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Short communication

Effect of acadesine on myocardial ischaemia in patients with coronary artery disease

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Abstract

Acadesine, an adenosine regulating agent, attenuates the adverse effects of ischaemia on ventricular function in animals. This study examined its influence on pacing-induced ischaemia in 47 patients undergoing coronary angiography. After 15 min of recovery from control pacing, an infusion of acadesine (5, 10, 20, 50 mg/kg i.v.) was commenced and after a further 15 min the protocol was repeated with the infusion continued. At higher doses, minor beneficial effects on ejection fraction and myocardial lactate metabolism were observed. Haemodynamics were unaffected. Systemic lactate rose in relation to acadesine, up to 60% ($P < 0.001$ versus placebo). The data may indicate that acadesine stimulates anaerobic glycolysis in man. © 1997 Elsevier Science B.V.

Keywords: Adenosine; Coronary artery disease; Lactate; Myocardial ischaemia; Ventricular function

1. Introduction

In experimental models, acadesine (5-amino-4-imidazole carboxamide riboside), an adenosine regulating agent, limits the deleterious effects of ischaemia on left ventricular function (Galiñanes et al., 1992). Acadesine appears to act by increasing myocardial adenosine concentrations (Gruber et al., 1989), which may then improve regional perfusion, contractility and metabolism (Ely and Berne, 1992). Its actions are unusual in being event- and site-specific. The drug is thought to be only effective in ischaemic myocardium, and pharmacologically inert, rendering it a potential therapeutic agent in ischaemic heart disease. When studied in man (Holdright et al., 1994), acadesine does not produce the undesirable systemic effects of adenosine.

Although the effects of acadesine in regional as opposed to global myocardial ischaemia have not been wholly consistent, acadesine attenuated the decrease in left ventricular wall thickening provoked by atrial pacing in a model of circumflex coronary artery stenosis (Young and Mullane, 1991). Encouraged by the experimental evidence, we investigated the effect of acadesine on left ventricular function, and myocardial lactate metabolism, in relation to pacing stress in coronary patients.

2. Materials and methods

2.1. Patients

The study group was drawn from patients undergoing cardiac catheterisation for the investigation of suspected coronary artery disease, with $> 50\%$ stenosis in at least one coronary artery. Patients with unstable angina, acute myocardial infarction, left main coronary artery stenosis, diabetes mellitus, or chronic renal failure, were excluded.

2.2. Protocol

All medications were discontinued ≥ 48 h prior to the study. Cardiac catheterisation was performed through the femoral artery and vein. Heparin (5000 U) was adminis-

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tered intravenously. Following angiography of the left and right coronary arteries, a dual tip micromanometer pigtail catheter was positioned in the left ventricle and a bipolar coronary sinus catheter was introduced. Baseline left ventricular angiography was performed and left ventricular and aortic pressures and pressure-derived indices were measured. Atrial pacing commenced at 10 beats/min above the spontaneous heart rate, with increments of 10 beats/min at 2-min intervals. Pacing end-points were a rate of 180 beats/min, angina, or atrioventricular block. Measurements were recorded during maximal pacing and ventricular angiography was repeated immediately on cessation of pacing. After 15 min rest, an i.v. infusion of placebo (0.28% NaCl) or acadesine (5, 10, 20 or 50 mg/kg) was commenced in a randomized, double-blind fashion. After a further 15 min, with acadesine infusion continued, an identical protocol was followed. Coronary sinus and femoral arterial blood samples were taken before, during and after maximal pacing and during recovery.

2.3. Assessment of function and haemodynamics

Global and regional left ventricular function was evaluated as described elsewhere (Slager et al., 1986). Left ventricular parameters were measured using the micromanometer catheter (Meester et al., 1975). The following indices were computed: peak left ventricular pressure, its derivatives and the time constants for early relaxation (Brower et al., 1983).

2.4. Lactate measurement

Blood samples of approx. 1.5 ml were collected and processed as described (Bonnier et al., 1990). In deproteinized samples, lactate was assayed in duplicate with lactate oxidase and peroxidase on a Merck ELAN analyser.

