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Ischaemia-induced loss or reversal of the effects of the class I antiarrhythmic drugs on vulnerability to fibrillation

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1 In the last decade, a number of clinical observations have questioned the efficacy of certain class I antiarrhythmic drugs against ischaemia-induced ventricular fibrillation. The effects of three drugs of this class, disopyramide (Ia), lignocaine (Ib) and flecainide (Ic) on the vulnerability to fibrillation during experimental ischaemia were investigated.

2 The study was carried out in anaesthetized, open-chest pigs ($n=8$ for each of the drugs, in addition to the control group, $n=6$). Vulnerability to fibrillation was evaluated by measuring electrical fibrillation threshold (EFT) by means of stepwise increased intensity of wide (100 ms) diastolic impulses applied to the ischaemic tissue at a 180 beats min^{-1} rate. Monophasic action potential (MAP) duration and conduction time in the ischaemic region were also measured.

3 EFT determinations were performed before and during periods of ischaemia induced by complete occlusion of the left anterior descending coronary artery near its origin. Ischaemic periods of increasing duration (30, 60, 90, 120, 150 s) were induced to determine the electrophysiological changes, of EFT especially, leading to fibrillation.

4 In the absence of ischaemia, all three drugs, administered by intravenous route (1 mg kg^{-1} plus 0.04 mg kg^{-1} min^{-1}) increased EFT to a similar extent (from approximately 7 to 10 mA), despite a 25% prolongation of conduction time.

5 During ischaemia, none of the drugs prevented the fall in EFT towards 0 mA, resulting in spontaneous fibrillation. After 30 s of ischaemia, they no longer had any capacity for raising EFT and, after 60, 90 and 120 s of ischaemia, the decrease in EFT was exacerbated. This accelerated reduction in EFT shortened the time to onset of fibrillation (after 120 s of ischaemia, 62.5% of fibrillations with flecainide instead of 12.5 under control conditions, 75% instead of 25 with lignocaine and 50% instead of 25 with disopyramide). The reduction in MAP duration due to ischaemia was also significantly accelerated (at 60 s, 178 ± 5 ms instead of 192 ± 4 with flecainide, 175 ± 3 ms instead of 194 ± 5 with lignocaine and 180 ± 5 ms instead of 196 ± 3 with disopyramide) and the slowing of conduction was made worse (prolongation of conduction time by 70% instead of 50).

6 In conclusion, the antifibrillatory properties normally manifested by these drugs are first suppressed, then inverted by ischaemia, depending on oxygen debt varying with severity and duration of ischaemia.

Keywords: Antiarrhythmic drugs; disopyramide; lignocaine; flecainide; ventricular fibrillation; myocardial ischaemia

Introduction

The clinical practice of continuous electrocardiogram monitoring has shown an increasing incidence of ventricular fibrillation, as a cause of sudden death in ischaemic heart disease (Roeland *et al*., 1984; Janse & Wit, 1989). Sudden death should therefore occur less often in patients treated with class I antiarrhythmic drugs (Vaughan-Williams, 1984) which are potent agents for depressing ventricular excitability and automaticity. However, double-blind, randomized, placebo-controlled trials of flecainide in post-infarction management failed to demonstrate any reduction in mortality; indeed, there was a tendency to increased mortality (CAST, 1989; 1991). Although ventricular fibrillation was only one of the possible causes of death in these clinical trials, such findings to not support the concept that class I antiarrhythmic drugs prevent rhythm disorders related to ischaemia. Similar findings had been obtained with lignocaine used for the treatment of rhythm disorders observed in the prehospital phase of acute infarction or in the hospital phase of monitored, uncomplicated infarction, where mortality did not appear to be significantly decreased or even appeared to be slightly increased (MacMahon *et al*., 1988; Hine *et al*., 1989; Antman & Berlin, 1992). Since the cause of sudden death in patients with ischaemic heart disease cannot always be attributed to ventricular fibrillation, it is perhaps more appropriate to obtain results about beneficial or detrimental effects of antiarrhythmic drugs in experimental animals subjected to a standard protocol for induction of ischaemia. In this way, determination of vulnerability to fibrillation can be performed before and after the drug. The assessment of vulnerability to fibrillation by the time to onset of fibrillation before and after Ic antiarrhythmic drugs (flecainide, propafenone, cibenzoline) has revealed to us a substantial increase with doses equal to or hardly higher than clinical doses (Timour *et al*., 1991; Aupetit *et al*., 1993b). However, time to fibrillation, based on fibrillation which spontaneously occurs after coronary occlusion, does not enable the vulnerability to fibrillation throughout the ischaemia period and before ischaemia to be determined. In our study of the effect of lignocaine on ischaemic ventricular fibrillation, we have therefore, in preference, used electrical threshold for fibrillation which provides the means of following the time course of vulnerability to fibrillation in the absence and presence of the drug, from normal level to the occurrence of fibrillation, by measurements performed at the end of periods of ischaemia of increasing duration (Aupetit *et al*., 1995).

