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Short communication

Delayed exercise-induced protection against arrhythmias in dogs—effect of celecoxib

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Abstract

A 20-min period of treadmill exercise in dogs, sufficient to increase heart rate by 90–100 beats min^{-1}, markedly decreases the severity of the life-threatening ventricular arrhythmias that result when, following anaesthesia 24 h later, the left coronary artery is occluded. This protection was unaffected by the administration of the selective cyclooxygenase-2 inhibitor celecoxib (two times 3 mg kg^{-1} given intravenously). These results show that prostacyclin, derived from cyclooxygenase-2, plays no role in this pronounced delayed cardioprotection.

Keywords: Delayed preconditioning; Arrhythmias; Celecoxib

1. Introduction

We have suggested that cardioprotective prostanoids may be involved in pacing-induced delayed cardioprotection (Végh et al., 1994) and there is recent support for this conclusion from the observation that cyclooxygenase-2 is involved in the protective effects (infarct size reduction; protection against myocardial stunning) of the late phase of ischaemic preconditioning when this is induced by multiple short occlusions of a coronary artery (reviewed by Bolli et al., 2002). The possible clinical relevance of this is that cyclooxygenase-2 inhibition might thus be associated with increased cardiovascular risk, especially when such drugs are used in patients with arthritis (Pitt et al., 2002); indeed, there is evidence for an increase in atherosclerotic cardiovascular events in patients so treated.

It has been shown recently (Babai et al., 2002) that treadmill exercise in dogs results in a marked, delayed protection against those arrhythmias that result from coronary artery occlusion. We now describe the effect of cyclooxygenase-2 inhibition on this exercise-induced reduction in arrhythmia severity. Such studies should reveal any possible involvement in this protection of prostacyclin, a major product of cyclooxygenase-2 activation (McAdam et al., 1999). Prostacyclin is antiarrhythmic, released during myocardial ischaemia (Coker et al., 1981) and contributes to the early protective effect of ischaemic preconditioning against arrhythmias (Végh et al 1990). Our aim was to determine whether there might therefore be an increased risk from ventricular fibrillation should a coronary artery be occluded when a cyclooxygenase-2 inhibitor is present.

2. Methods and materials

These have been described in detail elsewhere (Babai et al., 2002). In brief, mongrel dogs (mean weight 26.7±0.8 kg) were exercised on a treadmill for 21 min; this was sufficient to increase heart rate (chest lead electrocardiogram) by between 90 and 100 beats min^{-1}

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over the entire exercise period (Babai et al., 2002). Twenty-four hours later, the dogs were anaesthetised (α-chloralose and urethane, 80 and 200 mg kg^{-1}, respectively). Arterial blood and left ventricular pressures (and dP/dt) were also measured. After a left thoracotomy, the anterior descending branch of the left coronary artery was occluded for 25 min. This was followed by rapid reperfusion. Arrhythmias were assessed (Babai et al., 2002) by determining the incidences (Fisher exact test) of ventricular tachycardia and fibrillation as well as survival from the combined ischaemia–reperfusion insult. The risk area was measured by injecting patent blue V dye at the end of the ischaemia/reperfusion period.

The selective cyclooxygenase-2 inhibitor celecoxib was given intravenously both before the exercise protocol and again 24 h later, i.e. 20 min prior to the coronary occlusion, in a dose, 3.0 mg kg^{-1}, which has been shown to selectively inhibit the enzyme in dogs (Hennan et al., 2001).

3. Results

Exercise increased heart rate from 119±7 to 215±6 beats min^{-1} (measured at the end of the exercise period; $P<0.01$) in dogs not given celecoxib and from 109±9 to 212±19 beats min^{-1} in those dogs given the drug ($P<0.001$). This degree of exercise markedly reduced arrhythmia severity when the coronary artery was occluded on the following day (Fig. 1). This protection was not modified by celecoxib; indeed, the drug itself tended to reduce arrhythmias in dogs not subjected to exercise (Fig. 1). There were no differences between the groups in the haemodynamic responses to coronary artery occlusion. There were slight decreases in arterial pressure (of 8±3 mm Hg from a pre-occlusion mean pressure of 104±3 mm Hg) and in left ventricular dP/dt (of 269±121 mm Hg s^{-1} from 2192±246 mm Hg s^{-1}) and increases in heart rate (of 9±3 beats min^{-1} from 153±8 beats min^{-1}) and in left ventricular end-diastolic pressure (of 6.8±1.6 mm Hg from 4.0±0.7 mm Hg). There was no difference in the risk areas (32±1% in the controls, 34±2% in the exercised dogs, 39±3% in the control celecoxib dogs and 32±1% in the exercised dogs given celecoxib).