2.5. Statistical analysis

The effect of acadesine on pacing-induced changes (infusion versus pre-infusion) was assessed by analysis of variance to detect differences between dosage groups. A paired Student's *t*-test was then applied or linear regression analysis was used to examine the dose–response relationship. Mean values are reported ± S.E.M. Statistical significance was accepted at the 5% level.

3. Results

3.1. Demographics, drug tolerance

The inclusion criteria were met by 47 patients, including eight females, who all provided informed consent. Their median age was 58 years (range: 38–70 years). Acadesine was well tolerated and there were no adverse clinical events.

3.2. Atrial pacing

In all the groups, the maximal heart rates achieved during the second pacing period were similar to those in the first (approx. 150 beats/min).

3.3. Ejection fraction and haemodynamics

The left ventricular ejection fraction before pacing was 63 ± 2%. Atrial pacing induced a small decline in ejection fraction (Table 1). During the second pacing period, fol-

Table 1
Effect of acadesine on ventricular function and haemodynamics during atrial stress testing

Variable		Acadesine (mg/kg)				
		placebo	5	10	20	50
Left ventricular pressure (mmHg)	(1) [a]	127 ± 5	135 ± 5	124 ± 5	152 ± 8	136 ± 8
	(2)	132 ± 6	132 ± 6	123 ± 5	143 ± 8	127 ± 11
LVEDP [b] (mmHg)	(1)	10 ± 3	13 ± 2	9 ± 2	13 ± 2	7 ± 2
	(2)	9 ± 1	12 ± 2	9 ± 2	11 ± 2	10 ± 3
LV$dP/dt$ [b] (mmHg/s)	(1)	1783 ± 153	1728 ± 144	1711 ± 130	1790 ± 127	2010 ± 163
	(2)	1775 ± 161	1700 ± 150	1711 ± 103	1684 ± 85	1841 ± 221
Tau_1 (ms)	(1)	45 ± 5	49 ± 5	43 ± 3	52 ± 4	39 ± 2
	(2)	46 ± 4	50 ± 5	43 ± 3	53 ± 4	40 ± 2
Ejection fraction (%)	(1, pre)	66 ± 4	57 ± 4	66 ± 4	63 ± 5	65 ± 2
	(1, post)	62 ± 3	54 ± 3	62 ± 5	58 ± 6	63 ± 3
	(2, pre)	66 ± 3	56 ± 3	65 ± 5	61 ± 6	65 ± 2
	(2, post)	63 ± 4	55 ± 4	63 ± 5	60 ± 5	63 ± 3

[a] Measurements were made during first (1 = no acadesine) and second (2 = with acadesine) pacing periods at maximal pacing, except for ejection fraction, where data were obtained before (pre) and immediately after maximal pacing (post). Means ± S.E.M., $n = 9–10$.
[b] LVEDP and LV$dP/dt$ = left ventricular end-diastolic pressure and its peak first derivative, respectively.

lowing acadesine infusion, this decline was attenuated, significantly so at the 20 mg/kg dose (pacing 2: decrease from 61 to 60% versus pacing 1: decrease from 63 to 58%, $P = 0.036$; see Table 1). The parameters of left ventricular function were not influenced by acadesine at rest, at maximal pacing (Table 1), or during recovery. Differences observed between the first and second stress tests were $< 5\%$.

3.4. Lactate metabolism

In general, arterial and coronary sinus lactate levels were higher in relation to acadesine infusion (Table 2). For instance, the rise in arterial lactate during the post-pacing recovery period varied between the groups ($P < 0.001$, analysis of variance) and lactate levels following the higher doses of acadesine, 20 and 50 mg/kg, were greater than control (both $P < 0.001$). Regression analysis confirmed an incremental effect of acadesine at these doses (20 mg/kg: $P = 0.026$, 50 mg/kg: $P = 0.01$) suggesting dose-dependency.

