Br. J. Pharmac. (1978), **63**, 587–591

RELATIONSHIP BETWEEN ATRIAL AND VENTRICULAR RATES OF FIBRILLATION AND CARDIAC CONTRACTILE TISSUE EFFECTIVE REFRACTORY PERIODS IN THE DOG

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1 During total cardiopulmonary bypass, acetylcholine-, isoprenaline-, ouabain- and quinidine-induced variations in the atrial and ventricular rates of fibrillation were studied and compared with the variations in effective refractory periods (ERP) of atrial and ventricular contractile tissue obtained under the same experimental conditions.

2 Acetylcholine significantly shortened the ERP and accelerated the rate of fibrillation in the atrium but did not provoke any change in ventricular tissue. A parallel decrease in atrial and ventricular ERP and a parallel increase in atrial and ventricular rates of fibrillation were observed with isoprenaline.

3 Ouabain exerted a biphasic effect on the atrium, with an initial decrease in the ERP and an initial acceleration of the rate of fibrillation. It produced only a slight decrease in the ventricular ERP and no significant variation in the ventricular rate of fibrillation.

4 Quinidine induced a greater increase in the ERP and a greater slowing of the rate of fibrillation in the atrium than in the ventricle.

5 The variations in percentage change of refractoriness and rate of fibrillation were strictly correlated: $r = 0.89$ ($P < 0.001$); the equation of the regression line was $y = -0.86 \times -2.98$.

Introduction

Over the last twenty years, a great deal of information about the mode of action of antifibrillatory and of fibrillatory agents has become available. As early as 1955, McBrooks, Hoffman, Suckling & Orias, after a study of the effects of some drugs, of hypothermia, and of variations in potassium and calcium concentrations, on the sensitivity of the myocardium to arrhythmias, concluded that there was no definite and uniform relationship between changes in various parameters of excitability and vulnerability to fibrillation. Nevertheless, they advanced the hypothesis that, among other elements, the shortening of the duration of refractoriness was directly related to the induction of fibrillation, since vagal stimulation, acetylcholine and catecholamines (which decrease the effective refractory period of atrial fibres) sensitized the atrium to fibrillation, whilst high potassium and antiarrhythmic drugs such as quinidine (which lengthen the duration of refractoriness) exerted an antifibrillatory effect. Moreover, it has been shown that, when long-lasting fibrillation occurs, additional vagal stimulation and acetylcholine administration shorten the f – f interval and, thus, accelerate the rate of fibrillation (Rosenblueth, 1953; McBrooks *et al.*, 1955).

Although the shortening of the duration of the effective refractory period is not the only influence in the production of fibrillation (since slow conduction, impaired contractility, level of resting excitability have been shown to be effective, McBrooks *et al.*, 1955), the possible relation between refractoriness and fibrillation (either threshold or rate) appeared to be worth studying.

The aim of the present study was to record the changes in atrial and ventricular rates of fibrillation following the administration of fibrillatory agents such as acetylcholine, isoprenaline and ouabain and of antifibrillatory agents such as quinidine, and to compare these results with the changes in the atrial and ventricular tissue effective refractory periods under the same experimental conditions. The studies

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were performed on dogs' hearts *in situ* (Farges, Ollagnier & Faucon, 1977).

Methods

The experiments were performed on 48 mongrel dogs under chloralose anaesthesia (10 ml/kg i.v. of a 0.8% solution in saline). For each drug, 6 dogs were used to study atrial rate of fibrillation and 6 to study ventricular rate of fibrillation.

Total cardiopulmonary bypass

Total cardiopulmonary bypass (Faucon, Evreux, Bazaugour, Ollagnier & De Clavière, 1974) was performed in dogs with ventricular fibrillation, and with atrial fibrillation. By this technique, oxygenated blood was pumped through a heat exchanger and could be kept at a constant temperature (37.1 ± 0.2°C) to avoid hypothermia-induced variations in the rates of fibrillation.

The auricles were incised and bronchial and coronary venous returns were continuously drained by two catheters, one in each ventricle, to maintain intracardiac blood volumes at a minimal level during fibrillation.

Determination of atrial and ventricular rates of fibrillation

Atrial and ventricular fibrillations were obtained by suprathreshold electrical stimulation directly applied to atrial and ventricular contractile fibres. The rates of fibrillation were studied during the 10 s following the stimulation: a) under 'physiological conditions' i.e. before drug administration, b) after administration of acetylcholine, isoprenaline, ouabain or quinidine. The number of fibrillation waves were counted in each unit of time. The selected value is the mean of three determinations.