4. Discussion

These results show that even a single period of exercise in untrained dogs markedly reduces the severity of arrhythmias following anaesthesia and acute coronary artery occlusion 24 h later. The prior administration of a selective cyclooxygenase-2 inhibitor celecoxib does not modify this protection. More importantly, the results show that there is no increased 'cardiovascular risk' from life-threatening arrhythmias following a non-thrombotic coronary artery occlusion. Indeed, there is a tendency for the drug to itself reduce arrhythmia severity; fewer ventricular ectopic beats (Fig. 1) and episodes of ventricular tachycardia (2.3±1.2) than in the controls (15.0±8.1), a lower incidence of ventricular fibrillation and an increased survival.

Bolli et al. (2002) have suggested that cyclooxygenase-2 activation is important for delayed cardioprotection

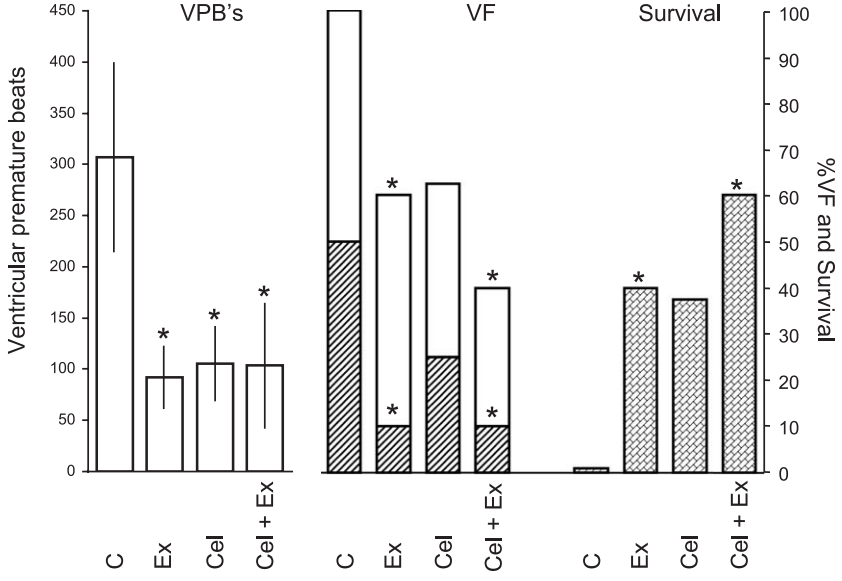

Fig.1. Severity of ventricular arrhytmias during a 25-min coronary artery occlusion in control dogs (C), in control dogs given celecoxib (Cel), in dogs subjected to exercise 24 h previously (Ex) and in exercised dogs given celecoxib (Cel+Ex). Shown are the number of ventricular premature beats (VPBs; means±S.E.M.) the incidence of ventricular fibrillation (VF) during occlusion (stippled columns) and reperfusion (open columns) and survival from the combined ischaemia/reperfusion insult. *$P<0.05$ cp controls.

when several brief coronary artery occlusions are used to induce preconditioning. This suggests that such brief periods of ischaemia, necessary in these (rabbit and mouse) models to induce delayed preconditioning, lead to cyclooxygenase-2 activation, perhaps because of a local inflammatory response. However, the present study shows that preconditioning by other means (exercise) does not depend for efficacy on such activation and that cardioprotective prostanoids, such as prostacyclin do not have an important role. Our conclusion (Babai et al., 2002) that the key mediator in exercise-induced preconditioning is nitric oxide stands.

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