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Effect of infused adenosine on cardiac output and systemic resistance in normal subjects

A. BUSH[1], CAROLYN M. BUSST[1], B. CLARKE & P. J. BARNES[3]
The Departments of [1]Clinical Physiology, [2]Cardiology and [3]Thoracic Medicine, Brompton Hospital, Fulham Road, London, SW3 6HP

1 The purine nucleoside adenosine relaxes smooth muscle *in vitro* and is a vasodilator in animals, but its effects on cardiac output and systemic vascular resistance have not been measured in normal conscious human subjects.
2 We have studied the effects of infused adenosine in doses of 0.005, 0.03 and 0.07 mg kg^{-1} min^{-1} on pulmonary blood flow and systemic vascular resistance in eight healthy volunteers, using a non-invasive, inert gas method and mass spectrometry.
3 At a dose of 0.07 mg kg^{-1} min^{-1}, there was a rise in effective pulmonary blood flow (which is approximately equivalent to cardiac output) of 0.52 ± 0.08 l min^{-1} m^{-2} (mean ± s.e. mean) and a fall in estimated systemic vascular resistance of 357 ± 44 dyn s cm^{-5}. Despite this marked systemic vasodilation, there was no significant change in mean heart rate.
4 The effects of this dose of adenosine were maximal 2 min after starting the infusion, and had disappeared within 5 min of stopping it.
5 Adenosine may be therapeutically useful in the reduction of left ventricular afterload, where the absence of reflex tachycardia may be advantageous. We suggest that adenosine in doses of 0.03 mg kg^{-1} min^{-1} should be evaluated as a selective pulmonary vasodilator.

Keywords adenosine pulmonary circulation vasodilator agents

Introduction

Adenosine is a purine nucleoside intermediary in the pathway of purine nucleotide degradation, which is formed by the hydrolysis of adenosine triphosphate by 5′ nucleotidase. It has a half-life in blood of less than 1 min (Klabunde, 1983), and is broken down by adenosine deaminase, adenosine kinase or S-adenylhomocysteinase to the inactive metabolites hypoxanthine and inosine (Fox & Kelley, 1978). Infused adenosine causes tachycardia and a rise in skin temperature without any change in blood pressure in normal volunteers (Fuller *et al.*, 1987). It is also a coronary vasodilator (Watt *et al.*, 1987). It has been used clinically to prevent platelet aggregation (Sollevi *et al.*, 1985), as an anti-arrythmic agent (Berne *et al.*, 1984; Clarke *et al.*, 1987) and as a systemic vasodilator during anaesthesia (Sollevi *et al.*, 1984; Torsell *et al.*, 1985). Its short half-life potentially makes its effects easy to control. The aim of this study was further to investigate the cardiovascular effects of infused adenosine in normal subjects. We have measured pulmonary blood flow using a non-invasive, inert gas method, in order to determine its effect on cardiac output and systemic resistance.

Correspondence: Dr A. Bush, Brompton Hospital, Fulham Road, London SW3 6HP

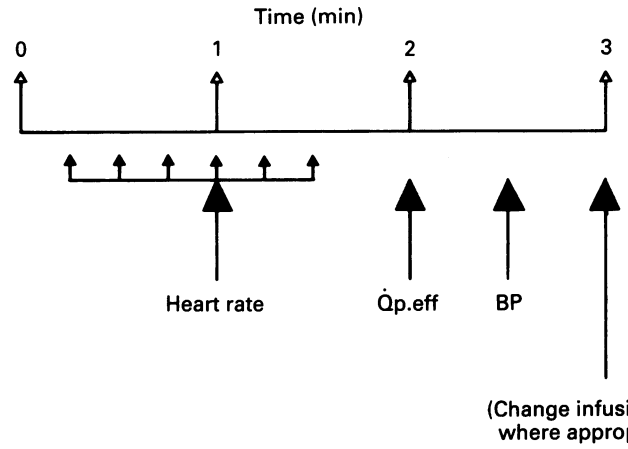

Figure 1 The 3 min cycle of measurements. Mean heart rate was nominally at 1 min, and was the mean of six readings, 15 s apart from time 15 to time 90 s. Effective pulmonary blood flow (Qp.eff) was taken at 2 min, the time of starting the slow expiration from full inspiration. Blood pressure (BP) was taken at time 2 min 30 s, the time the measurement was started. Any alterations in infusion rate were at 3 min.

