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Pharmacological analysis of established ventricular fibrillation

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1 The effects of anti-arrhythmic drugs on the power spectrum of established ventricular fibrillation induced by endocardial electrical stimulation, have been studied in greyhounds anaesthetized with sodium pentobarbitone (35 mg kg^{-1}, i.v.).

2 In dogs receiving no drug, initial recording of ventricular fibrillation showed a dominant frequency of 9.9 ± 0.7 Hz (lead II) and 10.0 ± 0.6 Hz (endocardium). After 3.3 min the frequency had fallen to 4.0 ± 0.4 Hz in lead II, but remained high in the endocardium (10.7 ± 0.5 Hz).

3 Lignocaine significantly reduced the dominant frequency for fibrillation recorded from lead II at (0–80 s), and for endocardial fibrillation at (0–200 s).

4 Pretreatment with propranolol or bretylium had little effect on the time course of the dominant frequency of fibrillation in lead II or the endocardium.

5 Verapamil prevented the fall in frequency seen in lead II after 80 s in the no drug group. A significantly higher frequency was maintained in both lead II (14.7 ± 0.9 Hz) and the endocardium (14.8 ± 0.9 Hz) for 3.3 min, compared with the no drug group ($P < 0.01$).

6 Activation of fast sodium channels may determine the rapid frequency of the initial stages of ventricular fibrillation. The rapid fall in dominant frequency in lead II after fibrillation for 80 s can be prevented by calcium channel blockade and may be due to intracellular accumulation of calcium.

Introduction

Ventricular fibrillation develops in some 18% of patients treated within the first hour after acute myocardial infarction (Pantridge *et al.*, 1974). Antiarrhythmic agents are often administered to prevent ventricular fibrillation in patients with acute infarction, or with arrhythmias associated with chronic ischaemic heart disease. For example, class I and class III drugs are often given to prevent ventricular arrhythmias such as ventricular fibrillation, and early intervention with class II drugs is reported to reduce mortality after acute myocardial infarction (First International Study, 1986). Many studies have been made of the effects of such drugs on the electrical activity in normal and diseased myocardium, and the drugs have been classified on this basis (Singh & Vaughan Williams, 1972; Vaughan Williams, 1984). However the effects of such drugs on established fibrillation are largely unknown.

It is now recognized that ventricular fibrillation is not a totally random arrhythmia, and that the ECG signal shows a degree of electrical regularity. The frequency content of ventricular fibrillation changes with time in a characteristic fashion (Worley *et al.*, 1985; Martin *et al.*, 1986), with a dissociation in endocardial and epicardial activity (Carlisle *et al.*, 1990). The reasons for this deterioration in the waveform are uncertain. To investigate further the electrophysiological changes occurring during fibrillation, we have studied the effects of antiarrhythmic drugs on the frequency content of electrically-induced ventricular fibrillation in the dog. Some of these results have been presented to the Physiological Society (Adgey *et al.*, 1987).

Methods

Greyhound dogs (weight range 20–36 kg) were anaesthetized after intravenous sodium pentobarbitone (Sagatal, May & Baker, 35 mg kg^{-1}). After endotracheal intubation, ventilation with room air was started (Palmer Ideal pump; tidal volume 12 ml kg^{-1}, ventilation rate 18 min^{-1}). A cannula was inserted into the femoral artery and connected to a transducer (Statham) for blood pressure monitoring, with the ECG (Devices). Under X-ray control, 2 endocardial pacing catheters (U.S.C.I. 6F) were positioned transvenously in the apex of the right ventricle via the external jugular vein, one for inducing ventricular fibrillation electrically and the other for recording endocardial ventricular fibrillation. A foreleg vein was cannulated for the administration of drugs.

A blood sample was taken from the femoral artery for assay of plasma potassium during the control period and just after the onset of ventricular fibrillation. Oesophageal temperature was monitored by an electronic thermometer (Comark 1604-2).

