resulted in a significant reduction in the rate of efflux of TEA in both species, but had no effect on PAH runout. The absence of the metabolic substrates acetate or lactate had no effect on the efflux of either the anion or the cation. The addition of DNP, a metabolic inhibitor, markedly enhanced the efflux of PAH and TEA in both the rat and the rabbit compared to control.

The DNP-induced enhancement of efflux correlates with previous observations on the efflux of PAH from dog kidney[9] and supports hypotheses suggesting a highly energy-dependent intracellular accumulation process which, when inhibited, would allow an increase in a more readily diffusable pool available for diffusion (or transport) out of the cell[11,12].

The marked depression of DNP-enhanced efflux of TEA resulting from the further addition of cyanine to the efflux media suggests that transport from the second or 'readily diffusable pool' described above is mediated by a transport system, perhaps at the cell membrane itself, that can be inhibited by cyanine. Cyanine had no effect on PAH efflux from rabbit cortical slices in the presence of DNP and only slightly decreased DNP-enhanced PAH efflux from slices of rat renal cortex. The data emphasize the specificity of the inhibition for organic cation efflux as opposed to a more generalized inhibitory effect. Thus, the cyanine dye, cyanine 863, appears to specifically inhibit the transport of the organic cation, TEA, out of the cells of the renal cortex. Additionally, these studies indicate that the rate of efflux of TEA from rabbit renal cortical slices in the absence of any inhibitor is considerably slower than the efflux of TEA from rat renal cortex or that of PAH in either species (K = 0.021 vs 0.030–0.038).

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Are anticholinergic effects responsible for the heterogeneous quinidine-induced modifications of heart muscle refractoriness?

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Summary. Vagal tone is responsible for the heterogeneous reactivity of atrial and ventricular contractile tissues to quinidine. Acetylcholine may make atrial cells more sensitive to the effects of quinidine.

Over the last 20 years, a dissimilarity in the sensitivity of the different parts of the heart to antiarrhythmic drugs and to quinidine in particular has been shown by means of intracellular recording techniques[2-5]. These results have been confirmed in vivo in our laboratory with experiments on dogs' heart in situ with independent atrial and ventricular activity following the removal of the interventricular septum performed under total cardiopulmonary by-pass: quinidine develops a depressive effect on ventricular ectopic pacemakers, whereas it respects sino-atrial automaticity[6]; it induces a larger increase in the effective refractory period in the atrial contractile tissue than in the ventricular one[7].

With regard to this latter effect on cardiac contractile tissues, the question is whether this dissimilarity is the consequence of quinidine anticholinergic effects[8], since acetylcholine has been shown to be more effective on the atrium[7], or the consequence of an intrinsic disparity in the reactivity of atrial and ventricular contractile fibre due to different electrophysiological properties, since this heterogeneity of response of cardiac contractile tissues to quinidine still exists in dogs with denervated hearts[9].

This present work has been carried out on dogs' heart in situ with independent atrial and ventricular activity, by administering cumulative doses of quinidine after modification of cardiac cholinergic impregnation: either inhibition by atropine, or enhancement by acetylcholine perfusion after bivagotomy.

Methods. The experiments were performed on 6 mongrel dogs for each experimental condition (inhibited and enhanced cardiac cholinergic impregnation) under chloralose anaesthesia (10 ml/kg of a 0.8% solution in saline). In all our experiments, total cardiopulmonary by-pass was performed to remove the interventricular septum and to obtain independent atrial and ventricular activity[6]. With this technique, heart-induced changes in blood pressure are avoided and the recordings are easier to interpret.

The determination of the effective refractory periods (ERP) of atrial and ventricular contractile tissues was made by the extra-stimulus method. The right atrium and the left ventricle were successively stimulated at a basic frequency: period of stimulation 350 msec, by arbitrarily defined suprathreshold (approximate mean threshold, i.e. 1 mA, increased by a factor of 2) square-wave pulses of 5 msec duration delivered by means of 2 myocardial atrial and ventricular unipolar electrodes. The ERP was defined as the shortest interval after the basic stimulus at which an identical extra-stimulus produced a propagated response. 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 atrial tissue.

The functional inhibition of cholinergic influence was realized by administration of 0.2 mg/kg of atropine into the extra-corporal circulation circuit. The enhancement of cardiac cholinergic impregnation was realized, after bivagotomy, by a continuous perfusion of acetylcholine (1 mg/kg min) sufficient to produce a significant decrease in atrial frequency ($p < 0.01$) and in atrial contractile tissue ERP ($p < 0.01$), compared to the reference values checked before bivagotomy. Cumulative doses (5, 10 and 20 mg/kg) of quinidine sulphate dissolved in saline were administered after stabilization of the effects of the atropine injection or