The arteriovenous lactate data during the first pacing stress test showed that ischaemia was induced: Lactate uptake before pacing, 0.13 ± 0.03 mM ($n = 39$), decreased both during (-0.01 ± 0.04 mM) and immediately post-pacing (-0.08 ± 0.06 mM), with return to lactate uptake during recovery (0.09 ± 0.05 mM). Arteriovenous lactate tended to increase during pacing in relation to acadesine, but this did not reach significance (Table 2). However, when the effects of low dose (0–10 mg/kg) and high dose acadesine (20–50 mg/kg) on arteriovenous lactate were compared, there were differences throughout the pacing protocol. The acadesine-induced decline in lactate production was significant during maximal pacing and recovery. Arteriovenous differences during pacing were: low dose, 0.09 ± 0.03 mM versus high dose, 0.17 ± 0.08 mM; $P = 0.016$, $n = 27$ and 12, respectively; those during recovery were: low dose, 0.06 ± 0.04 mM versus high dose, 0.23 ± 0.06 mM; $P = 0.019$.

4. Discussion

4.1. Cardiac function and metabolism

This is the first report of the effects of acadesine on both left ventricular function and lactate metabolism in relation to myocardial ischaemia in man. The decline in left ventricular ejection fraction provoked by pacing stress in patients with coronary artery disease tended to be less in the presence of acadesine (Table 1). This was small, but significant at a dose of 20 mg/kg. Further, myocardial lactate uptake during and after pacing tended to be increased with a high dose as opposed to low dose acadesine (Table 2). The latter is in line with canine data (Hori et al., 1994). Left ventricular haemodynamics were not affected (Table 1), confirming that acadesine was free of negative inotropic actions. The data suggest that acadesine exerted

Table 2
Effect of acadesine on blood lactate and arteriovenous differences

Group	Phase	Lactate (mmol/l)					
		− acadesine			+ acadesine		
		arterial	CS [a]	arterial-CS	arterial	CS	arterial-CS
Placebo ($n = 9$–10)	pre-pacing	0.76 ± 0.09	0.63 ± 0.05	0.13 ± 0.05	0.79 ± 0.07	0.56 ± 0.05	0.23 ± 0.05
	max. pacing	0.75 ± 0.08	0.76 ± 0.04	0.00 ± 0.07	0.72 ± 0.06	0.64 ± 0.06	0.06 ± 0.05
	post-pacing	0.68 ± 0.06	0.81 ± 0.08	−0.13 ± 0.10	0.76 ± 0.07	0.73 ± 0.08	0.02 ± 0.09
	recovery	0.70 ± 0.08	0.60 ± 0.04	0.11 ± 0.07	0.81 ± 0.07	0.54 ± 0.06	0.27 ± 0.06
5 mg/kg ($n = 10$)	pre-pacing	0.81 ± 0.11	0.68 ± 0.11	0.13 ± 0.06	0.84 ± 0.12	0.74 ± 0.11	0.11 ± 0.06
	max. pacing	0.77 ± 0.09	0.73 ± 0.11	0.04 ± 0.08	0.80 ± 0.10	0.84 ± 0.12	−0.04 ± 0.09
	post-pacing	0.79 ± 0.09	0.85 ± 0.14	−0.06 ± 0.12	0.88 ± 0.12	0.87 ± 0.16	0.01 ± 0.13
	recovery	0.85 ± 0.12	0.73 ± 0.10	0.12 ± 0.08	0.86 ± 0.12	0.76 ± 0.12	0.09 ± 0.09
10 mg/kg ($n = 7$–9)	pre-pacing	0.82 ± 0.17	0.52 ± 0.16	0.25 ± 0.08	0.84 ± 0.16	0.49 ± 0.13	0.36 ± 0.11
	max. pacing	0.77 ± 0.14	0.56 ± 0.16	0.14 ± 0.06	0.79 ± 0.13	0.57 ± 0.14	0.19 ± 0.05
	post-pacing	0.80 ± 0.13	0.58 ± 0.13	0.16 ± 0.08	0.84 ± 0.16	0.56 ± 0.12	0.21 ± 0.12
	recovery	0.84 ± 0.14	0.48 ± 0.11	0.32 ± 0.09	0.91 ± 0.16	0.53 ± 0.16	0.35 ± 0.07
20 mg/kg ($n = 6$–8)	pre-pacing	0.80 ± 0.16	0.82 ± 0.16	0.01 ± 0.09	0.95 ± 0.14	0.74 ± 0.16	0.19 ± 0.09
	max. pacing	0.80 ± 0.14	0.94 ± 0.10	−0.13 ± 0.09	1.03 ± 0.15	1.04 ± 0.18	0.08 ± 0.07
	post-pacing	0.83 ± 0.12	1.16 ± 0.12	−0.30 ± 0.16	1.02 ± 0.13	1.19 ± 0.18	−0.08 ± 0.15
	recovery	0.87 ± 0.13	0.97 ± 0.10	−0.08 ± 0.14	1.12 ± 0.15	1.02 ± 0.18	0.20 ± 0.08
50 mg/kg ($n = 5$–7)	pre-pacing	0.67 ± 0.06	0.59 ± 0.05	0.11 ± 0.03	0.84 ± 0.13	0.79 ± 0.11	0.13 ± 0.12
	max. pacing	0.65 ± 0.08	0.88 ± 0.17	−0.17 ± 0.12	1.10 ± 0.14	1.10 ± 0.14	0.11 ± 0.20
	post-pacing	0.70 ± 0.09	0.87 ± 0.11	−0.06 ± 0.16	1.18 ± 0.13	1.12 ± 0.10	0.20 ± 0.14
	recovery	0.76 ± 0.09	0.87 ± 0.14	−0.07 ± 0.18	1.23 ± 0.11	1.09 ± 0.10	0.25 ± 0.11