The aim of this study was to investigate with this method the effects on vulnerability to fibrillation of flecainide, lignocaine and disopyramide and to determine whether vulnerability is similarly influenced by the drugs belonging to the three subgroups Ic, Ib and Ia, from the start to the end of the coronary occlusion.

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Methods

Experimental conditions

The experiments were carried out in 30 domestic pigs of either sex, about six weeks of age and weighing 22–28 kg. After approval of the protocol by the Animal Care Committee, the animals were premedicated with droperidol (1.25 mg kg^{-1}, i.m.) one hour before the experiment and anaesthetized with flunitrazepam (0.05 mg kg^{-1}, i.v.) and chloralose (80 mg kg^{-1}, i.v.) injected via the marginal ear vein. Ventilation was provided by a PR2 respirator (Bennett, Santa Monica, CA, U.S.A.) which delivered an air-oxygen mixture (40 and 60%, respectively) through a cuffed endotracheal tube. Depth and rate of ventilation were adjusted to maintain PaO_2, $PaCO_2$ and pH within satisfactory ranges. Core temperature was monitored by an electronic oesophageal thermometer and kept constant by means of an infrared heater placed at an adequate distance from the animals. A carotid artery was cannulated to record arterial pressure on a Narcotrace 80 polygraph (Narco-Biosystem, Houston, TX, U.S.A.) and a catheter placed in a jugular vein for administration of the experimental drugs.

The heart was exposed through a left thoracotomy with resection of the 4th and 5th ribs. The pericardium was incised and the left anterior descending coronary artery was dissected free close to its origin and prepared for occlusion by passing a snare around it. This snare did not inferfere with blood circulation when it was not tightened. By tightening the snare, the artery could be occluded and released as required.

Measurement of electrical fibrillation threshold (EFT)

The measurement of EFT was performed according to a technique described previously (Aupetit *et al*., 1993a; 1995) using trains of diastolic stimuli synchronized with respect to the R waves in lead II. Impulses were delivered to the myocardium by a S1 stimulator (Hugo Sachs, Freiburg im Brisgau, Germany) through a bipolar electrode the tip of which was positioned near the centre of the zone subjected to ischaemia. The duration was much greater than the duration of stimuli ordinarily used for pacing (100 ms instead of 2) and the intensity was increased in a stepwise manner with 1.0 or 0.5 mA increments. The rate was 180 beats min^{-1}, i.e. close to the rate during ventricular tachycardia. This 180 beats min^{-1} rate was also the rate of ventricular pacing, achieved with the same electrode, but with stimuli of 2 ms duration and 0.3–0.4 mA intensity for a period of 60 s before coronary occlusion and throughout the occlusion periods.

In order to follow the changes in EFT from normal level to the occurrence of fibrillation, coronary occlusion was induced for serial increasing periods of 30, 60, 90, 120 and 150 s, EFT being measured at the end of each period. Biochemical and electrical disorders generated by occlusions which do not exceed these durations are rapidly reversible. Consequently, apart from the first occlusion which is to be excluded (Fleet *et al*., 1985; Shiki & Hearse, 1987), such successive periods of occlusion give rise to reproducible results, provided that the occlusion is identical in its degree, as the complete occlusion in the present experiments, and an appropriate interval for recovery is respected between two occlusions: 10 to 20 min (Janse & Wit, 1989) or even less, 2.5 to 15 min depending on duration of the occlusion periods (Aupetit *et al*., 1993a). The duration of occlusion periods and the intervals between them in the present experiments are indicated in Figure 1.

With wide diastolic impulses, fibrillation needs relatively high intensity to be triggered under normal conditions (Figure 2). The intensity required for fibrillation declines first rapidly, then more slowly in an exponential way (Timour *et al*., 1994), with the increase in duration of the ischaemia periods and falls down to near 0 mA. At this time, impulses of 0.3–0.4 mA intensity and 100 ms duration and even increasingly shorter, down to a few milliseconds, become sufficient to initiate fibrillation. Definitively, after ischaemia periods of 120–150 s, fibrillation will occur with impulses the characteristics of which are similar to those of the threshold pacing stimuli applied to the myocardium in these experiments. These stimuli will therefore result in the asynchronous activity of each ventricular fibre instead of inducing a wave of coordinated activity of the various ventricular fibres. Consequently, the time to onset of fibrillation correlates with the steepness of the EFT fall: time to fibrillation is shortened when the fall is accelerated and lengthened when slowed. Physiological stimuli are capable of similarly eliciting spontaneous fibrillation instead of ordering coordinated activity.

