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Adenosine causes transient dilatation of coronary arteries in man

A. H. WATT[1], W. J. PENNY[2], H. SINGH[2], P. A. ROUTLEDGE[1] & A. H. HENDERSON[2]
Department of Pharmacology and [1]Therapeutics and [2]Cardiology, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN

We investigated the effects of i.v. adenosine on coronary blood flow in 10 normal subjects undergoing investigation for chest pain. Coronary flow transiently doubled after ≥ 3.5 mg adenosine without increase in perfusion pressure, systolic load or inotropic state at a constant, paced heart rate. The data provide direct evidence that adenosine dilates coronary arteries in man. The transience of the effect suggests a possible role for adenosine in repeated estimations of coronary flow reserve.

Keywords adenosine coronary blood flow

Introduction

Adenosine is an endogenous nucleoside with a variety of pharmacological effects (Watt & Routledge, 1986a). Particular attention has been paid to its effects on coronary flow (Berne, 1980). The coronary vasodilator effect of adenosine has been demonstrated in a number of laboratory animals (Merrill *et al.*, 1978; Olsson *et al.*, 1979; Rembert *et al.*, 1980). Release of adenosine and related purines in response to increased metabolic demand or myocardial ischaemia has been shown in laboratory animals (Katori & Berne, 1966; Olsson, 1970; Schrader *et al.*, 1977; Watkinson *et al.*, 1979) and during pacing-induced ischaemia in man (Fox *et al.*, 1974; Edlund *et al.*, 1985) at concentrations capable of exerting a coronary vasodilator effect (McKenzie *et al.*, 1982; Ely *et al.*, 1983). Whether adenosine totally fulfils the role of mediating local metabolic regulation (Berne, 1980; 1985) *in vivo* remains uncertain, however. We studied the effect of adenosine on coronary blood flow and left ventricular function in man in whom it has not previously been defined.

Methods

Ten patients (aged 41–65 years, four men) were studied during the course of routine investigation of chest pain, having been shown to have no significant stenosis at coronary arteriography and no other obvious cardiovascular disease. The protocol was approved by the hospital ethics committee and each subject gave informed, written consent.

Coronary blood flow was measured using a Baim thermodilution catheter (Baim *et al.*, 1980) advanced to the coronary sinus from the left subclavian vein. Systemic arterial pressure was recorded from a sheath in the right femoral artery. Left ventricular end diastolic pressure (LVEDP) and indices of contractility (peak LV dP/dt and peak LV dP/dt/P) were recorded using a Millar micromanometer-tipped catheter positioned in the left ventricle. Hearts were paced at 100 beats min^{-1}, using a bipolar pacing electrode in the right ventricle, to prevent adenosine-induced alterations in heart rate (Watt & Routledge, 1986b).

Measurements were made immediately before and after each of four single-blind bolus injections into the femoral vein of adenosine (3.5, 6 and 8.5 mg) and 0.9% saline. Each injection was immediately followed by a flushing bolus of 2 ml saline. The sterile adenosine preparation

Correspondence: Dr P. A. Routledge, Department of Pharmacology and Therapeutics, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN

contained adenosine (Sigma) in a final concentration of 5 mg ml^{-1} dissolved in 0.9% sodium chloride solution.

Continuous recordings were obtained of systemic arterial pressure, LVEDP, LV dP/dt and LV dP/dt/P. Great cardiac vein flow was measured continuously before and for 60 s after each injection, to provide a relative measure of coronary flow in preference to measurement of coronary sinus flow, because of difficulty in maintaining coronary sinus catheter position so that the proximal thermistor was unaffected by right atrial blood flow.

Data are presented as the mean ± s.d. and compared using two way analysis of variance and Student-Newman-Keuls test for multiple comparisons, $P < 0.05$ being the minimal level of statistical significance.

Results

Intravenous injections of adenosine increased coronary flow by 98, 105 and 75% from pretreatment flow rates of 103 ± 42, 101 ± 48 and 102 ± 32 ml min^{-1} at doses of 3.5, 6 and 8.5 mg, respectively, to peak flow rates of 204 ± 74, 207 ± 71 and 189 ± 63 ml min^{-1} ($P < 0.001$ compared with control in all cases), whereas saline injection had no effect (106 ± 42 and 103 ± 42 ml min^{-1}, before and after saline (Figure 1). The adenosine-induced increase in coronary flow was transient, flow increasing to a peak at approximately 20 s and returning to normal within a further 60 s.