Drugs

Five groups, each with 5 dogs, were studied. There was a control period of 1 h after the surgical stress. The selected drug was then administered intravenously over 5 min. *Group 0* No drug: ventricular fibrillation was induced without administering any antiarrhythmic drug. *Group 1* Lignocaine hydrochloride (Antigen Ltd.; 10 mg kg^{-1}). *Group 2* Propranolol hydrochloride (Inderal, ICI; 0.4 mg kg^{-1}). *Group 3* Bretylium tosylate (Bretylate, Wellcome; 10 mg kg^{-1}). *Group 4* Verapamil hydrochloride (Cordilox, Abbott; 1 mg kg^{-1}).

In Groups 2 and 4, ventricular fibrillation was induced 15 min after the drug was given. In Group 1, ventricular fibrillation was induced 5 min after drug administration, as lignocaine has a particularly short half-life. In the bretylium group (3), ventricular fibrillation was not induced until 2 h later, due to the long delay in onset of its maximum electrophysiological (Anderson *et al.*, 1980) and antiarrhythmic effects.

In Groups 1 and 2, the plasma concentrations of lignocaine and propranolol were measured in arterial blood samples taken before injection of the drug (control samples), and just after the onset of ventricular fibrillation (effective concentrations).

Ventricular fibrillation was induced by stimulating the right ventricle with a short train of electrical pulses (100 Hz; 10 V; 5 ms pulse duration) delivered by an isolated stimulator

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(Devices 2533) via one of the endocardial catheters. At the onset of ventricular fibrillation, ventilation was stopped to reduce low frequency variation in lung volume. Fibrillation was recorded on tape from both lead II and the endocardial lead for at least 15 min. At the end of each experiment the heart was excised and weighed.

After amplification (Hellige Multiskriptor EK22) the lead II and right ventricular endocardial ECG signals were converted independently to digital form and stored on dual-channel cassette-tape (Sony Stereo Cassette Corder TCS-350). An 8 bit A-D converter was used at a sampling rate of 430 Hz. The frequency response of the recording and play-back system was determined to be 0.35–55 Hz (Carlisle *et al.*, 1990).

Fast Fourier transform analysis of the reconstituted ventricular fibrillation signal was performed by use of a Bruel & Kjaer Spectrum Analyzer Type 2031. This microprocessor-based system transforms data from the time domain to the frequency domain, giving a 400 channel, constant bandwidth, logarithmic plot of the root mean square power against frequency. The reference level for amplitude was always 1 microvolt rms.

Individual time windows of 4 s duration were analysed. The resulting power spectra were then averaged linearly to give analyses of 40 s periods of ventricular fibrillation. Discontinuity between the windows was reduced by the use of a Hanning weighting. When the power spectrum was obtained, the frequency with the largest amplitude was found with the screen cursor and alphanumeric display. A hard copy of the spectrum was taken for future reference (Bruel & Kjaer X-Y Recorder Type 2308). During the analysis, the signal was monitored on an oscilloscope (Gould 0S4020) to avoid artefact.

Statistical methods

The null hypothesis, that there was no significant difference between the values observed in separate groups, or between the values at different times, was tested. The significance level for the rejection of this hypothesis was $P < 0.05$. Analysis of variance was performed with Duncan's multiple range test for multiple comparisons between means (ONEWAY, SPSS Inc, ICL 2900 computer). Paired or unpaired t tests were used if only 2 groups were being compared. All results are reported as mean ± standard error of the mean (s.e.mean).

Results

Body weight and heart weight did not differ significantly between the groups (Table 1). Both plasma potassium values (Table 1) and body temperature (not shown) did not change significantly during the experiments and were similar between groups.

Haemodynamics

There were no significant changes in heart rate and mean arterial blood pressure during the control period in the dogs given no drug (Table 1).

