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ADENOSINE ON MYOCARDIAL OXYGEN CONSUMPTION

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1 A 3 min intracoronary infusion of adenosine (50 μg/min) produced a significant decrease in coronary artery perfusion pressure, left ventricular systolic pressure and myocardial O_2 consumption in the isolated supported heart preparation of the dog perfused at a constant coronary blood flow. Heart rate was controlled at 150, 190 or 230 beats/minute.

2 Myocardial contractile force and maximal left ventricular dp/dt were not changed by adenosine infusion.

3 The absolute decrease in myocardial O_2 consumption was greater at increasing heart rates whereas the decrease in coronary artery perfusion pressure and peak left ventricular systolic pressure were similar.

4 The results suggest that the reduction in myocardial O_2 consumption produced by adenosine is not related to coronary vasodilatation or to a negative chronotropic or inotropic action, but may be due to a functional shunting of blood flow from high O_2 extracting regions of the myocardium to low O_2 extracting ones and/or to important effects on myocardial substrate utilization.

Introduction

Adenosine has been shown to be a potent coronary vasodilator and Berne, Rubio, Dobson & Curnish (1971) have proposed an important role for this compound in coronary vascular autoregulation. However, the effect of adenosine on myocardial O_2 consumption is controversial. Raberger, Kraupp, Stuhlinger, Nell & Chirikdjian (1970) showed a decrease, Bache, Cobb & Greenfield (1973) no change and Afonso & O'Brien (1970) an increase in myocardial O_2 utilization during the administration of adenosine. The present series of experiments was designed to investigate further the role of adenosine on myocardial haemodynamics and O_2 consumption in the isolated supported heart preparation of the dog perfused at a constant coronary blood flow. Adenosine was administered into the coronary artery while the heart rate was held constant at 150, 190 or 230 beats/minute. The results demonstrate that adenosine produces a significant decrease in myocardial O_2 consumption independent of changes in coronary blood flow, heart rate or myocardial contractile force.

Methods

Mongrel dogs weighing between 15 and 20 kg were anaesthetized with sodium pentobarbitone (30 mg/kg, i.v.). The procedure for isolation and perfusion of the recipient heart has been described (Somani, Laddu & Hardman, 1970). Briefly, the heart was isolated *in situ* and the coronary arteries perfused at constant flow with heparinized (5.0 mg/kg) arterial blood from a donor dog. Coronary blood flow was adjusted initially to provide a coronary artery perfusion pressure of 90 mmHg. A thin latex balloon was placed in the left ventricle and inflated with 0.9% w/v NaCl solution (saline) to provide a peak left ventricular systolic pressure of 100 mmHg. Maximal left ventricular dp/dt was obtained by electronic differentiation of the left ventricular pressure pulse. Myocardial contractile force was determined by a Brodie-Walton strain gauge arch sutured to the left ventricular free wall. Heart rate was controlled by right atrial pacing. Before and during drug infusion simultaneous arterial and coronary venous blood samples were withdrawn and used for measurement of blood pH, P_{O_2}, P_{CO_2}, haemoglobin, oxyhaemoglobin and O_2 content.

Myocardial oxygen consumption ($M\dot{V}O_2$)

Direct measurements of arterial and coronary venous blood O_2 content were determined with duplicate 20 μl samples by an electrolytic cell method (Lex-O_2-Con, Lexington Instrument Company). Myocardial O_2 consumption was calculated from the following equation:

$$M\dot{V}O_2 = \frac{(AO_2 - VO_2) \times CBF}{\text{heart weight (g)}} \times 100$$

where $M\dot{V}O_2$ = total myocardial O_2 consumption expressed as ml O_2 utilized/minute per 100 g heart

Table 1 Isolated supported dog heart preparation: summarized haemodynamic and O_2 consumption data ($n=6$)