Some difficulty occurred in producing atrial fibrillation during the administration of quinidine, because of the drug's antiarrhythmic effects. Consequently, we had first to produce a long-lasting atrial fibrillation by means of an acetylcholine perfusion (1 mg kg^{-1} min^{-1}) (Farges, Lièvre, Ollagnier & Faucon, unpublished observations) and then to test the effects of quinidine on atrial fibrillation.

Recording

Ventricular electrical activity was recorded by means of the derivative of the electrocardiogram (lead I or II) and atrial electrical activity was recorded by means of a direct unipolar electrode fixed on myocardial tissue.

Drugs

The following drugs were used in this study: chloralose, acetylcholine chloride, isoprenaline hydrochloride, ouabain and quinidine sulphate. All the drugs were dissolved in 0.9% w/v NaCl solution (saline) before the beginning of each experiment. Injections and perfusions were administered to the animals directly into the extracorporeal circuit.

When drug perfusions were performed, a period of 20 min was allowed to elapse after the end of each perfusion before setting new stable reference values of atrial and ventricular rates of fibrillation.

Statistics

The significance of the variations in the rate of fibrillation and effective refractory period (ERP) were analyzed according to Student's unilateral t test.

The dependence between the changes in atrial and ventricular rates of fibrillation and of the contractile tissue ERP was determined by calculating the coefficient of linear correlation and the rate of the regression to obtain the regression line.

Results

The control values of ERP and rates of fibrillation before the administration of acetylcholine, isoprenaline and ouabain were respectively 109 ± 25 ms and 1065 ± 181 waves/min for the atrial tissue and 167 ± 17 ms and 832 ± 105 waves/min for the ventricular tissue. The control values before the quinidine injections were quite different since we had first to produce a long-lasting atrial fibrillation by means of an acetylcholine perfusion. The values were 48 ± 12 ms and 1569 ± 176 waves/min for the atrium and 164 ± 16 ms and 819 ± 117 waves/min for the ventricle. The results are therefore recorded as percentage changes.

Acetylcholine-induced variations of atrial and ventricular ERP and rates of fibrillation (Figure 1)

Two minute-perfusions of acetylcholine at increasing concentrations (0.5, 1 and 2 mg kg^{-1} min^{-1}) provoked a considerable decrease in atrial ERP (55.5 ± 18.9% ($P < 0.01$), 65.4 ± 20.8% ($P < 0.001$) and 71.6 ± 21.6% ($P < 0.001$), respectively) and a marked increase in the rate of fibrillation (24.8 ± 15.0% ($P < 0.05$), 64.4 ± 35.2% ($P < 0.01$) and 99.9 ± 45.0% ($P < 0.001$), respectively). No significant variations in ventricular ERP and rate of fibrillation were noted.

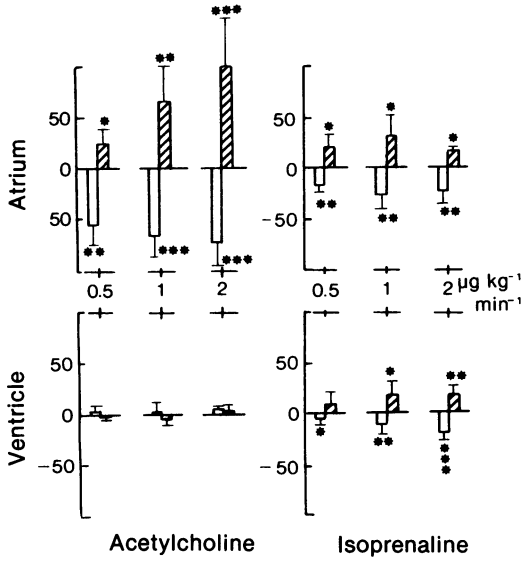

Figure 1. Percentage changes (reference value = 0%) of atrial and ventricular rates of fibrillation (hatched columns), and of atrial and ventricular effective refractory periods (open columns), during successive perfusions with acetylcholine and isoprenaline in increasing concentrations. Vertical bars indicate s.e. means. One, two and three asterisks refer to the significance of the variations at the 5%, 1% and 0.1% fiducial limits respectively.