When ventricular fibrillation had occurred, either induced by strong stimuli or by pacing stimuli or spontaneously, defibrillation was performed, generally in less than 30 s, with a 350 J current shock from a Sirecard F defibrillator (Siemens, Erlangen, Germany), applied to the thoracic wall. Earlier investigations (Aupetit *et al*., 1995) had checked the absence of EFT alterations produced by defibrillations, repeated as required by the coronary occlusions of this protocol. However, in the case of difficult defibrillations, when more than 4 or 5 shocks were necessary, haemodynamic disorders resulted in decreases in EFT which could be serious enough to invalidate the experiment.

Determination of electrophysiological parameters

Monophasic action potential (MAP) was continuously monitored through a Catronic ORX electrode 6F (Plastimed, Saint-Leu-La-Forêt, France), implanted in the subepicardial area subjected to ischaemia, 1–2 cm from the pacing electrode. The MAP recording electrode was connected to a EM 531 oscilloscope (Siemens, Erlangen, Germany), via a Mingograf 34 electrocardiograph (Elema-Schönander, Stockholm, Sweden). The MAP was recorded just before the measurement of EFT, i.e. after 60 s pacing in the absence of coronary occlusion and at the end of each occlusion period. As MAP duration correlates with resting membrane potential (Janse & Wit, 1989), depolarization resulting from ischaemia could be estimated, since variations due to heart rate were all excluded by pacing the ventricles at a constant rate of 180 beats min^{-1}. Conduction time in ventricular contractile fibres was determined by measuring the interval between the spike of stimulation and the steep upstroke of the MAP. A surface electrocardiogram from standard limb leads was also continuously monitored on the oscilloscope and recorded at the same time as local electrical activity.

Experimental protocol

The animals were randomly assigned to four groups. A first group ($n=6$) served as control to demonstrate the reproducibility of the changes in EFT during increasing periods of ischaemia. This group was used more particularly to make sure of reproducibility of the results in two sets of EFT measurements (Figure 2), the two sets being separated from each other by an interval of 20 min, as indicated in Figure 1. In each set, the measurements were performed in the absence of occlusion and after 30, 60, 90, 120 and 150 s occlusions. In other words, the protocol was exactly that of the three other groups of animals, except that the animals did not receive any drug. Therefore, the three other groups were subjected to the first set of EFT measurements and then given flecainide ($n=8$), lignocaine ($n=8$) or disopyramide ($n=8$) before the second set of EFT measurements (Figure 1). All drugs were administered in a loading dose of 1 mg kg^{-1}, followed by an infusion of 0.04 mg kg^{-1} min^{-1} over 60 min (i.e. until the end of the experiment).

MAP duration, conduction time and mean blood pressure were measured just before EFT measurements. Sampling of 1 or 2 ml of blood from a jugular vein immediately before determination of the electrophysiological and haemodynamic

measurements performed at the end of the coronary occlusions enabled the drug to be assayed by immunofluorescence (TDX apparatus, Abbott, Rungis, France).

Drugs

Anaesthetic drugs used in this study were: droperidol (Janssen Laboratories, Boulogne-Billancourt, France); flunitrazepam (Roche Products, Neuilly-sur-Seine, France) and chloralose (Merck Laboratory, Darmstadt, Germany). Flecainide (acetate) was obtained from 3 M Health Laboratories (Malakoff, France), lignocaine (hydrochloride) from Astra-France (Nanterre, France) and disopyramide (base) from Roussel Laboratories (Paris, France).

Statistics

Two-way (drug and time) analysis of variance (ANOVA) was used to compare the values obtained with the three drugs at each time of measurement, before ischaemia and after each ischaemia period. When a significant difference was apparent depending on time, the test values were compared at baseline and for each ischaemia period to the corresponding control values by Dunnett's test.

Results are expressed as arithmetic means $\pm$ s.e.mean and differences were considered significant at $P<0.05$.

Results

Effects of flecainide, lignocaine and disopyramide in the absence of ischaemia

Under normal conditions, EFT was substantially increased by all three drugs (Figures 3–5). No significant difference was observed between the magnitude of the increase in EFT induced by the three drugs. Since the heart was electrically driven at a constant rate, 180 beats min^{-1}, the drug-induced rise in EFT was not accompanied by any prolongation in MAP duration (Table 1). This was despite the prolongation of intraventricular conduction time from 31 ± 1 to 40 ± 2 ms ($P<0.001$) with flecainide (Figure 6), from 34 ± 2 to 40 ± 2 ms ($P<0.01$) with lignocaine and from 29 ± 3 to 37 ± 3 ms ($P<0.01$) with disopyramide. These alterations were not associated with any significant variations in blood pressure, since neither the slight increases in mean blood pressure after the loading doses nor the slight decreases at the end of the infusions reached the significance threshold.

