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Beneficial effects of dexmedetomidine on ischaemic myocardium of anaesthetized dogs†

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Summary

We have studied the effect of dexmedetomidine during coronary artery stenosis (CAS) in dogs. Three periods of 15 min of CAS were induced at 40-min intervals in two groups of dogs (dexmedetomidine compared with placebo). Dexmedetomidine was administered before the second and third periods of CAS in doses of 1 and 3 μg kg^{-1}, respectively. Dexmedetomidine decreased plasma concentrations of noradrenaline by mean 71 (SEM 9) %, heart rate by 8 (4) %, cardiac output by 30 (6) % and increased mean arterial pressure by 23 (10) %. Dexmedetomidine reduced blood flow in non-ischaemic myocardium and in the ischaemic epicardial layer by 16 (8) %, but blood flow was preserved in the ischaemic mid-myocardial and subendocardial layers. Consequently, dexmedetomidine increased the ischaemic–non-ischaemic blood flow ratio. Dexmedetomidine did not change myocardial oxygen demand from 4.91 (0.33) to 3.76 (0.25) μmol min^{-1} g^{-1}, thereby reducing the oxygen deficiency of the ischaemic myocardium from 1.47 (0.37) to 0.29 (0.32) μmol min^{-1} g^{-1}. (*Br. J. Anaesth.* 1996;**77**:427–429)

Key words

Sympathetic nervous system, adrenergic agonists. Heart, myocardial function. Sympathetic nervous system, dexmedetomidine. Heart, ischaemia. Heart, blood flow, myocardial. Dog.

Preliminary studies suggest that perioperative use of dexmedetomidine may result in a decreased risk of adverse cardiac events, including myocardial ischaemia[1]. This probably depends on a centrally mediated sympatholytic effect which decreases catecholamine-mediated stress responses. In contrast with these beneficial central effects, α_2 agonists may also cause peripheral and coronary vasoconstriction by stimulation of postjunctional α_2 adrenergic receptors. The effect of this vasoconstriction during myocardial ischaemia is controversial. Heusch and Deussen presented evidence that α_2 adrenoreceptor activation can worsen ischaemia[2]. In contrast, other investigators reported that α adrenoreceptor stimulation can beneficially modulate coronary blood flow during myocardial ischaemia by preventing transmural redistribution of blood flow away from ischaemic endocardium[3].

The aim of this study was to determine if systemic dexmedetomidine has beneficial effects on ischaemic myocardium in an animal model known to be highly sensitive to the direct, peripheral vasoconstrictor effect of α_2 agonists.

Methods and results

After obtaining animal Ethics Committee approval, mongrel dogs were anaesthetized with pentobarbitone and their lungs ventilated with 1% halothane and nitrous oxide in oxygen. The dogs were instrumented, as described previously[4], to measure aortic and left ventricular pressure and cardiac output. A cuff was placed on the left descending coronary artery (LAD). Coronary pressure was measured distal to the cuff. The degree of stenosis was controlled by keeping constant mean perfusion pressure distal to the stenosis using a Servo system feeding a motor pump, which determined the degree of cuff inflation. Global myocardial oxygen demand was estimated using the pressure–work index[5]. Regional oxygen consumption was measured from blood flow (radioactive microspheres) and local arterial–coronary venous oxygen content difference. Oxygen deficiency was calculated by subtracting oxygen consumption from oxygen demand.

Five minutes before the first period of CAS, control blood samples were obtained and haemodynamic measurements were performed. Thereafter, CAS 1 was induced by reducing mean pressure in the LAD distal to the stenosis to 40% of mean arterial pressure. After 12 min of stenosis, microspheres were injected. Two minutes later, blood samples were obtained and haemodynamic measurements performed. Thereafter, the CAS was released. Twenty minutes after release of the stenosis, measurements were repeated, followed by administration of dexmedetomidine 1 μg kg^{-1} in the active drug group ($n=11$) and saline in the placebo group ($n=9$). Twenty minutes after administration of dexmedetomidine, measurements were repeated followed by a second period of stenosis. Measurements during stenosis and the subsequent recovery period were the same as during the first episode of stenosis. This procedure was repeated a third time after administration of dexmedetomidine 3 μg kg^{-1} in the drug group.