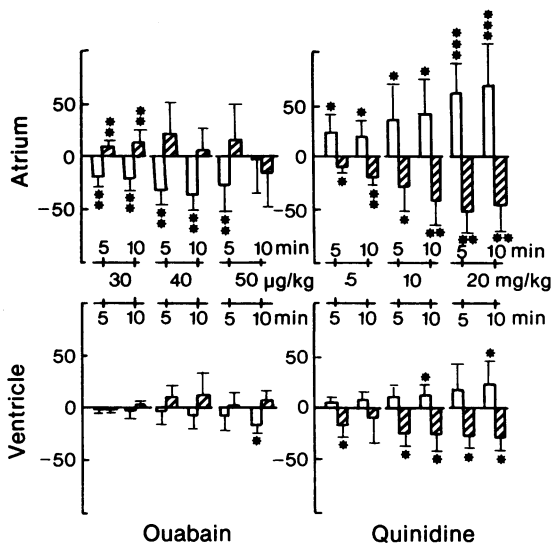

Figure 2. Percentage changes (reference value = 0%) of atrial and ventricular rates of fibrillation (hatched columns), and of atrial and ventricular effective refractory periods (open columns), with cumulative doses of ouabain and quinidine. Vertical bars indicate s.e. means. One, two and three asterisks refer to the significance of the variations at the 5%, 1% and 0.1% fiducial limits respectively.

Isoprenaline-induced variations of atrial and ventricular ERP and rates of fibrillation (Figure 1)

Effects of increasing perfusion concentrations (0.5, 1 and 2 μg kg^{-1} min^{-1}) were examined after 5 min. In the atrium, isoprenaline induced significant decreases in the ERP.; 17.4 ± 5.0%, 27.0 ± 14.4% and 23.0 ± 10.9% respectively ($P < 0.01$), and a significant increase in the rate of fibrillation; 19.9 ± 12.0%, 30.4 ± 22.0% and 15.4 ± 3.7% respectively ($P < 0.05$).

In the ventricle, the changes in ERP and of the rate of fibrillation were similar to those recorded in the atrium i.e. a significant decrease in ERP of 6.0 ± 5.4% ($P < 0.05$), 12.0 ± 9.0% ($P < 0.01$) and 21.2 ± 6.3% ($P < 0.001$) respectively, and a significant increase in the rate of fibrillation of 16.0 ± 13.4% ($P < 0.05$) and 14.3 ± 10.1% ($P < 0.01$), with concentrations of 1 and 2 μg kg^{-1} respectively.

Ouabain-induced variations of atrial and ventricular ERP and rates of fibrillation (Figure 2)

The effects of cumulative doses of ouabain (30, 40 and 50 μg/kg) were recorded 5 and 10 min after each injection. For the atrium, a dose-dependent decrease in the ERP., significant at the 1% level when 30 and 40 μg/kg doses were administered, and a significant increase in the rate of fibrillation of 9.8 ± 5.2% ($P < 0.01$) and 13.8 ± 12.4% ($P < 0.01$) 5 and 10 min after the administration of the 30 μg/kg dose, were noted. An inversion of these effects followed which became obvious 10 min after the injection of the 50 μg/kg dose. Termination of atrial fibrillation was often observed with this dose.

For the ventricle, a slight decrease in the ERP (which became significant only at the 5% level with the largest dose) developed and no significant variation of the rate of fibrillation was noted.

Quinidine-induced variations of atrial and ventricular ERP and rates of fibrillation (Figure 2)

Effects of cumulative doses of quinidine (5, 10 and 20 mg/kg) were recorded 5 and 10 min after each injection.

An increase of both atrial and ventricular ERP and a decrease of both atrial and ventricular rates of fibrillation, depending on the dose and the time after injection, were recorded. The atrium seemed to be more sensitive than the ventricle, since we recorded with

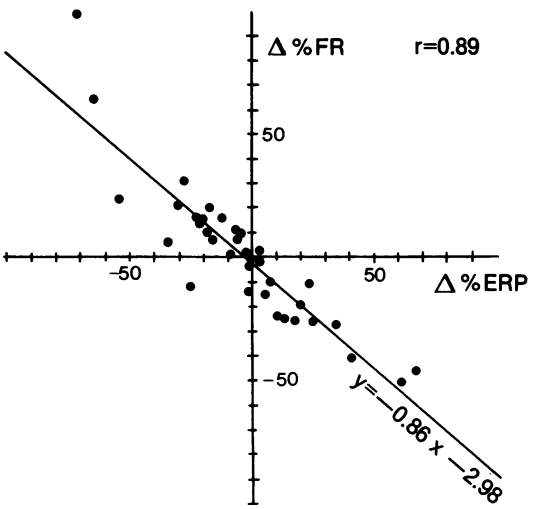

Figure 3. Correlation between the percentage variations of effective refractory periods of cardiac contractile tissues (△% ERP; abscissa scale) and the percentage variations of rates of fibrillation (△% FR; ordinate scale).

the largest dose of quinidine a 67.6 ± 42.0% increase ($P < 0.001$) in atrial ERP as against a 24.4 ± 22.0% increase ($P < 0.05$) in ventricular ERP and a 46.4 ± 25.6% decrease ($P < 0.01$) in atrial rate of fibrillation as against a 25.9 ± 13.0% decrease ($P < 0.05$) in ventricular rate of fibrillation.