Methods

Subjects

We studied eight normal healthy volunteers (five males, three females), of mean age 32 (range 24–39) years. All gave informed consent, and the protocol was approved by the Ethics Committee of the National Heart and Chest Hospitals. Several days prior to the study, subjects were familiarised with the apparatus and practised the single breath manoeuvre (below) until proficient. The design was a double-blind, crossover study with the order of infusion randomised, and each subject was studied on two separate days.

Protocol

The same protocol was followed on each occasion. The subjects attended the laboratory after an overnight fast. A cannula was inserted in a forearm vein, the blood pressure cuff wrapped around the (opposite) upper arm, and the electrocardiographic leads positioned. The subject then rested seated in front of the apparatus, in silence, for 15 min. The study then ran without a break for 126 min, that is, while 42 3 min sets of identical measurements (see below) were made. The first twelve sets (36 min) were prior to the infusion of drug. There were six subsequent stages of 5 sets (15 min) each. Adenosine (Fluorochem, Derby, UK) was made up into sterile ampoules containing 5 mg ml^{-1} in 0.9% saline, and was given by continuous intravenous infusion (Braun ED2 perfusor pump). The rate was adjusted so that successively doses of 0.005, 0.03, 0.07 0.03, 0.005 mg kg^{-1} min^{-1} were given. For the final 15 min, no drug was infused. On the placebo day, 0.9% saline was administered at the same flow rates.

Measurements

Every 3 min throughout the study the same cycle of measurements was made in the identical order (Figure 1).

The heart rate was recorded every 15 s on a single channel ECG machine, and measured from the R-R interval. Since we had previously shown that the measurement of Qp.eff significantly affects heart rate (Bush *et al.*, 1988), we took the mean of the six measurements from 15 to 90 s in the cycle illustrated in Figure 1. All other heart rate data were discarded.

Accessible lung volume (VA) and effective pulmonary blood flow (Qp.eff) were measured by the single breath argon-freon test (Denison *et al.*, 1980; Denison & Waller, 1982). In this technique subjects inspired a vital capacity of a test gas containing 10% argon, 3.5% freon-22 (chlorodiflouromethane), and 35% oxygen in nitrogen. After a 1–2 breath-hold at total lung capacity, they then exhaled slowly to residual volume at a rate of 0.08 l s^{-1}. The changing partial pressures of argon and freon-22 were monitored at the lips by a mass spectrometer (MGA 200, Centronics Ltd) and plotted against

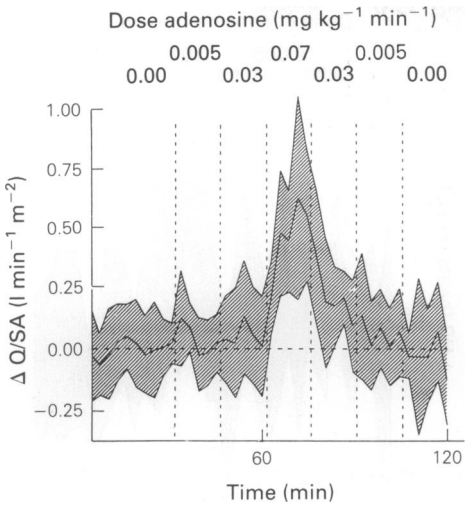

Figure 2 Change in surface area corrected effective pulmonary blood flow (Q/SA) in l min^{-1} m^{-2}. The placebo results were subtracted from the adenosine results, the mean baseline result subtracted from all points, and the mean and 95% confidence intervals of the difference plotted against time (min).

time on a flat bed, four channel pen recorder (Linseis, Selb, West Germany). The traces were digitised on a Tektronix tablet, linked via a graphics terminal to a Prime 750 computer. The calculations were as described elsewhere (Denison *et al.*, 1980). VA, the dilution volume of argon, is within 85% of total lung capacity measured in a body plethysmograph in normal subjects, and Qp.eff, that part of pulmonary blood flow which takes part in gas exchange, is within 95% of cardiac output in normal people (Davidson *et al.*, 1972). It was measured from the time constant of the fall in the partial pressure of freon-22. A fixed time interval was used for the calculation (12–24 s from the start of the manoeuvre for all subjects), because a previous study had shown that this yielded more reproducible results than selecting a linear portion by eye (Bush *et al.*, 1988), using this method. The mean coefficient of variation of Qp.eff within a study is 5.5% (Bush *et al.*, 1988), and between studies is 6.5% (Waller, 1982).