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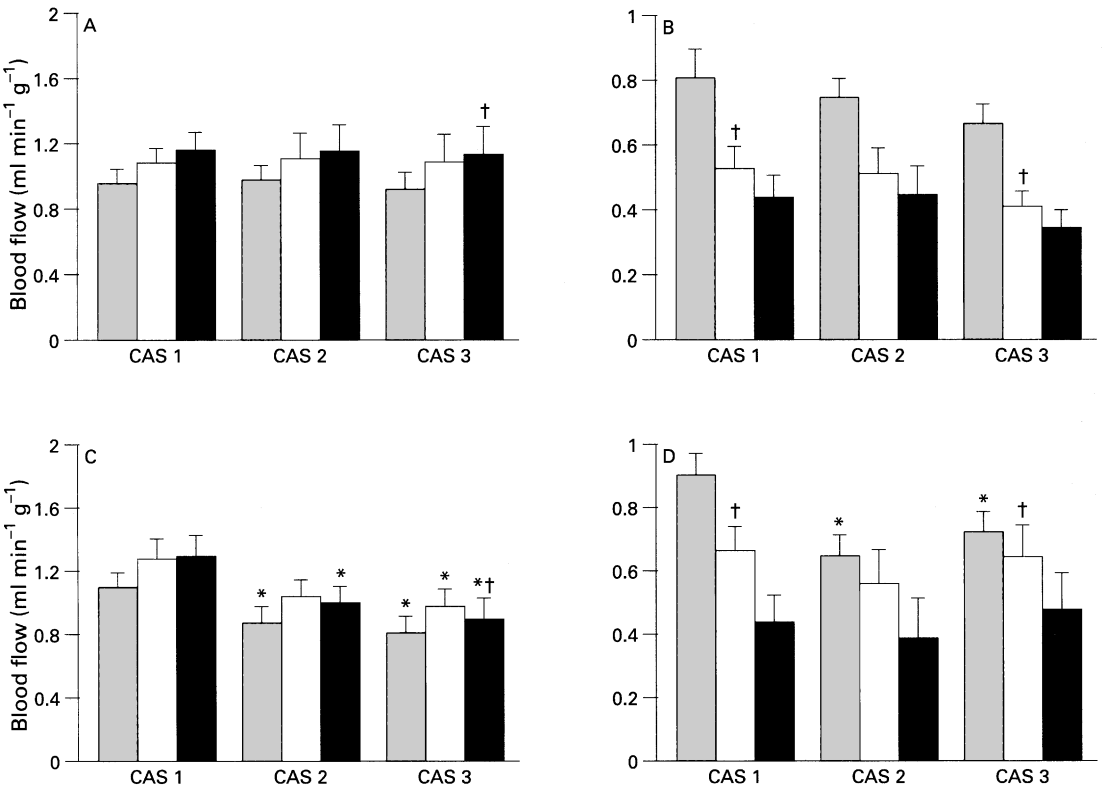

Figure 1 Regional blood flow distribution in non-ischaemic (left, A and C) and ischaemic (right, B and D) myocardium in the placebo (upper, A and B) and drug (lower, C and D) groups, measured with radioactive microspheres. Transmural samples were obtained from the perfusion area of the LAD (ischaemic myocardium) and from the posterior wall and interventricular septum (non-ischaemic myocardium). Samples were divided into subendocardial, mid-wall and subepicardial layers. In this way, coronary blood flow was measured simultaneously in non-ischaemic and ischaemic myocardium during the three stenoses. Shaded bars = epicardial flow; open bars = mid-myocardial flow; solid bars = endocardial flow. CAS = Coronary artery stenosis. Data are mean (SEM); $n = 9$ in the placebo group, $n = 11$ in the drug group. *Significantly different from corresponding CAS 1 value; †significantly different from corresponding value in other group.