Effects of drug intervention during periods of myocardial ischaemia of increasing duration

Contrary to what might have been expected from the above data, neither flecainide, lignocaine nor disopyramide increased EFT after coronary occlusion. After 30 s occlusion, EFT was not significantly different from control in any of the three groups (Figures 3–5). After a period of 60 s ischaemia, EFT

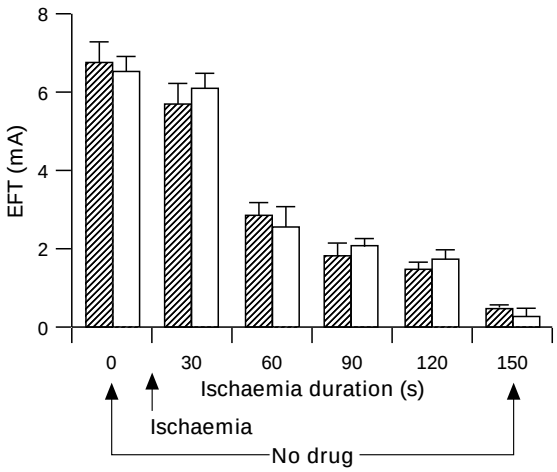

Figure 2 Reproducibility of the results in two sets of measurements of electrical fibrillation threshold (EFT), the two sets being separated from each other by an interval of 20 min. In each set, the measurements were performed in the absence of occlusion and after 30, 60, 90, 120 and 150 s occlusions. No significant difference was seen between the first set (hatched columns) and second set (open columns). Means $\pm$ s.e.mean are shown.

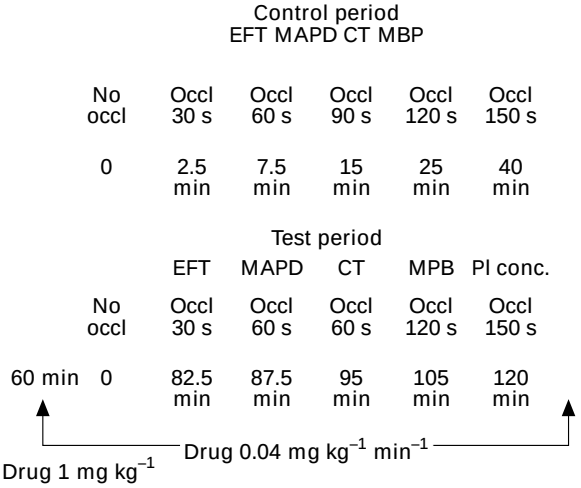

Figure 1 Scheme of the protocol. Sequential coronary occlusions of increasing duration under control and test conditions to follow the decline of electrical fibrillation threshold (and the time course of the other parameters) from normal level to fibrillation, initiated by pacing or occurring spontaneously. The occlusion periods (OCCL) are separated by increasing intervals for the disappearance of biochemical and electrical disorders induced by ischaemia. EFT, electrical fibrillation threshold. MAPD, monophasic action potential duration. CT, conduction time. MBP, mean blood pressure. Pl conc. plasma concentration.

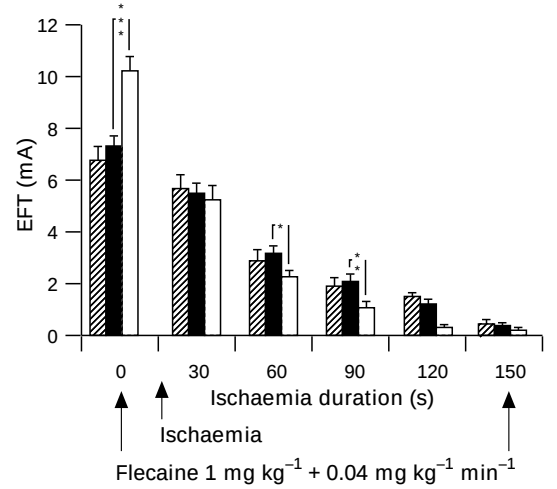

Figure 3 Effects of flecainide on electrical fibrillation threshold (EFT) at the end of ischaemia periods of increasing duration. Ischaemia resulted in a loss of the increase in EFT by flecainide seen in the absence of ischaemia. With increasing periods of ischaemia, flecainide accelerated the reduction in EFT. Control group (hatched columns); before flecainide (solid columns); after flecainide (open columns). Means $\pm$ s.e.mean are shown. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$.