Systolic, diastolic and mean blood pressure (respectively SBP, DBP, MBP; mm Hg) were measured ultrasonically using a Dinamapp vital signs monitor (Critikon Ltd, USA), which is in good agreement with aortic pressure measured invasively (Borow & Newburger, 1982).

Systemic vascular resistance (SVR, dyn s cm^{-5}) was estimated using the equation: SVR = (80 × MBP)/Qp.eff. This slightly overestimates SVR because cardiac output is slightly greater than Qp.eff. We also assumed that the ratio of Qp.eff to cardiac output is not altered by adenosine.

Statistical methods

Since the first two Qp.eff manoeuvres consistently yield higher results than subsequent measurements (Waller, 1982), all the data for the first 6 min of the study were discarded, leaving 30 min (10 sets of measurements) to be analysed for the pre-infusion baseline. For each parameter (VA, Qp.eff, HR etc) the value for each of the remaining time points for placebo was subtracted from that for adenosine. In addition, Qp.eff was divided by body surface area, to remove some of the individual variation in this measurement. The small differences in baseline measurements between the two study days was removed for each parameter in turn by finding the mean of the 10 baseline measurements, and subtracting this mean from all 40 time points for that parameter. Thus the final analysis was performed on the arrays of data consisting of the change over baseline for (drug minus placebo). All subsequent references in this paper are to these arrays, and not to the original absolute measurements.

Results

The mean and 95% confidence intervals of the change with adenosine were found for VA, Qp.eff, HR, SBP, DBP, MBP and SVR. Inspection of these data revealed significant changes only for Qp.eff (Figure 2) and SVR (Figure 3) at the highest dose of adenosine. Since tachycardia has been reported during adenosine infusion (Sollevi, 1986; Fuller *et al.*, 1987; Conradson *et al.*, 1987), the heart rate data are also plotted (Figure 4), but there is no convincing evidence of any effect of the drug at the concentrations used.

Inspection of the plots suggested that the first measurement after starting or stopping the highest dose of adenosine might be significantly different from the next four. Hence the mean effect of any dose of adenosine was taken as the average of the second to the fifth measurements of each stage (Table 1).

Analysis of variance showed that neither Qp.eff nor SVR changed significantly between the first and subsequent measurements on 0.07 mg kg^{-1} min^{-1} ($F = 2.57$ and 1.38 respectively), suggesting that a plateau had been reached. When the rate of infusion was reduced, Qp.eff did not change significantly between the first and

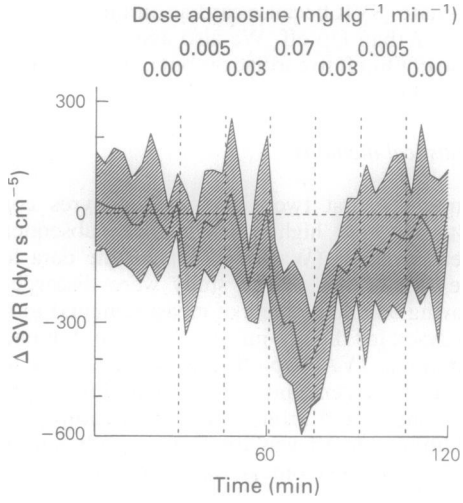

Figure 3 Change in systemic vascular resistance (SVR) in dyn s cm^{-5}. The placebo results were subtracted from the adenosine results, the mean baseline result subtracted from all points, and the mean and 95% confidence intervals of the difference plotted against time (min).

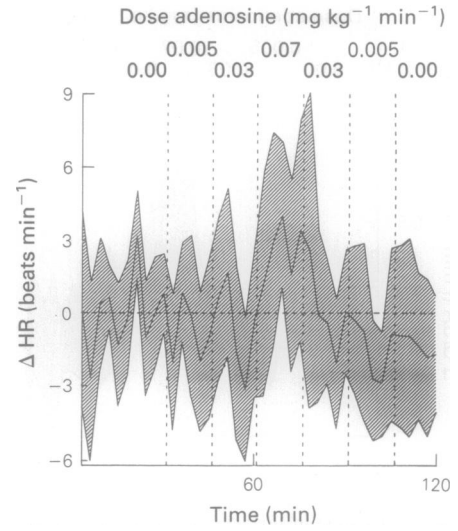

Figure 4 Change in heart rate (HR) in beats min^{-1}. The placebo results were subtracted from the adenosine results, the mean baseline result subtracted from all points, and the mean and 95% confidence intervals of the difference plotted against time (min).