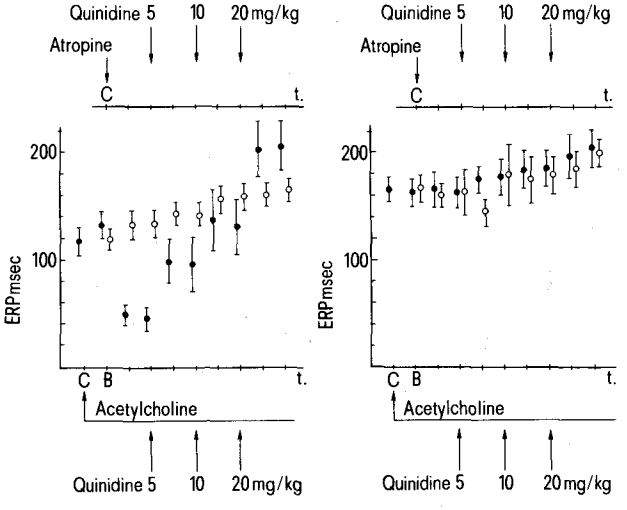
acetylcholine perfusion (10 min), and the effects of each dose of quinidine were observed 5 and 10 min after administration. Statistical comparisons were made according to Student's t-test.

Results. Functional inhibition of vagal influences in each kind of experimental conditions, obtained either by bivagotomy or by atropine injection, provoked a significant increase ($p < 0.05$) in atrial ERP: 135±12 msec as against 118±19 msec for the control values, whereas it did not affect the ERP of ventricular contractile tissue.

The evolutions of ERP of atrial contractile fibres after quinidine injections in dogs treated with atropine and of the ERP of ventricular contractile fibres (both in dogs treated with atropine and in those perfused with acetylcholine) were similar, since no significant difference appeared when we compared, in pairs, the magnitude of the increases of ERP for each dose of quinidine after 5 and 10 min.

The ERP of atrial tissue undergoing cholinergic stimulation was more sensitive to quinidine than the ERP of atrial tissue with cholinergic receptors blocked by atropine: the smallest dose of quinidine was sufficient to provoke a significant increase ($p < 0.01$) in the former, whereas the largest dose was required to provoke a significant increase ($p < 0.05$) in the latter. Furthermore, the maximal values of ERP (203±24 msec) obtained with the largest dose of quinidine (20 mg/kg) were significantly higher ($p < 0.05$) than the maximal values obtained with the same dose in dogs treated with atropine (160±11 msec), although it is well known that the action potential of dog atria becomes shorten as a result of vagus stimulation[10].

Discussion. In dogs treated with atropine, there is no significant difference between the quinidine-induced increases in the ERP of atrial and ventricular contractile tissues. Thus, it appears that the heterogeneity of responses of atrial and ventricular contractile tissues, recorded in normal dogs[7] and in dogs under acetylcholine perfusion, does not depend on the proper action of quinidine on cardiac cells but is closely linked with cholinergic impregnation, especially since acetylcholine has been shown to be effective only on the atrium[7,11-12] and to shorten the ERP of atrial contractile tissue by shortening the action potential[10].



Compared variations of the ERP of atrial and ventricular contractile tissues (in msec) checked 5 and 10 min after injection of cumulative doses of quinidine (5.10 and 20 mg/kg), in dogs after suppression of vagal influences by atropine (0.2 mg/kg) (○), in dogs with enhanced cholinergic impregnation by perfusion of acetylcholine (1 mg/kg/min) after bivagotomy (B) (●). Vertical bars indicate SE of the means and C the initial values before any experimental procedure.

Although the increase in atrial ERP after bivagotomy or atropine injection is significant ($p < 0.05$), it is smaller than that usually observed in normal dogs, i.e. in non-anaesthetized dogs without cardiopulmonary by-pass (G. Faucon, unpublished results). The explanation is the reduced vagal tone of the dogs in our experiments provoked by chloralose anaesthesia[13-15] and by thoracotomy. This is in concordance with what is recorded after administration of quinidine: the levels of the increased atrial ERP after 20 mg/kg doses of quinidine are not significantly different in normal dogs[7] and in dogs treated with atropine, and the evolutions of atrial ERP are similar.

The sharp quinidine-induced increase in atrial ERP in dogs with enhanced cholinergic impregnation is consistent with the development of the classically reported anticholinergic effect of quinidine[8], more visible in these conditions than in normal dogs and in dogs treated with atropine. This increase in atrial ERP was observed in concurrence with an enlargement of the acetylcholine-shortened atrial complexes we checked on our approximately monophasic records. However, the enlargement did not seem to increase the duration of action potential beyond that recorded under quinidine alone. Therefore, the ERP lengthening under acetylcholine and quinidine is thought to have at least 2 reasons, a) a slight lengthening of the action potential and b), more importantly, a slowing of the processes responsible for re-gaining excitability.

In any case, the anticholinergic effect of quinidine cannot explain the fact that the quinidine-induced atrial ERP values are greater when cardiac cholinergic impregnation is enhanced by acetylcholine perfusion than when vagal influences are suppressed by atropine. It is thus suggested that acetylcholine-induced modifications of atrial cell membranes make the atrium more sensitive to the effects of quinidine.

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