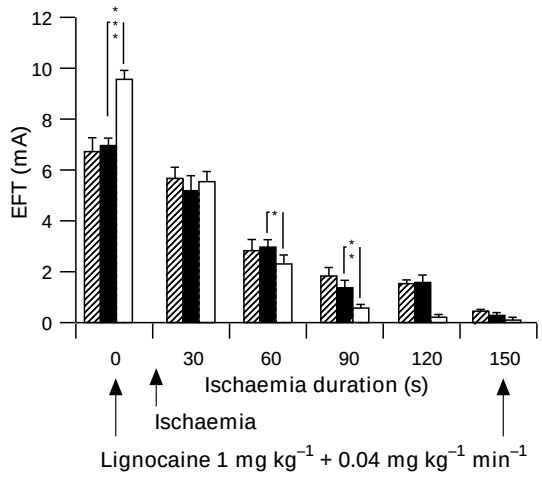

Figure 4 Effects of lignocaine on electrical fibrillation threshold (EFT) at the end of ischaemia periods of increasing duration. Ischaemia resulted in a loss of the increase in EFT by lignocaine seen in the absence of ischaemia. With increasing periods of ischaemia, lignocaine accelerated the reduction in EFT. Control group (hatched columns); before lignocaine (solid columns); after lignocaine (open columns). Means±s.e.mean are shown. $*P<0.05$, $**P<0.01$, $***P<0.001$.

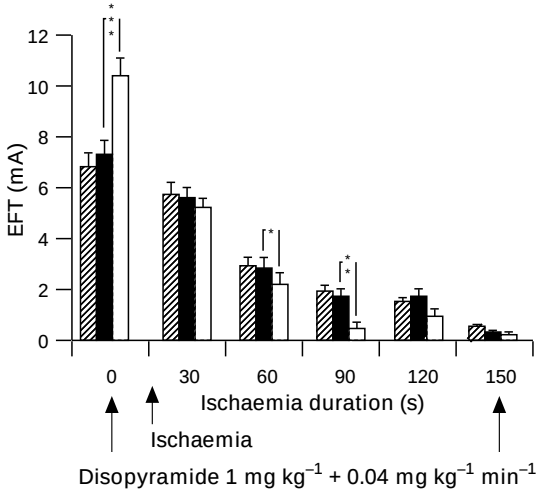

Figure 5 Effects of disopyramide on electrical fibrillation threshold (EFT) at the end of ischaemia periods of increasing duration. Ischaemia resulted in a loss of the increase in EFT by disopyramide seen in the absence of ischaemia. With increasing periods of ischaemia, disopyramide accelerated the reduction in EFT. Control group (hatched columns); before disopyramide (solid columns); after disopyramide (open columns). Means±s.e.mean are shown. $*P<0.05$, $**P<0.01$, $***P<0.001$.

was significantly reduced. With increasing periods of ischaemia, the fall in EFT was even more marked.

The incidence of spontaneous ventricular fibrillation was increased following drug treatment after 90, 120 and 150 s occlusions: the results were not statistically analysed, but the percentage of animals which had fibrillated was always higher after flecainide, lignocaine or disopyramide than before (Table 2). More accurately, the time elapsing from coronary occlusion to the onset of fibrillation induced by threshold pacing stimuli or natural stimuli (time to fibrillation) fell from 170 ± 14 to 128 ± 12 s ($P<0.01$) with flecainide, from 162 ± 12 to 118 ± 10 s ($P<0.01$) with lignocaine and from 178 ± 11 to 110 ± 14 s ($P<0.01$) with disopyramide. Analysis of variance did not reveal any significant difference within the group in the values of EFT underlying these times to fibrillation.

The increased rate of decline of EFT was accompanied by an accelerated reduction in MAP duration mirroring an acceleration of depolarization. After 60 and 90 s occlusions, MAP durations were significantly shorter after flecainide, lignocaine or disopyramide than before (Table 1) and, thus, as the critical level for triggering fibrillation was reached sooner, time to fibrillation was also shorter.