The intravenous administration of lignocaine caused an increase in heart rate ($P < 0.02$), and a transient fall in blood pressure ($P < 0.005$) which recovered before ventricular fibrillation was induced 5 min later (Table 1).

Propranolol caused an immediate and persistent fall in heart rate ($P < 0.05$), with no significant effect on blood pressure (Table 1).

Bretylium had powerful haemodynamic effects, causing a sharp increase in heart rate ($P < 0.02$) and mean arterial pressure. At 2 h after injection, blood pressure was still significantly elevated (Table 1).

Verapamil caused transient atrio-ventricular conduction disturbances, with second degree block in 3 of the 5 dogs, followed by complete block in 2 of these 3. A pronounced fall in blood pressure followed administration of the drug in all of the dogs ($P < 0.005$), with some recovery before induction of fibrillation 15 min later (Table 1).

Lead II ECG

In the no drug group, the dominant frequency of ventricular fibrillation recorded from lead II was initially 9.9 ± 0.7 Hz. There was a slight increase at 80 s, and then it fell rapidly to 5.2 ± 0.4 Hz (Figure 1).

In the lignocaine-treated animals (mean plasma concentration 5.0 ± 0.5 $\mu g\,ml^{-1}$; Figure 1), the dominant frequency was significantly lower than that in the no drug group for the first 80 s ($P < 0.05$), beginning at 7.25 ± 0.54 Hz. Subsequent frequencies of fibrillation were not significantly lower than in the no drug group.

Propranolol had no significant effect on the time course of the frequency of ventricular fibrillation in lead II (mean plasma concentration 117.8 ± 22 $ng\,ml^{-1}$; Figure 1).

Pretreatment for 2 h with bretylium was also without effect on the initial dominant frequency of fibrillation in lead II, but prevented the subsequent rise in frequency at 80 s ($P < 0.05$; Figure 1). It had no apparent effect after this time.

While the dominant frequency of the verapamil-treated group was similar to the no drug group for the first 40 s, verapamil prevented the rapid fall in frequency seen in these control dogs after this time. Later there was a significant rise in frequency to 14.7 ± 0.9 Hz ($P < 0.01$; Figure 1).

Endocardial ECG

The dominant frequency of fibrillation recorded from the right ventricular endocardium in the no drug dogs was similar to that in lead II for the first 80 s. However, after this time the frequency did not fall rapidly as in lead II, and remained above 9 Hz (Figure 2).

Lignocaine significantly reduced the dominant frequency of endocardial fibrillation at 40–200 s ($P < 0.05$; Figure 2). Moreover, there was a fall in frequency with time which was not present in the no drug group.

Propranolol had no significant effect on endocardially-recorded ventricular fibrillation (Figure 2). As in the no drug group, the dominant frequency was well maintained.

Table 1 Body and heart weights, heart rates and arterial blood pressures before and after drug, and plasma potassium concentrations at the onset of ventricular fibrillation in the 5 groups of dogs

	Body weight (kg)	*Heart weight* (g)	*Heart rate* (min^{-1}) *Pre-drug*	*Pre-VF*	*Arterial BP* (mmHg) *Pre-drug*	*Pre-VF*	*Plasma* K^+ (mM)
No drug	25.3 ± 1.0	272 ± 12	131 ± 18	131 ± 18	122 ± 12	122 ± 12	3.8 ± 0.2
Lignocaine	28.1 ± 1.4	331 ± 25	107 ± 7	129 ± 10*	114 ± 8	110 ± 9	4.2 ± 0.3
Propranolol	27.0 ± 0.9	292 ± 22	124 ± 9	110 ± 6*	123 ± 7	123 ± 8	3.9 ± 0.1
Bretylium	27.1 ± 1.5	315 ± 21	109 ± 13	123 ± 21	125 ± 8	166 ± 8**	3.7 ± 0.1
Verapamil	28.8 ± 2.7	318 ± 27	102 ± 17	91 ± 8	120 ± 11	90 ± 9*	3.7 ± 0.2

The arterial blood pressures after bretylium ($P < 0.01$) and verapamil ($P < 0.05$) were the only significant differences from values for the control No Drug group. Significant within-group differences between pre- and post-drug values are indicated (* $P < 0.05$; ** $P < 0.01$).