Table 1 Group mean ± s.e. mean for changes in accessible lung volume (VA, litres); effective pulmonary blood flow (Q/SA, l min^{-1} m^{-2}); heart rate (HR, beats min^{-1}); systolic, diastolic and mean blood pressure (respectively SBP, DBP, MBP, mm Hg); and systemic vascular resistance (SVR, dyn s cm^{-5}).

	Dose of adenosine (mg kg^{-1} min^{-1})						
	0.00	*0.005*	*0.03*	*0.07*	*0.03*	*0.005*	*0.00*
VA	0.00 ±0.03	0.02 ±0.04	−0.03 ±0.04	0.15 ±0.05	0.04 ±0.04	0.13 ±0.04	0.13 ±0.04
Q/SA	0.00 ±0.02	0.02 ±0.03	0.05 ±0.05	0.52 ±0.08	0.16 ±0.05	0.04 ±0.04	−0.03 ±0.06
HR	0.0 ±0.4	−0.6 ±0.7	−0.8 ±0.9	3.0 ±1.0	−0.6 ±0.7	−1.8 ±0.8	−1.5 ±0.8
SBP	0.0 ±0.7	−3.5 ±1.4	−4.4 ±1.3	0.9 ±1.7	−0.3 ±2.0	−1.3 ±1.4	−2.8 ±1.4
DBP	0.0 ±0.5	0.6 ±0.9	1.2 ±1.0	−2.1 ±1.2	−2.5 ±0.8	−2.6 ±1.1	−0.7 ±1.1
MBP	0.0 ±0.6	−3.1 ±1.5	−3.6 ±1.4	−1.9 ±1.6	−2.4 ±1.6	−2.5 ±1.7	−2.9 ±1.3
SVR	0 ±21	−52 ±33	−82 ±43	−357 ±44	−157 ±37	−76 ±48	−37 ±47

subsequent measurements on 0.03 mg kg^{-1} min^{-1} ($F = 1.45$). However the first measurement of SVR was significantly lower than subsequent measurements (347 ± 81, $n = 4$; *vs* 157 ± 37, $n = 31$, $F = 2.77$, $P < 0.05$).

There was considerable variation in the individual responses to 0.07 mg kg^{-1} min^{-1} adenosine in terms of cardiovascular effects (Table 2) and side-effects. Increase in HR, which was not significant for the group, varied from 13.8 to −3.7 beats min^{-1} increase in Qp.eff from 0.84 to −0.26 l min^{-1} m^{-2}, and fall in SVR from 69 to 571 dyn s cm^{-5}. No side-effects were encountered except on the highest dose of adenosine. These

Table 2 Individual responses (mean ± s.e. mean) to the infusion of adenosine (0.07 mg kg^{-1} min^{-1}) for heart rate (HR, beats min^{-1}), pulmonary blood flow (Q/SA, l min^{-1} m^{-2}) and systemic vascular resistance (SVR, dyn s cm^{-5}).

Number	*HR*	*Q/SA*	*SVR*
1	4.8 ± 1.0	0.84 ± 0.14	−571 ± 70
2	2.8 ± 0.9	0.72 ± 0.04	−177 ± 56
3	13.8 ± 1.4	0.57 ± 0.03	−511 ± 88
4	2.7 ± 2.2	0.60 ± 0.09	−416 ± 44
5	−0.2 ± 1.6	0.53 ± 0.12	−312 ± 131
6	2.8 ± 2.4	0.83 ± 0.35	−536 ± 191
7	−3.7 ± 2.3	0.34 ± 0.07	−262 ± 108
8	0.8 ± 0.8	−0.26 ± 0.04	−69 ± 50

varied from none to very severe discomfort, including waves of nausea, headaches and pain in the chest and abdomen. Six subjects said that they would not have tolerated a higher dose. All side-effects were rapidly reversed on reducing the infusion rate. Side-effects were not reported with placebo infusion.