Parameter	*Control HR (150 beats/min)*	*Adenosine (1)*	*Control HR (190 beats/min)*	*Adenosine (2)*	*Control HR (230 beats/min)*	*Adenosine (3)*
A, O_2 content (vol. %)	20.7 ± 1.0	20.7 ± 1.1	20.7 ± 1.2	20.5 ± 1.1	20.9 ± 1.3	20.8 ± 1.3
V, O_2 content (vol. %)	15.1 ± 1.1	15.5 ± 1.1*	13.5 ± 1.2‡	14.2 ± 1.1†	12.1 ± 1.4‡§	13.2 ± 1.4†
A-V, O_2 content (vol. %)	5.7 ± 0.4	5.2 ± 0.4*	7.2 ± 0.5‡	6.4 ± 0.5†	8.8 ± 0.5‡§	7.7 ± 0.4†
O_2 extraction (AO_2-VO_2/AO_2 %)	27.7 ± 2.3	25.5 ± 2.1*	35.3 ± 2.7‡	31.3 ± 2.4†	43.2 ± 3.9‡§	37.9 ± 3.7†
Myocardial O_2 consumption (ml min^{-1} 100 g^{-1})	4.6 ± 0.5	4.2 ± 0.5*	5.8 ± 0.6‡	5.1 ± 0.6†	7.2 ± 0.7‡§	6.3 ± 0.7†
Heart rate (beats/min)	150	150	190	190	230	230
Contractile force (mm)	22.5 ± 2.5	22.7 ± 2.7	24.4 ± 3.0‡	24.3 ± 3.1	24.2 ± 3.1	23.8 ± 3.2
Coronary artery perfusion pressure (mmHg)	91.0 ± 2.4	78.0 ± 2.9†	87.7 ± 5.0	73.5 ± 6.0†	86.0 ± 7.6‡	75.2 ± 8.0†
Left ventricular systolic pressure (mmHg)	100.0 ± 1.3	90.7 ± 4.4*	100.7 ± 0.7	87.0 ± 3.5*	102.2 ± 1.6	89.5 ± 2.9*
dp/dt (mmHg/s)	875.0 ± 125.0	825.0 ± 125.0	880.0 ± 120.0	875.0 ± 125.0	850.0 ± 50.0	850.0 ± 50.0
Coronary blood flow (ml min^{-1} 100 g^{-1})	82.2 ± 9.2	82.2 ± 9.2	82.2 ± 9.2	82.2 ± 9.2	82.2 ± 9.2	82.2 ± 9.2

Results are mean ± s.e. mean.

* Effect of a 3 min intracoronary infusion (50 μg/min) of adenosine at each heart rate (HR). Significantly different from preceding control by a paired comparison ($P<0.05$).

† Effect of a 3 min intracoronary infusion (50 μg/min) of adenosine at each heart rate (HR). Significantly different from preceding control by a paired comparison ($P<0.01$).

‡ Effect of right atrial pacing. Significantly different from control at a heart rate of 150 beats/min by a paired comparison ($P<0.05$).

§ Effect of right atrial pacing. Significantly different from control at a heart rate of 190 beats/min by a paired comparison ($P<0.05$).

weight; AO_2 and VO_2 = arterial and venous O_2 content in volumes percent (ml/100 ml); CBF = total coronary blood inflow (ml/minute). Percent extraction of O_2 by the myocardium was calculated from the arterial-venous O_2 content difference divided by the arterial O_2 content.

Experimental design

After isolation the recipient heart was allowed to stabilize for 15 min, then paced at 150 beats/min for 15 min during which time coronary artery perfusion pressure and left ventricular systolic pressure were adjusted to 90 and 100 mmHg, respectively. After control arterial and coronary venous blood samples were withdrawn, adenosine (50 μg/min) was infused into the coronary arterial inflow tubing for 3 minutes. Blood samples were again withdrawn 2–3 min after the start of drug infusion. The preparation was then allowed to return to the control state (30 min) and the process repeated for heart rates of 190 and 230 beats/minute.

Results

After surgery the isolated supported heart usually remained stable. Preparations with ventricular ectopic beats were considered unsuccessful and not used in data analysis. Haemodynamic and metabolic data are summarized in Table 1.