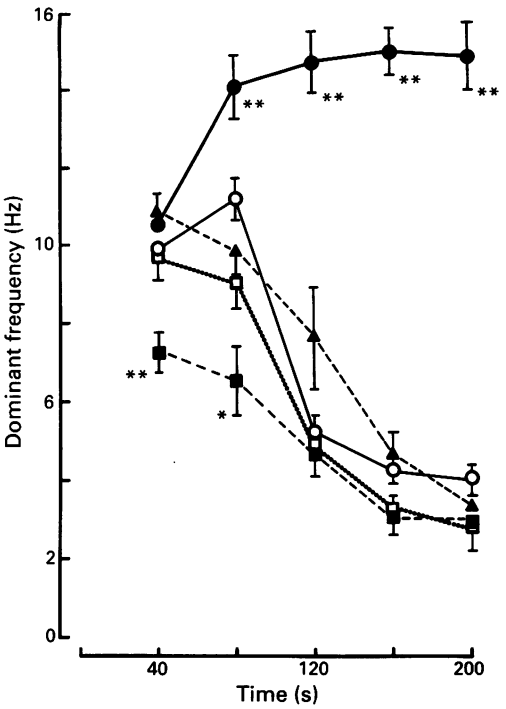

Figure 1 The change with time of the dominant frequency of electrically-induced ventricular fibrillation, recorded from lead II, in dogs receiving no drug (○) and in dogs pretreated with lignocaine (10 mg kg^{-1}, ■), propranolol (0.4 mg kg^{-1}, ▲), bretylium (10 mg kg^{-1}, □) or verapamil (1 mg kg^{-1}, ●). The significances of differences from values in the no drug group is shown: * $P < 0.05$; ** $P < 0.01$.

Bretylium reduced the dominant frequency recorded from the endocardium after fibrillation for 160 s ($P < 0.01$). Before this time it had no apparent effect (Figure 2).

Verapamil had no effect on the initial frequency of fibrillation in the endocardium, but significantly increased the frequencies at all times at 80–200 s ($P < 0.02$; Figure 2). Although endocardial and lead II fibrillation in the dogs given no drugs had quite different time courses, this difference was not seen in the animals treated with verapamil.

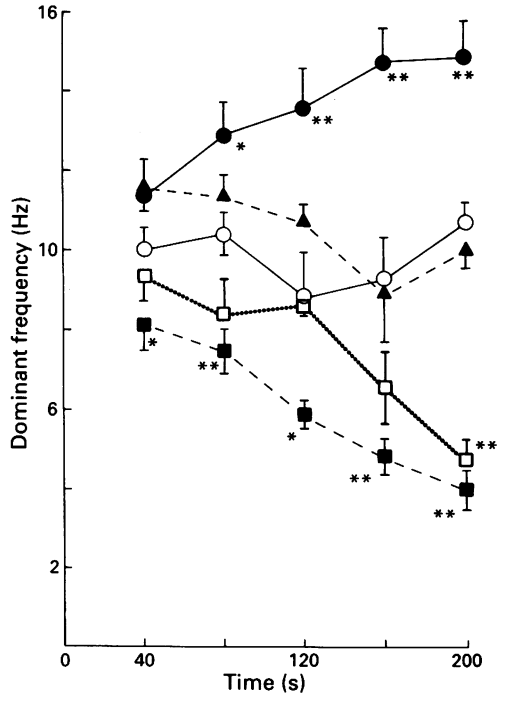

Figure 2 The change with time in dominant frequency of electrically-induced ventricular fibrillation, recorded on a right ventricular endocardial lead in Groups 0–4. (○) No drug; (●) verapamil; (■) lignocaine; (▲) propranolol; (□) bretylium. Note that with no drug the frequency was maintained.