Discussion

The main findings of this study are that peripheral intravenous infusion of adenosine at a dose of 0.07 mg kg^{-1} min^{-1} caused an increase in Qp.eff and a fall in estimated SVR. The lower doses used (0.005 and 0.03 mg kg^{-1} min^{-1}) had no measurable cardiovascular effects. The acute changes with the highest dose of adenosine appeared to be complete within 2 min of increasing the dose, and to have worn off 5 min after reducing the dose. Inspection of the confidence intervals suggests that it might be safest to allow five minutes for the maximum effect to develop when adenosine is used clinically. Each dose was given for 15 min only, so we cannot exclude the possiblility of either progressive increases or decreases in the effects of adenosine over several hours.

This study was not designed to look at any possible effect of intravenous adenosine on the bronchial tree. Changes in VA are, however, a sensitive indicator of small airway function. The absence of any reduction in VA implies no interference with the small airways, at least in normal subjects. We would have been unlikely to observe an increase in VA, because gas mixing is normally so efficient that it is unlikely that it could be further improved by drugs.

Our findings accord with the *in vitro* and animal data, and the limited studies in man. Adenosine relaxes systemic arterial strips (Herlihy *et al.*, 1976; Silver *et al.*, 1984), and causes hypotension in animals (Lagerkranser *et al.*, 1984). In much larger doses (0.2 to 0.3 mg kg^{-1} min^{-1}) adenosine has been used to produce controlled perioperative hypotension (Sollevi *et al.*, 1984). One study in normal volunteers using 0.14 mg kg^{-1} min^{-1} showed that adenosine caused tachycardia, systolic hypertension and a reduction in DBP (Sollevi *et al.*, 1986). Cardiac output was not measured directly, although it has been shown to rise in anaesthetised subjects in similar doses to those used by us (Torssel *et al.*, 1985).

We suggest that adenosine, in doses of around 0.07 mg kg^{-1} min^{-1} can be used to reduce left ventricular afterload. We and others (Sollevi *et al.*, 1984; Torsell *et al.*, 1985) have not observed any reflex tachycardia, which could be an advantage compared with agents such as sodium nitroprusside or prostacyclin (Sollevi, 1986; Bush *et al.*, 1988). However, some workers have reported tachycardia in supine subjects (Fuller *et al.*, 1987; Watt *et al.*, 1987; Conradson *et al.*, 1987) and with higher doses (0.14 mg kg^{-1} min^{-1}) of adenosine (Sollevi, 1986). The differences may be related to posture, dose, or differences in individual sensitivity. It is unlikely that much higher doses could be used in conscious subjects because of the side-effects we encountered, similar to those reported previously (Sollevi, 1986; Fuller *et al.*, 1987; Conradson *et al.*, 1987). We confirmed the rapid decay of the effects of adenosine, which would make it safe in clinical practice.

There might also be a potential use for adenosine in selectively reducing right ventricular afterload. Pulmonary vasodilators currently available have the undesirable effects of causing systemic vasodilatation and arterial hypoxaemia. This may critically reduce right heart filling pressure and compromise myocardial oxygen delivery, and, especially if severe pulmonary vascular disease is present, death may result (Packer *et al.*, 1982). A pulmonary vasodilator which was devoid of effects on the systemic circulation would be very useful. Adenosine has been shown to relax human pulmonary arteries *in vitro* (McCormack *et al.*, 1987). In addition, it is catabolised by pulmonary endothelial cells (Bakhle & Chelliah, 1983; Hellewell & Pearson, 1983), and it is possible that adenosine in doses of 0.03 mg kg^{-1} min^{-1} might act as a selective pulmonary vasodilator. We have shown that when this dose is given into a peripheral vein, it is devoid of any systemic cardiovascular effects, at least in subjects with a normal pulmonary circulation, presumably because this dose does not saturate

the pulmonary vascular clearance pathways. It is virtually impossible to demonstrate pulmonary vasodilatation in normal humans (Harris & Heath, 1986), so we are currently studying the effects of adenosine in adults and children with a variety of pulmonary vascular diseases, to evaluate its possible use as a selective pulmonary vasodilator.

In summary, we have shown that adenosine at a dose of 0.07 mg kg^{-1} min^{-1} causes a rise in Qp.eff and a fall in SVR in conscious normal volunteers. The maximum effect is reached within 2 min of starting an infusion, and is reversed within 5 min of stopping it. There were no effects on small airway function. We speculate that lower doses of adenosine (0.03 mg kg^{-1} min^{-1} or less) might selectively reduce right ventricular afterload in patients with pulmonary hypertension, whereas in higher doses, adenosine could prove clinically useful in reducing left ventricular afterload without increasing heart rate.

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