The impairment of intraventricular conduction by ischaemic depolarization was simultaneously worsened by the antiarrhythmic drugs which added their own depressant effect on conduction to that of ischaemia. In the case of flecainide, for instance, the lengthening of conduction time was approxi-

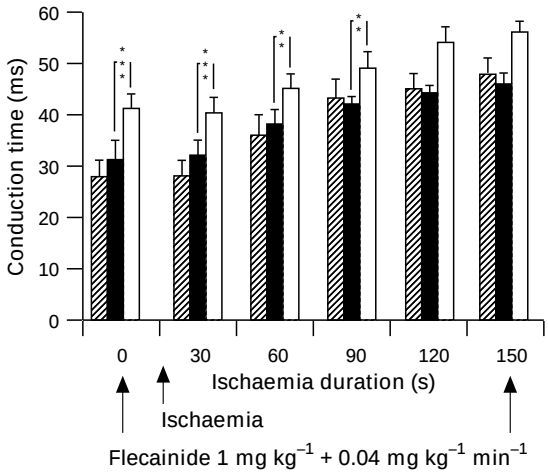

Figure 6 Effects of flecainide on conduction time in the ischaemic area at the end of ischaemia periods of increasing duration. The lengthening of conduction time induced by flecainide in the absence of ischaemia was added, at least partially, to the lengthening due to ischaemia. Control group (hatched columns); before disopyramide (solid columns); after disopyramide (open columns). Means±s.e.mean are shown. $*P<0.05$, $**P<0.01$, $***P<0.001$.

Table 1 Monophasic action potential duration in the absence of ischaemia and at the end of ischaemia periods of increasing duration

	No Occl	*Occl 30 s*	*Occl 60 s*	*Occl 90 s*	*Occl 120 s*	*Occl 150 s*
Before flecainide	210±6	208±5	192±4	182±5	170±4	166±5
After flecainide	214±5	214±6	178±4**	168±3*	165±3	165±3
Before lignocaine	216±6	216±4	194±5	186±4	174±4	160±3
After lignocaine	218±6	220±5	176±3**	170±4*	162±3	164±4
Before disopyramide	208±4	212±3	196±3	190±3	178±4	164±3
After disopyramide	210±5	216±2	180±5*	176±4*	170±5	166±5

Comparison of the values before and after the drug: $*P<0.05$, $**P<0.01$.

Table 2 Percentage of spontaneous fibrillations in each group (flecainide, lignocaine, disopyramide) at the end of ischaemia periods of increasing duration

	Occl 30 s			*Occl 60 s*			*Occl 90 s*			*Occl 120 s*			*Occl 150 s*		
	Flec	Lig	Dis	Flec	Lig	Dis	Flec	Lig	Dis	Flec	Lig	Dis	Flec	Lig	Dis
Treated	0	0	0	0	0	0	12.5	25	37.5	62.5	75	50	87.5	87.5	75
Control	0	0	0	0	0	0	0	0	12.5	12.5	25	25	50	62.5	37.5

mately equal with a 60 s ischaemia period to that observed with 120 or 150 s of ischaemia alone (Figure 6). Although the effect of flecainide on conduction is known to be particularly pronounced, this effect was not significantly different from the effect of lignocaine and disopyramide in the dose used the present experiments.

The reduction of mean blood pressure due to ischaemia (76 ± 3 to 67 ± 2 mmHg, $P < 0.001$) was not significantly altered by either flecainide (65 ± 2 mmHg), lignocaine (63 ± 3 mmHg) or disopyramide (64 ± 1 mmHg).

In contrast, these similar effects were obtained at plasma concentrations which were unequal: 1.08 to 1.12 μg ml^{-1} with flecainide, 6.18 to 7.16 with lignocaine and 6.24 to 6.38 with disopyramide between the 20th and the 60th minute following the bolus injection, i.e. during the period of measurements (Figure 1).

Discussion

Validity of the EFT measurement for the assessment of vulnerability to fibrillation

EFT, as measured in the present experiments with wide diastolic stimuli, has been demonstrated previously to provide a measure of the vulnerability to ventricular fibrillation (Aupetit *et al*., 1993a; 1995). Under normal conditions, the EFT is extremely high in comparison with the pacing threshold (at the rate of 80–100 beats min^{-1}, about 14 mA with stimuli of 100 ms instead of 0.4 mA with stimuli of 2 ms). A factor which contributes to the development of ischaemia-induced fibrillation is a decrease in EFT. A gradual exponential decline of EFT, from normal to near 0 mA, has been associated with triggering of fibrillation (Timour *et al*., 1994). However, the repetition of ischaemia periods at brief intervals for the monitoring of EFT from normal level to the occurrence of fibrillation might be criticized, since 'preconditioning' due to previous ischaemia has been claimed to protect against the arrhythmogenic effect of a subsequent ischaemia (Hagar *et al*., 1991; Vegh *et al*., 1992). In fact, sensitization of the myocardium to ischaemia-induced fibrillation by earlier ischaemia periods has also been demonstrated (Murry *et al*., 1986; Aupetit *et al*., 1993a). Evidence has been obtained (as cited above) that the result of the EFT determination is reproducible with the following conditions: exclusion of the first ischaemia, brief periods of ischaemia (4–5 min), sufficient intervals for recovery (2.5 to 15 min depending on the duration of the preceding ischaemia).