The ratio of the peak frequency in lead II as a % of the peak frequency in the simultaneous endocardial recording was used to express the degree of heterogeneity in the myocardium. In the dogs given no drugs the initial value of 104 ± 2% fell to 61 ± 14% after 3.3 min ($P < 0.01$). Similar values were obtained in the dogs receiving propranolol (initial 95 ± 3, final 34 ± 7: $P < 0.01$) and bretylium (initial 99 ± 3, final 37 ± 3: $P < 0.01$). These data contrast with those in the dogs given verapamil, where the initial ratio (92 ± 4%) did not change significantly with time (100 ± 4% after 3.3 min). Since lignocaine depressed frequencies in both lead II and the endocardium, these ratios did not change significantly (90 ± 3 initially, 85 ± 26 after 3.3 min).

Discussion

In this study, it was found that the frequency characteristics of ventricular fibrillation were greatly altered by lignocaine and verapamil, but changed little by propranolol and bretylium. The effects of each drug on endocardial fibrillation were generally similar to the effects on fibrillation recorded from lead II. Large doses of drugs were deliberately used, and this was reflected in their haemodynamic effects. However, the plasma concentrations of lignocaine and propranolol just after the onset of fibrillation were in the therapeutic range (Rosen *et al.*, 1975; Coltart & Shand, 1970).

Lignocaine

In the present study, lignocaine reduced the dominant frequency of ventricular fibrillation recorded at the body surface for the first 80 s, but had no significant effect thereafter. This suggests that the electrical activity in ventricular fibrillation depends initially on mechanisms which can be depressed by lignocaine, namely the conductance of the fast sodium channels in the cardiac cell membrane (Singh & Vaughan Williams, 1971). Prolongation of the effective refractory period and slowing of conduction by lignocaine are the likely physiological mechanisms. Its lack of effect after 80 s, when the frequency is lower in the untreated animals, suggests that other mechanisms associated with global myocardial ischaemia have caused depression of fast channel activity by this time. It is unlikely that the effect of lignocaine was inhibited, as it exerts greater effects in the presence of hyperkalaemia (Singh & Vaughan Williams, 1971), and ischaemia (Kupersmith, 1979).

In the endocardium, lignocaine significantly reduced the dominant frequency throughout the 3 min period of analysis. Thus during ventricular fibrillation, fast sodium channels remain of importance in the endocardium for at least 3 min, longer than in the myocardium. Fast channel activity may continue in the Purkinje fibre network of the endocardium due to slower metabolic deterioration, from a smaller metabolic rate, large glycogen stores, or perhaps direct oxygenation from the ventricular blood (Worley *et al.*, 1985). Further studies are required to confirm that these effects are possessed by other Class 1 drugs.

Propranolol

Circulating catecholamine levels are some 4–9 times higher at the onset of ventricular fibrillation than after myocardial infarction (Little *et al.*, 1985), giving some basis for expectations that β-adrenoceptor blocking drugs would slow the dominant frequency of fibrillation. Furthermore pretreatment with propranolol is known to reduce myocardial oxygen consumption, and myocardial necrosis after coronary artery ligation (Reimer *et al.*, 1973). However, propranolol had little effect on the time course of fibrillation in these experiments.

Both the dose of propranolol and the plasma concentrations ($118 \pm 22\,ng\,ml^{-1}$) are sufficient to cause β-adrenoceptor blockade (Coltart & Shand, 1970; Taggart *et al.*, 1984). Inhibition of fast sodium channels by β-adrenoceptor blocking drugs (class I effects) occurs at concentrations some 30 times those used in the present study (Davis & Temte, 1968), and propranolol has no class III action after acute administration (Taggart *et al.*, 1984).