Two-way ANOVA for repeated measures was used for inter-group comparisons. Intragroup comparisons were evaluated using one-way ANOVA for repeated measures and Fisher's protected LSD test as *post hoc* test. Baseline values between the two groups were compared using Student's *t* test. $P < 0.05$ was considered significant. Results are expressed as mean (SEM).

Dexmedetomidine decreased heart rate (from 126 (6) to 114 (5) beat min^{-1}), d*P*/d*t*max (from 1371 (128) to 1177 (62) mm Hg s^{-1}) and cardiac output (from 4.2 (0.3) to 2.4 (0.4) litre min^{-1}) and increased mean arterial pressure (from 81 (4) to 98 (4) mm Hg) and systemic vascular resistance (from 1572 (131) to 3902 (563) dyn s cm^{-5}). In the placebo group, no haemodynamic changes were observed throughout the study.

Dexmedetomidine decreased plasma concentrations of noradrenaline from 121 (17) to 25 (12) pg ml^{-1}.

After dexmedetomidine 3 μg kg^{-1}, ischaemic–non-ischaemic blood flow ratios were significantly higher in the epicardial (from 0.81 (0.07) to 0.93 (0.09) and endocardial (from 0.33 (0.06) to 0.47 (0.10) layers compared with placebo (fig. 1).

Dexmedetomidine increased haemoglobin concentration from 7.2 (0.2) to 8.4 (0.3) mmol litre^{-1} and decreased myocardial oxygen demand from 4.91 (0.33) to 3.76 (0.25) μmol min^{-1} g^{-1}. Regional myocardial oxygen consumption did not change after dexmedetomidine (from 3.08 (0.39) to 3.20 (0.51) μmol min^{-1} g^{-1}). Dexmedetomidine decreased myocardial oxygen deficiency from 1.47 (0.37) to 0.29 (0.32) μmol min^{-1} g^{-1}.

Comment

In this study, dexmedetomidine decreased myocardial oxygen demand and reduced blood flow in non-ischaemic myocardium. This was related to its haemodynamic effects; reduction in heart rate and d*P*/d*t*max. Blood flow in the ischaemic inner layers was preserved. In this way, the ischaemic–non-ischaemic blood flow ratio decreased and myocardial oxygen deficiency was reduced.

The effects of dexmedetomidine on regional blood flow in ischaemic myocardium are in accordance with studies on the effects of aspecific α block or stimulation during ischaemia[3]. Preservation of blood flow in ischaemic myocardium by α_2 agonists is probably caused by more powerful local metaboic stimuli during ischaemia, which overrule adrenergic vasoconstriction. As the degree of ischaemia is most severe in the inner layers during hypoperfusion, adrenergic vasoconstriction in this region is inhibited to a greater extent than in the outer layer.

Distal to a flow-limiting stenosis, such specific epicardial vasoconstrictive effect may lead to improvement in endocardial perfusion, the "reverse steal" effect[3]. The decrease in heart rate after dexmedetomidine could be an additional explanation for this beneficial effect on blood flow, because slowing of the heart rate favours endocardial relative to epicardial perfusion. The different findings of Heusch and Deussen[2] who found that α_2 adrenergic activation can worsen myocardial ischaemia, may be explained by differences in preparation, degree of ischaemia, anaesthesia, and intensity and mode of α adrenergic stimulation.

Our preparation was expected to be highly sensitive to the direct, peripheral vasoconstrictor effects of dexmedetomidine[4]. Compared with humans, we therefore may have overstimated the coronary vasoconstrictive effects and underestimated the central sympatholytic effects of dexmedetomidine. This could also underestimate a possible anti-ischaemic effect of dexmedetomidine, because it was shown that systemic clonidine had anti-ischaemic properties, while intracoronary administration caused vasoconstriction[6]. However, these results should be extrapolated with caution to potential clinical use in humans as the results relate only to halothane-anaesthetized dogs. Halothane not only has marked haemodynamic effects, but could also have influenced the sympathetic responses.

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