrenoceptors, the α-adrenoceptor blocking agent phentolamine was added to the perfusion fluid to give a concentration of 1 μM. Phentolamine had no effect on the VFT and it did not prevent adrenaline from lowering it (Table 1) indicating that the reduction of the VFT produced by adrenaline is not exerted via the α-receptors. This was confirmed by the finding that the α-agonists phenylephrine and methoxamine failed to lower the VFT. When propranolol (0.3 μM) or pindolol (1 μM) was included in the perfusion fluid they prevented adrenaline or noradrenaline from lowering the VFT, indicating that the reduction of the VFT by the catecholamine is exerted via the β-adrenoceptors. In the concentrations used the two β-adrenoceptor blocking agents alone did not alter the VFT.

Effect of the sympathomimetic amines on the duration of the arrhythmia

In order to determine whether the sympathomimetic amines influenced the duration of the arrhythmia, the proportion of trials in which the induced arrhythmia was persistent was recorded. In 98 out of 163 trials the arrhythmia was persistent in the control and in 22 out of 30 trials during the test in those hearts where adrenaline was infused. The respective values for the control and test with the other sympathomimetic amines were: noradrenaline 26/42 and 10/12, isoprenaline 58/103 and 13/13, dopamine 25/41 and 6/8, phenylephrine 24/41 and 11/11 and methoxamine 20/31 and 10/15. Although adrenaline, noradrenaline, isoprenaline and dopamine increased the proportion of persistent arrhythmias when com-

Table 2 Effect of sympathomimetic amines on vulnerable times in rabbit isolated heart

	Control (ms)	*Test (ms)*	P *value*
Adrenaline	82 ± 1.7(175)	71 ± 5.1(30)	< 0.02
Adrenaline + carbachol	94 ± 4.2 (17)	60 ± 18.6 (4)	NS
Adrenaline + chloroform	111 ± 3.0 (10)	63 ± 13.8 (4)	< 0.001
Adrenaline + β-blockade	66 ± 7.5 (5)	90 ± 5.8 (3)	NS
Adrenaline + phentolamine	106 ± 3.7 (16)	43 ± 14.4 (4)	< 0.001
Noradrenaline	62 ± 2.1 (46)	50 ± 5.3(12)	< 0.05
Noradrenaline + β-blockade	50 ± 5.8 (3)	45	NS
Isoprenaline	84 ± 1.6(121)	61 ± 5.8(12)	< 0.001
Isoprenaline + chloroform	96 ± 3.9 (16)	74 ± 17.6 (6)	NS
Dopamine	77 ± 3.1 (37)	78 ± 11.2 (6)	NS
Phenylephrine	63 ± 3.0 (49)	62 ± 4.6(11)	NS
Methoxamine	75 ± 1.9 (31)	74 ± 5.0(16)	NS

Mean value with s.e. mean in ms is given. Number of values indicated in parentheses.

pared with the corresponding controls, the increase was not significant except for isoprenaline ($P < 0.01$) or for all four catecholamines combined ($P < 0.01$). Of the remaining two sympathomimetic amines only phenylephrine significantly increased ($P < 0.05$) the proportion of arrhythmias which were persistent.

Chloroform and carbachol alone did not alter the proportion of the arrhythmias which were persistent. During the adrenaline infusion the arrhythmia was persistent whether chloroform or carbachol was or was not present. There was no indication that the drugs used altered the type (fibrillation or tachycardia) of the induced arrhythmia.

Effect on the vulnerable time

The vulnerable times (VT), i.e. the minimal times in ms after the R-wave at which the electrical square-wave 10 ms pulse was effective in inducing the arrhythmia, are listed in Table 2. Adrenaline alone or when combined with chloroform or phentolamine and noradrenaline and isoprenaline alone significantly shortened the VT. Beta-blockade by propranolol and pindolol prevented this. Although the mean values of adrenaline with carbachol and isoprenaline with chloroform were less than that due to carbachol and chloroform alone respectively, the differences were insignificant because of occasionally large or small values in the former groups. Chloroform and phentolamine alone significantly lengthened the VT from the control McEwen solution values. Beta-blockade and carbachol alone had no significant effect.