Bretylium

The benzyl quaternary ammonium compound, bretylium tosylate has a number of actions on the heart. Class III antiarrhythmic properties (Vaughan Williams, 1984) increase the action potential duration and the effective refractory period of canine ventricular muscle and Purkinje fibres in the dog heart (Bigger & Jaffe, 1971). After administration noradrenaline is released from peripheral adrenergic nerve endings (Gilmore & Siegel, 1962), with a marked rise in heart-rate and blood-pressure. In the present study pretreatment with bretylium prevented the increase in the dominant frequency of ventricular fibrillation occurring at 80 s, but otherwise had no significant effect on ventricular fibrillation recorded from lead II. Bretylium, like propranolol, had little effect on endocardial fibrillation, and demonstrated no effects attributable to a Class 3 drug. Since bretylium ($4–6\,mg\,kg^{-1}$, i.v.) is one of the few drugs reported to be capable of chemical defibrillation in man (Sanna & Arcidiacono, 1973), its lack of effect in our study was surprising.

Verapamil

Verapamil, a calcium channel blocker, had striking effects on the dominant frequency of ventricular fibrillation, preventing the rapid fall in frequency seen in the untreated dogs after 80 s of fibrillation. Indeed, there was a rise in dominant frequency to almost 14 Hz at 3 min in recordings from both Lead II and the endocardium.

What is the explanation for these effects? Low concentrations of verapamil ($0.5\,mg\,l^{-1}$) reduced the duration of the action potential during rapid stimulation in the canine papillary muscle (Hirata *et al.*, 1979). A reduction in action potential duration induced by verapamil could lead to a shorter refractory period, faster conduction and an increase in the dominant frequency of ventricular fibrillation. In open chest dogs, verapamil increased the conduction velocity and reduced the delay in activation time caused by myocardial ischaemia (Elharrar *et al.*, 1977). In the ischaemic pig heart, verapamil also reduced the release of K^+, delayed the onset of slow conduction, and often prevented conduction block (Fleet *et al.*, 1986).

It may be proposed that these electrophysiological changes determine the effect of verapamil on the dominant frequency of ventricular fibrillation. However, this is unlikely to be the important mechanism. An effect on the dominant frequency of ventricular fibrillation resulting from action potential shortening due to pretreatment with verapamil should be evident at the very beginning of ventricular fibrillation, and not just after 80 s. Furthermore, nifedipine, which is virtually devoid of electrophysiological effects on the heart (Singh & Nadamanee, 1982) also increases the dominant frequency of ventricular fibrillation in a fashion similar to verapamil (Martin *et al.*, 1986).

This suggests that the main action of verapamil is to prevent calcium accumulation. After verapamil ($2\,\mu M$) Vaughan Williams (1984) has observed a faster rate of rise at the onset of the action potential, indicative of improved cell-to-cell coupling. It is well established that cardiac intercellular nexuses are uncoupled by a raised intracellular calcium concentration (Dahl & Isenberg, 1980), and that this may follow reduced activity of the Na^+-K^+ pump (De Mello, 1976). Calcium overload may also be an important primary or secondary agent in ischaemic myocardial damage (Cheung *et al.*, 1986), as calcium-channel blocking drugs reduce the extent of myocardial damage from acute regional (Reimer *et al.*, 1977) and global ischaemia (Clark *et al.*, 1977).

What are the clinical implications if intracellular calcium overload is responsible for the rapid fall in the dominant frequency of ventricular fibrillation after 80 s? This time has already been noted as critical for recovery from fibrillation. In dogs, if the heart was defibrillated before 60–90 s recovery was usual, but after 90 s of fibrillation the animals invariably died (Geuze & DeVente, 1983; Martin *et al.*, 1986). If the chance of defibrillation success is indeed related to the dominant frequency of ventricular fibrillation, then frequency analysis of fibrillation may be useful in future research on resuscitation. However, the negative inotropic effects of verapamil may militate against widespread use of this drug in clinical cardiac arrest.

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