Adenosine 3.5 mg, 6 mg and 8.5 mg reduced mean femoral artery pressure by 19, 24 and 22% respectively from 108 ± 15, 103 ± 11 and 114 ± 4 mmHg, to 87 ± 11, 77 ± 9, 89 ± 9 mmHg at the nadir of the response ($P < 0.001$ compared with control in all cases), whereas saline injection had no effect (106 ± 14 and 106 ± 14 mmHg, before and after saline, $n = 10$) (Figure 2). The nadir of the response also occurred approximately 20 s after each injection. Peak LV dP/dt was not significantly altered by the three doses of adenosine or saline: pretreatment values 1436 ± 363, 1431 ± 295, 1638 ± 323 and 1507 ± 413 mmHg s^{-1} and post treatment values 1541 ± 341, 1492 ± 403; 1635 ± 322 and 1523 ± 400 mmHg s^{-1} respectively. Peak LV dP/dt/P was likewise unaltered by the three doses of adenosine or saline: pretreatment values 38 ± 7, 36 ± 5, 35 ± 3 and 37 ± 7 s^{-1} and post treatment values 40 ± 9, 39 ± 6, 34 ± 3, 36 ± 6 s^{-1} respectively.

All subjects reported awareness of increased depth of ventilation. Nine subjects experienced transient chest pain, severe enough in three to lead to omission of the 8.5 mg dose. No other symptoms were reported.

Discussion

These results provide direct evidence that adenosine increases coronary flow in man. Coronary flow was approximately doubled at each concentration used. The increases in coronary flow occurred despite a fall of about 20 mmHg in systemic arterial pressure, with no significant change in isovolumic indices of contractility, and at constant, paced heart rate. These findings are in accord with previous reports of negligible effects of adenosine on inotropic state in either direction (Buckley *et al.*, 1961; Lammerant & Becsei, 1973; Urthaler *et al.*, 1981; Burnstock & Meghji, 1983). The increase in coronary flow cannot therefore be attributed to a metabolic

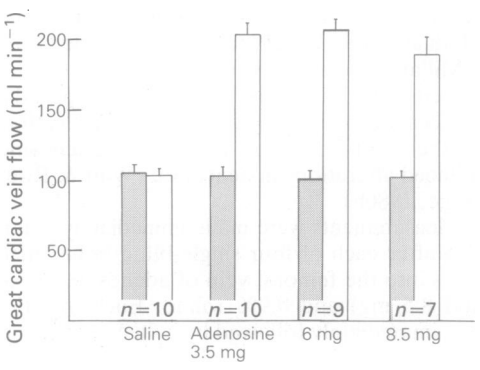

Figure 1 Great cardiac vein flow (mean ± s.d.) at baseline prior to each injection (▩) and after saline or adenosine injections (□).

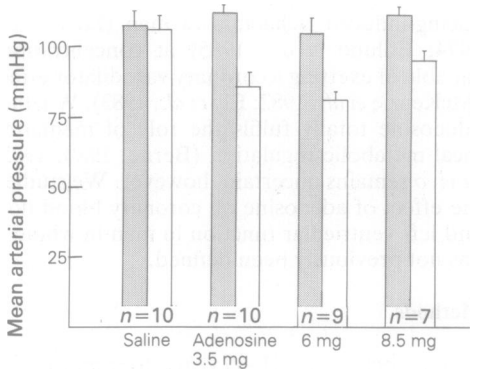

Figure 2 Right femoral artery pressure (mean ± s.d.) at baseline prior to each injection (▩) and after saline or adenosine injections (□).

response to increased cardiac work. It indicates a direct coronary vasodilator response. It was transient in each case, lasting no more than 1 min. The vasodilator response, both of the coronaries and the systemic arteries, appeared to be almost maximal at the lowest dose tested (3.5 mg). This dose has been reported to cause minimal cardiac electrophysiological effects (Watt & Routledge, 1986b), suggesting a difference in the dose response with respect to these two effects of adenosine.

Transient retrosternal chest pain was experienced by nine of the 10 patients, as previously described (Watt & Routledge, 1985; Sylven *et al.*, 1986). This angina-like pain was shown in the present study to be associated with an increase in coronary flow. Despite a demonstrable increase in overall coronary flow and circumstantial evidence of a reduction in cardiac 'workload' and oxygen requirements (lower systemic arterial pressure implies reduced myocardial systolic wall stress), the lack of simultaneous coronary sinus oxygen measurements leaves the theoretical possibility that adenosine could have induced 'coronary steal' with shunting across the capillary bed. This is intrinsically unlikely, however, because adenosine dilates small arteries, and 'coronary steal', whose mechanism remains unresolved, occurs at the expense of beds supplied by stenosed arteries. The mechanism remains unknown. There is evidence that adenosine can reproduce pain in other organs and tissues (Watt *et al.*, 1986).

Adenosine-induced changes in coronary blood flow are transient and might be usefully applied in the measurement of coronary flow reserve, as an alternative to atrial pacing (Cannon *et al.*, 1985) or intravenous dipyridamole (Opherk *et al.*, 1981), particularly where repeated measurements are required to assess physiological or pharmacological interventions.

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