The results obtained from the EFT measurement for evaluating vulnerability to fibrillation are consistent with those of other methods such as the determination of the time to onset of ischaemia-induced fibrillation (Timour *et al*., 1991; Aupetit *et al*., 1993b; Loufoua *et al*., 1993). Ischaemia both shortens the time to fibrillation in proportion to its severity and hastens the fall of EFT: vulnerability to fibrillation may thus be considered to be inversely correlated to EFT or time to fibrillation. EFT measurement has the advantage over measuring time to fibrillation in that it allows vulnerability to be monitored from the start to the end of a period of ischaemia of moderate duration. Moreover, vulnerability can be evaluated in the same animal under both non-ischaemic and ischaemic conditions. Accordingly, EFT measurement can be used to predict the effects of antiarrhythmic drugs in the absence and presence of ischaemia. In the former case, these drugs which are expected to protect against fibrillation raise EFT. In the latter, their efficacy against fibrillation is questioned and EFT is not raised, but unchanged or even lowered.

Ischaemia and protective effects against fibrillation of class I antiarrhythmic drugs

There is no doubt that antiarrhythmic drugs, whether they belong to subgroups Ia, Ib or Ic, are capable of preventing electrically induced ventricular fibrillation in animals (Jaillon *et al*., 1980; Timour *et al*., 1983) or ventricular fibrillation occurring in the clinical setting in man (Harrison *et al*., 1963; Anderson *et al*., 1981). However, the beneficial effects have generally been demonstrated is non-ischaemic hearts.

Indeed, these drugs have also been shown to facilitate ventricular fibrillation. The factors responsible for this change in the effects of class I antiarrhythmics are poorly defined (Winkle *et al*., 1981; Velebit *et al*., 1982), although ischaemia is probably the most important. Quinidine and procainamide have been demonstrated to induce arrhythmogenic and profibrillatory rather than antiarrhythmic and antifibrillatory effects in the ischaemic myocardium (Gamble & Cohn, 1972; Bergey *et al*., 1982). The increased incidences of serious ventricular arrhythmias, often leading to fibrillation, which were obtained shortly after the clinical introduction of Ic drugs (Winkle *et al*., 1981; Velebit *et al*., 1982) have indicated caution should be exercised in their use. The increase in mortality in multicentre trials performed in post-infarction management (CAST, 1989; 1991) has justified this caution. Lastly, experimental studies have confirmed the possible harmful effects of such drugs under conditions of myocardial ischaemia, seen particularly as a reduction in the time to fibrillation (Timour *et al*., 1991; Aupetit *et al*., 1993b; Loufoua *et al*., 1993), almost immediately after their intravenous injection.

Lignocaine might perhaps not exert harmful effects in the same circumstances, since it is less negatively dromotropic in moderate doses (Gerstenblith *et al*., 1978; Badui *et al*., 1981; Carson & Dresel, 1983). Furthermore, its elimination half-life is short, allowing its effects to diminish rapidly after the intravenous infusion has ended. Nevertheless, when administered in the acute phase of clinical infarction, lignocaine did not reduce the incidence of sudden death; indeed, it appeared to increase mortality (Mac Mahon *et al*., 1988; Hine *et al*., 1989; Antman & Berlin, 1992). This finding was attributed to the development of ventricular fibrillation, since both the frequency of severe arrhythmias produced in animals by the transient occlusion of a large coronary artery (Patterson *et al*., 1982) and precipitation of fibrillation (Aupetit *et al*., 1995) were increased with lignocaine. Therefore, it is not surprising that lignocaine has been shown to increase the risk of the development of fibrillation during a maintained coronary occlusion (Patterson *et al*., 1988).

The effects of ischaemia on the activity of the class I antiarrhythmic drugs certainly first stem from the oxygen debt which, under pacing at a constant rate, is related to the degree of coronary flow reduction and the duration. As the occlusion of the left anterior descending coronary artery was complete and at the same level, the oxygen debt and the resulting de-

polarization of the myocardial fibres depended on the duration of occlusion only. Thus, the usual antifibrillatory influence was first lost with 30 s occlusion and reversed to a profibrillatory influence after 60 s occlusion.