After an atrial pacing stress test, the acadesine infusion started and pacing was repeated. Means ± S.E.M.
[a] CS = coronary sinus.

an anti-ischaemic effect on the heart, in line with results obtained in patients undergoing coronary artery bypass graft surgery (Mangano, 1997).

The 20 mg/kg dose appeared to be associated with a larger effect on left ventricular function than 50 mg/kg (Table 1). Also in animal models of myocardial ischaemia, the protective effects of acadesine diminished at higher doses (Galiñanes et al., 1992; Mentzer et al., 1988). This concentration dependent effect of acadesine remains to be explained. Although the precise cellular events underlying the effects of acadesine and adenosine are as yet undetermined, a G protein and ATP-dependent K^+-channels may be involved. Whether the ribose moiety in acadesine plays a role is unknown; ribose is a cardioprotectant, stimulating adenine nucleotide synthesis (Zimmer et al., 1984).

4.2. Peripheral lactate

Systemic lactate levels rose with acadesine, particularly at higher doses (Table 2). The effect of acadesine on arterial and coronary sinus lactate concentrations may be explained by increased glycolysis, in that it is well established that adenosine stimulates glucose uptake (Mainwaring et al., 1988). Although reports to the contrary exist (Vincent et al., 1992), many studies show that adenosine promotes glycolysis (e.g., Janier et al., 1993). Species and tissue differences in the capacity to accumulate the phosphorylation product of acadesine and differences in target enzymes sensitive to this product probably determine the effect of the drug on glycolysis (Javaux et al., 1995). In rat skeletal muscle, acadesine activates glycogen phosphorylase and glycogenolysis (Young et al., 1996). Since skeletal muscle is a major contributor to body mass, it could well be the source of the increases in arterial lactate concentrations seen with acadesine.

4.3. Conclusions

In summary, in this study of pacing-induced ischaemia in patients with coronary artery disease and stable angina, we found small protective effects on left ventricular function and myocardial lactate metabolism. We speculate that the rise in systemic lactate is due to acadesine-induced increases in adenosine, which could stimulate glucose uptake and its catabolism.

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References

Bonnier, J.J.R.M., Huizer, T., Troquay, R., Van Es, G.A., De Jong, J.W., 1990. Myocardial protection by intravenous diltiazem during angioplasty of single-vessel coronary artery disease. Am. J. Cardiol. 66, 145–150.

Brower, R.W., Meij, S., Serruys, P.W., 1983. A model of asynchronous left ventricular relaxation predicting the bi-exponential pressure decay. Cardiovasc. Res. 17, 482–488.