Since the vulnerable period occurs during the rapid repolarization phase these results indicate that adrenaline, noradrenaline and isoprenaline, but not dopamine, phenylephrine or methoxamine, either cause the vulnerable period to start at an earlier stage of repolarization or shorten the duration of the ventricular action potential. As adrenaline has been shown to shorten the duration of the Q-T interval the latter is the more probable. Shortening of the duration of electrical systole by these three catecholamines appears to be a prerequisite for lowering of the VFT to occur.

Discussion

The catecholamines adrenaline, noradrenaline and isoprenaline, but not dopamine, when infused at rates which produced similar moderate positive chronotropic and inotropic effects have been shown in this study to lower significantly the ventricular fibrillation threshold (VFT). In a previous preliminary study (MacConaill & Murnaghan, 1967) with adrenaline the results were equivocal. When the adrenaline was infused at the rate of 8 nmol/min, in 8 tests the mean VFT was just significantly lower than the control. However, with infusions of 32 nmol/min a fall in the VFT occurred in three experiments, no change occurred in one and there was a marked rise in the threshold to 5-10 times the control on three separate trials in one experiment only. In the present study where an infusion rate of adrenaline of 8-32 nmol/min was used the VFT was lowered in 22 out of 24 trials and a rise in threshold was never seen. At least one essential difference existed between the two studies. In the initial study the average time after the start of the adrenaline infusion at which the threshold was determined was approximately 2.5 min; in this study it was 6 minutes. These results would appear to suggest that the lowering effect on the VFT may be more apparent after a sufficient elapse of time. This fall in the VFT is clearly mediated via β-adrenoceptors because it is blocked by β- but not α-receptor blocking agents. Although Papp & Szekeres (1968a) had previously demonstrated this in the whole anaesthetized animal the present study clearly shows that the action can be exerted directly on the heart itself. It is presumed that this fall induced in the VFT during the administration of adrenaline, noradrenaline and isoprenaline predisposes to the initiation of the rapid ventricular tachycardia or fibrillation; whether it contributes to the maintenance of the arrhythmia remains equivocal. Although all the catecholamines increased the incidence of a persistent arrhythmia this change was only statistically significant with isoprenaline.

Han *et al.* (1964) showed that in the pentobarbitone anaesthetized dog an intravenous infusion of adrenaline or noradrenaline first lowered the VFT of the heart *in situ* and subsequently raised it but that left stellate ganglion stimulation only lowered it. Papp & Szekeres (1968a) in an extension of this study showed that isoprenaline only lowered the VFT in the dog. These results in conjunction with those in this present study suggest that the rise in the VFT is possibly extracardiac in origin and may involve excitation of α-adrenoceptors.

It is believed that ventricular fibrillation is usually triggered by an ectopic beat falling on the early part of the T-wave of the preceding beat. During this vulnerable period there is a lack of homogeneity in recovery of excitability of the ventricular fibres so that aberrant rhythms can arise if a sufficient flow of current occurs between fibres in different stages of polarization. Such a flow can be triggered by an ectopic beat or by an externally applied pulse of current when it occurs during this vulnerable phase of the cardiac cycle. If

this lack of homogeneity is magnified it is possible that the arrhythmia can originate spontaneously because the endogenous current generated will now be adequate to initiate it. Such a phenomenon is referred to as microre-entry. Adrenaline initially not only shortens the refractory period of ventricular muscle but also exaggerates the inhomogeneity as measured by the increase in temporal dispersion of the refractory period; subsequently it lengthens the refractory period and decreases its temporal dispersion in the whole animal (Papp & Szekeres, 1968b). These respective early and late changes appear to correlate well with the initial decrease and subsequent increase in the VFT.