Possible mechanisms of the alterations in the effects of antiarrhythmic drugs with ischaemia

The change in cardiac responsiveness to antiarrhythmic drugs is a consequence of the depolarizing action of a deprivation of blood flow, particularly of oxygen supply (Blake & Clusin, 1986). The defect in cellular energy resources required for active ion transfer across the membrane gives rise to a depletion of potassium ions and an accumulation of sodium and calcium ions in the cellular medium (Heijnis *et al*., 1991; Gettes *et al*., 1991). The subsequent depolarization, seen as a reduction in MAP duration (Janse & Wit, 1989), accounts for the major enhancement of excitability, which is inversely correlated with the difference between the diastolic potential and the threshold potential for spontaneous depolarization (Lyons *et al*., 1977). When the former is very close to the latter, hyperexcitability is changed into automaticity; no stimulus is necessary for maintaining cellular electrical activity. At the same time, conduction, which is dependent on transmembrane voltage (Weidmann, 1955), tends to be blocked (Kleber *et al*., 1986), as suggested by the progressive increase in conduction time observed with increasing periods of ischaemia in these experiments. Definitively, fibrillation might correspond to an automatic activity of each fibre, independent of that of the surrounding fibres (Clusin *et al*., 1982).

Therefore, depression of conduction and enhancement of excitability certainly take part in the genesis of ischaemic fibrillation. It is probable that they similarly take part in the profibrillatory action of the class I drugs. We first looked at intraventricular conduction impairment, since ischaemia adds the effect of a reduction in transmembrane voltage to that of the reduction in sodium conductance attributable to the drug. Fast channel, related to sodium inward current and underlying conduction velocity, is thus affected to such an extent that the propagation of the excitation wave to all the fibres of the ventricular mass becomes impossible (Janse & Wit, 1989) and re-entrant mechanisms are then responsible for fibrillation (Wit & Cranefield, 1978; Hoffman & Rosen, 1981). The critical level of conduction impairment for generating fibrillation is reached sooner when the inhibitory properties of the drug on conduction are more pronounced. Conceivably, Ic drugs which possess such properties (Lang *et al*., 1988; Timour *et al*., 1989) are known to be the class I drugs which give rise to the greatest number of fibrillatory accidents (Winkle *et al*., 1981; Velebit *et al*., 1982). Conversely, the risk of fibrillation seems to be less with Ib drugs, such as lignocaine which has little influence on conduction (Gerstenblith *et al*., 1978; Badui *et al*., 1981; Carson & Dresel, 1983). However, a re-entrant mechanism cannot be excluded as lignocaine does not develop an obvious depressant action on conduction in therapeutic doses under physiological conditions: its action is no longer negligible when worsened by the depolarization and acidosis elicited by ischaemia (Ye *et al*., 1993; Aupetit *et al*., 1995).

Nevertheless, hyperexcitability is also necessary for the induction of fibrillation by the combination of the effects of ischaemia and class I drugs. The fall in EFT bears witness to the enhancement of myocardial excitability. This fall cannot be explained by the inhibition of conduction, since high doses, bordering on toxic doses, of class I drugs to not clearly lower EFT, despite considerable prolongation of conduction time, when polarization of the fibres is normal and, consequently, their excitability is not increased (Lang *et al*., 1988). Moreover, the depression of excitability is undoubtedly the only determinant of the antifibrillatory activity manifested in the absence of ischaemia by these drugs, which raise EFT by several milliamperes in spite of an appreciable lengthening of conduction time, particularly when they are of the Ic type.

The loss of the depressant effect on excitability under ischaemia, assessed by EFT, may be easily interpreted as the disappearance of the role of sodium channel in the rhythmical depolarization of the fibres: the activation of the sodium channel, which requires high membrane potentials (Coraboeuf, 1978; Reuter, 1984), is inconsistent with ischaemic depolarization. As the activity of the class I drugs, which are relatively selective sodium channel blocking agents (Campbell & Vaughan-Williams, 1983; Nattel, 1991) is proportionate to the part played by the sodium channel, these drugs lose their fundamental effect on EFT with ischaemic depolarization. Furthermore, their beneficial influence on excitability will be counteracted by their opposite effect on depolarization (Lyons *et al*., 1977). In counterpart, the role of the calcium channel, activated at lower potentials, might be increased: calcium channel inhibitors, devoid of action on EFT, effective refractory period and conduction time under normal conditions (Timour *et al*., 1983), acquire with ischaemia the capacity to attenuate the fall in EFT and to delay the shortening of effective refractory period as well as the lengthening of conduction time (Timour *et al*., 1992; Aupetit *et al*., 1993a). All these effects become increasingly marked in proportion to the length of time of ischaemia and the resulting depolarization deteriorates during this time as the usual action of class I antiarrhythmic drugs disappears

In conclusion, complete occlusion of the left anterior descending coronary artery in pigs is rapidly followed by the disappearance of the antifibrillatory properties of the class I antiarrhythmic drugs such as disopyramide (Ia), lignocaine (Ib) and flecainide (Ic). As ischaemia progresses, these drugs exert effects which may be profibrillatory.

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