Ely, S.W., Berne, R.M., 1992. Protective effects of adenosine in myocardial ischemia. Circulation 85, 893–904.

Galiñanes, M., Mullane, K.M., Bullough, D., Hearse, D.J., 1992. Acadesine and myocardial protection. Studies of time of administration and dose–response relations in the rat. Circulation 86, 598–608.

Gruber, H.E., Hoffer, M.E., McAllister, D.R., Laikind, P.K., Lane, T.A., Schmid-Schoenbein, G., Engler, R.L., 1989. Increased adenosine concentration in blood from ischemic myocardium by AICA riboside. Circulation 80, 1400–1411.

Holdright, D.R., Sparrow, J.L., Wright, C.L., Steiner, J., Fox, K.M., 1994. Effect of acadesine, a new metabolic agent, on exercise-induced myocardial ischemia in chronic stable angina. Cardiovasc. Drugs Ther. 8, 193–197.

Hori, M., Kitakaze, M., Takashima, S., Morioka, T., Sato, H., Minamino, T., Node, K., Komamura, K., Inoue, M., Kamada, T., 1994. AICA riboside improves myocardial ischemia in coronary microembolization in dogs. Am. J. Physiol. 267, H1483–H1495.

Janier, M.F., Vanoverschelde, J.L., Bergmann, S.R., 1993. Adenosine protects ischemic and reperfused myocardium by receptor-mediated mechanisms. Am. J. Physiol. 264, H163–H170.

Javaux, F., Vincent, M.F., Wagner, D.R., Van den Berghe, G., 1995. Cell-type specificity of inhibition by 5-amino-imidazolecarboxamide riboside: Lack of effect in rabbit cardiomyocytes and human erythrocytes, and inhibition in FTO-2B rat hepatoma cells. Biochem. J. 305, 913–919.

Mainwaring, R., Lasley, R., Rubio, R., Wyatt, D.A., Mentzer, R.M., 1988. Adenosine stimulates glucose uptake in the isolated rat heart. Surgery 10, 445–449.

Mangano, D.T., 1997. Effects of acadesine on myocardial infarction, stroke, and death following surgery. A meta-analysis of the 5 international randomized trials. The Multicenter Study of Perioperative Ischemia (McSPI) Research Group. J. Am. Med. Assoc. 277, 325–332.

Meester, G.T., Bernard, N., Zeelenberg, C., Brower, R., Hugenholtz, P.G., 1975. A computer system for real-time analysis of cardiac catheterization data. Catheter Cardiovasc. Diagn. 1, 113–132.

Mentzer, R.M., Ely, S.W., Lasley, R.D., Berne, R.M., 1988. The acute effects of AICAR on purine nucleotide metabolism and post ischemic cardiac function. J. Thorac. Cardiovasc. Surg. 95, 286–293.

Slager, C.J., Hooghoudt, T.E.H., Serruys, P.W., Schuurbiers, J.C.H., Reiber, J.H.C., Meester, G.T., Verdouw, P.D., Hugenholtz, P.G., 1986. Quantitative assessment of regional left ventricular motion using endocardial landmarks. J. Am. Coll. Cardiol. 7, 317–327.

Vincent, M.F., Bontemps, F., van den Berghe, G., 1992. Inhibition of glycolysis by 5-amino-4-imidazole carboxamide riboside in isolated rat hepatocytes. Biochem. J. 281, 267–272.

Young, M.A., Mullane, K.M., 1991. Progressive cardiac dysfunction with repeated pacing- induced ischemia: Protection by AICA-riboside. Am. J. Physiol. 261, H1570–H1577.

Young, M.E., Radda, G.K., Leighton, B., 1996. Activation of glycogen phosphorylase and glycogenolysis in rat skeletal muscle by AICAR: An activator of AMP-activated protein kinase. FEBS Lett. 382, 43–47.

Zimmer, H.G., Ibel, H., Suchner, U., Schad, H., 1984. Ribose intervention in the cardiac pentose pathway is not species-specific. Science 223, 712–714.