Dopamine is a catecholamine which is being used increasingly to treat patients with congestive heart failure, shock and hypotension. It is of interest to note in this study that when used in an approximate equipressor concentration to that of noradrenaline it failed to lower the VFT. Katz, Lord & Eakins (1967) have recommended its use in hypotension and shock in patients anaesthetized with cyclopropane or halogenated hydrocarbons because it appeared less likely to induce cardiac arrhythmias than the other sympathomimetic amines which are used as vasoconstrictor agents.

Phenylephrine and methoxamine have also been advocated as the pressor agents of choice particularly during anaesthesia with cyclopropane and halogenated hydrocarbons (Orth, Leigh, Mellish & Stutzman, 1939; Stutzman, Pettinga & Fruggiero, 1949) as they were less likely to predispose to ventricular arrhythmias than the other sympathomimetic amines tested. This belief is confirmed by the evidence in this study in that both amines failed to lower the VFT. In fact Papp & Szekeres (1968a) showed in the anaesthetized dog that phenylephrine and methoxamine raised the VFT but as explained previously, this increase may be due to an indirect action as it did not occur here in the isolated heart. Although the results of this study suggest that methoxamine may be preferable to phenylephrine because it did not increase the proportion of persistent arrhythmias, it is improbable that this finding is of significance in man because ventricular fibrillation is invariably persistent in the human species.

The results of this and the previous study by the author clearly indicate that chloroform potentiates the lowering effect of adrenaline on the VFT. It appears logical to assume that this effect might play an important role in the production of ventricular fibrillation by adrenaline during sensitization with chloroform and other substituted and unsubstituted hydrocarbons. It is of interest to note that Garb & Chenoweth (1948) failed to induce ventricular fibrillation when isoprenaline was injected into the cat anaesthetized with chloroform. This would appear to substantiate the finding in this study that chloroform failed to increase the lowering effect of isoprenaline on the VFT. However, other factors apart from sensitization could account for this fortuitous agreement. These workers used a very large dose of isoprenaline which would have caused considerable hypotension due to its vasodilator property. This effect may be of significance because hypertension induced by a sympathomimetic amine may contribute, in part, towards the induction of an arrhythmia (Nickerson & Nomaguchi, 1949; Nickerson & Smith, 1949). Katz (1965) showed that chloroform sensitized the heart to a non-malignant arrhythmia when he used threshold doses of isoprenaline. It would appear that the sites of origin of tachycardias and ventricular fibrillation may be different (Dresel & Sutter, 1961). Nathanson & Miller (1949) have presented evidence to indicate that multifocal arrhythmias including fibrillation induced by adrenaline originate in ventricular and/or Purkinje muscle while those arrhythmias induced by isoprenaline arise invariably at the A-V node. Indeed Dresel & Sutter (1961) could only induce a nodal rhythm in the dog anaesthetized with cyclopropane despite the use of very large doses of isoprenaline.

The results on the effect of carbachol are equivocal. In four trials in the previous study by the author carbachol significantly ($P < 0.01$) potentiated the effect of adrenaline; in four trials in the present study it failed to do so. When the results are combined the effect is barely significant at the 5% level. As mentioned earlier, adrenaline alone in the previous study only lowered the VFT slightly but exerted a considerable lowering effect in this study. This suggests that carbachol can only potentiate adrenaline if the effect of adrenaline alone is marginal. It is difficult to compare these results with those in the literature where the experimental conditions have been completely different. It is highly unlikely that an infusion of a parasympathomimetic agent will have identical effects to vagal stimulation because the former could act at sites not reached by the acetylcholine liberated at the vagal nerve terminals. (Compare the effects of an infusion of noradrenaline with stimulation of the sympathetic nerve fibres to the heart on the VFT). Furthermore Dresel & Sutter (1961) have shown that the roles of the vagus in the initiation of ventricular arrhythmias and fibrillation are probably not identical because vagal stimulation in the cyclopropane anaesthetized dog increased the dose of adrenaline required to produce a bigeminy rhythm but not that required to cause ventricular fibrillation.

Apparently the effects of cholinergic activity on sensitization to adrenaline can be as contradictory in the isolated heart as on the heart *in situ*.

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