With increasing heart rate (150 to 190 to 230 beats/min) there was a progressive decrease in coronary artery perfusion pressure. Left ventricular systolic pressure was maintained near 100 mmHg. Coronary blood flow controlled by a roller pump remained constant. As heart rate was increased, there was a rate-dependent decrease in coronary venous blood O_2 content and a significant increase in A-V O_2 difference, O_2 extraction, and $M\dot{V}O_2$ (Table 1).

A 3 min intracoronary infusion of adenosine (50 μg/min) produced a significant decrease in A-V O_2 difference, O_2 extraction and $M\dot{V}O_2$ at each heart rate. The decrease in $M\dot{V}O_2$ was paralleled by a significant decrease in coronary artery perfusion pressure and peak left ventricular systolic pressure (Table 1). However, other measured haemodynamic determinants of $M\dot{V}O_2$ (heart rate, coronary blood flow, dp/dt, and contractile force) did not change significantly. Although the decreases in coronary artery perfusion pressure and left ventricular systolic pressure produced by adenosine were of similar magnitude at each heart rate, the decrease in $M\dot{V}O_2$ was greater at the higher rates.

Discussion

Conflicting reports exist concerning the direct cardiac effect of adenosine on $M\dot{V}O_2$. Lammerant, Becsei, Mertens-Strijthagen & de Schryver (1970) and Raberger *et al.* (1970) found a decrease, Hirche (1966) and Weissel, Brugger, Raberger & Kraupp (1974) an increase, and Bache *et al.* (1973) no change in $M\dot{V}O_2$ during infusions of adenosine in dog and cat hearts. The present study clearly demonstrates that adenosine produces a significant decrease in $M\dot{V}O_2$ by a direct cardiac action. The decrease in $M\dot{V}O_2$ occurs independently of any peripheral vascular or reflex changes and occurs independently of alterations in coronary blood flow, heart rate or myocardial contractile force. Moreover, the decrease in coronary artery perfusion pressure and left ventricular systolic pressure is unlikely to be responsible for the decrease in $M\dot{V}O_2$ produced by adenosine since these haemodynamic changes were nearly equivalent at each heart rate whereas the absolute decrease in $M\dot{V}O_2$ was greater with each incremental increase in heart rate.

In addition, large increases in left ventricular systolic pressure (0–225 mmHg) have been previously shown to change $M\dot{V}O_2$ by 0.2–0.5 ml min^{-1} 100 g^{-1} in the isolated supported heart (Somani *et al.*, 1970). Thus, it seems unlikely that a fall of 10–13 mmHg in left ventricular systolic pressure would be responsible for the decrease in $M\dot{V}O_2$ produced by adenosine.

Raberger *et al.* (1970) showed adenosine to have an effect on myocardial substrate utilization. These authors proposed that adenosine decreased $M\dot{V}O_2$ by a lipolytic and glycolytic action on the heart mediated through a stimulation of cyclic adenosine 3′,5′-monophosphate (cyclic AMP) production. In contrast, Schauman, Juhran & Dietmann (1970) suggested that adenosine produced a decrease in $M\dot{V}O_2$ via a decrease in myocardial cyclic AMP formation. However, considering the high concentrations of adenosine ($> \times 10$ μM) necessary to inhibit adenylate cyclase *in vitro* (Bär & McKenzie, 1973), it is unlikely that the decrease in $M\dot{V}O_2$ observed in the present study is via this mechanism.

Lammerant *et al.* (1970) suggested that the reduction in $M\dot{V}O_2$ produced by adenosine may be due to a functional shunting or redistribution of blood flow from a high O_2 extracting region (subendocardium) to a low O_2 extracting region (subepicardium) of the myocardium. It is possible that adenosine opens up vessels in the myocardium which do not participate in cellular gas exchange and thereby produces an apparent reduction in the calculated $M\dot{V}O_2$. Because regional myocardial blood flow was not measured in the present series of experiments, this mechanism could not be evaluated. Further work is needed to establish whether adenosine reduces $M\dot{V}O_2$ by producing a redistribution of blood flow within the myocardium or by a direct metabolic action.

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