High doses of quinidine usually terminated atrial fibrillation, whereas they only slowed down ventricular rate of fibrillation. A decrease of only 25.9 ± 13.0% ($P < 0.05$) was observed 10 min after the largest dose.

Correlation between ERP and rate of fibrillation (Figure 3)

The variations in atrial and ventricular contractile tissue ERP reported above and previously published (Farges *et al.*, 1977) and the variations in the atrial and ventricular rates of fibrillation, appear comparable with regard to absolute values but divergent with regard to evolution. Thus, the correlation between these results has been examined by establishing the regression line. The coefficient of linear correlation (0.89) was highly significant ($P < 0.001$) with the 36 pairs of values reported. Thus, the equation of the regression line was $y = -0.86 \times -2.98$.

Discussion

Our observations confirm the scattered data about the incidence of the shortening of the duration of refractoriness and the rate of fibrillation (Rosenblueth, 1953; McBrooks *et al.*, 1955), since the equation of the regression line is very close to the theoretical equation, $y = -x$, that would indicate a perfect quantitative correlation between the changes in the two parameters.

Furthermore, a relation between contractile tissue refractoriness and sensitivity to fibrillation is classically observed in clinical practice. Cardiac glycosides, in therapeutic dose ranges, are used for converting a flutter into fibrillation (probably in relation to the initial decrease in the refractory period) and, in large doses, for terminating atrial fibrillation (probably in relation to the secondary increase in the refractory period). In man, as in experimental animals, large doses of quinidine induce the disappearance of atrial fibrillation, and slow and amplified waves of fibrillation are recorded just before the reappearance of synchronous contractions.

Consequently, we can affirm that drugs which decrease the ERP of contractile tissue accelerate the rate of fibrillation and sensitize the heart to fibrillation. Conversely, drugs which increase contractile tissue ERP proportionately slow down the rate of fibrillation and may terminate atrial fibrillation.

Hence, it is not surprising to find with the change in the rates of fibrillation, the same heterogeneity of response of atrial and ventricular contractile tissues (i.e. a hypersensitivity of the atrial tissue compared to the ventricular one) as that recorded with atrial and ventricular refractory period after the administration of ouabain and quinidine under identical experimental conditions (Farges *et al.*, 1977). Nevertheless, it is not possible to tell whether the disparity is the consequence of intrinsic electrophysiological differences between atrial and ventricular cells or of an indirect action through the parasympathetic system. Thus potentiation of acetylcholine effects on the atrium has been demonstrated for ouabain (Gaffney, Kahn, Van Maaven & Acheson, 1958; Toda & West, 1966; Chai, Wang, Hoffman & Wang, 1967; Seifen & Seifen, 1967; Farges, Ollagnier, Lièvre & Faucon, 1977) and inhibition of the atrial effects of acetylcholine has been shown for quinidine (Moe & Abildskov, 1975).

Whatever the mechanism may be, since termination of atrial fibrillation occurs with quinidine only when large increases in the atrial ERP are recorded, sufficient increase of the ERP by antifibrillatory agents might be considered as a condition for the effectiveness of these drugs. One can suggest that the less effective action of quinidine on the ventricle in lengthening the duration of refractoriness, and thus in slowing down the rate of fibrillation, might be one reason for the failure of quinidine to terminate ventricular fibrillation.

With regard to the explanation of the correlation observed in the evolution of ERP and rate of fibrillation, the modification of K^+ transport can be considered fundamental. Acetylcholine particularly, and isoprenaline and ouabain to some extent, have been shown to facilitate the repolarizing K^+ outward current. This facilitation obviously decreases the ERP but also primarily induces in contractile fibres automatic properties responsible for their independent spontaneous depolarization and, secondarily, accelerates this depolarization (Moe & Abildskov, 1959; Puech & Grolleau, 1971). Quinidine should act in the opposite direction.

The authors are indebted to Mr McMullen for his linguistic review of the manuscript. Financial support from the U.E.R. Biologie Humaine is gratefully acknowledged.

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(*Received August* 1, 1977
Revised December 13, 1977)