Upsala J Med Sci 95: 137–145, 1990

Effects of Exogenous Adenosine in a Patient with Transplanted Heart. Evidence for Adenosine as a Messenger in Angina Pectoris

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ABSTRACT

In this pilot study some cardiac effects of exogenous adenosine on the denervated heart were studied in a patient with transplanted heart since 3 years. He was instrumented with catheters into the left coronary artery, the coronary sinus and the right ventricle. Adenosine was given in increasing doses intracoronarily, into the aorta at the diaphragmal level and into a peripheral vein.

When given into the aorta pain was provoked dose-dependently and not different from a reference group. When given intracoronarily no pain was provoked except at the highest dose when a slight discomfort of the chest was provoked. After intravenous injection no pain was provoked in the chest or in adjacent structures.

Coronary sinus flow increased dose-dependently and not different from the reference group. No increased heart rate response occurred after intravenous or intracoronary injections. Extensive degrees of sinus and AV nodal blockade occurred.

In conclusion, the results are in keeping with a role for adenosine as a messenger between myocardial ischaemia and angina pectoris and cardiac sympathetic pressure response. The importance of innervation for proper sinus and AV nodal function was also illustrated.

INTRODUCTION

Adenosine has been proposed to be a messenger between myocardial ischaemia and angina pectoris (10, 11, 7). During myocardial ischaemia adenosine is released in large quantities from myocardial cells into the interstitium (3). When adenosine is given as a bolus intravenously or intracoronarily a pain is provoked in the chest with radiations into adjacent parts of the body.This pain is reported by patients with ischaemic heart disease not to be different from their habitual angina pectoris (11,7). When adenosine is given intraarterially pain is also provoked in areas supplied by the artery. Adenosine induced pain response is attenuated by theophylline and increased irrespective of injection site by dipyridamole in keeping with activation of extracellular membrane bound adenosine receptors.

Thus a series of experiments has not been able to contradict the hypothesis that adenosine is a messenger between myocardial ischaemia and angina pectoris. As a further attempt to test this hypothesis we found it pertinent to give adenosine to patients with transplanted heart as such a heart is considered to be denervated. It has however been reported that 5 % of acute myocardial infarcts in transplants are accompanied by chest pain (6). In this preliminary report we describe effects of exogenous adenosine on pain, heart rate response, sinus and AV nodal blocks and coronary vasodilation in a patient with a transplanted heart.

METHODS

The patient being a 59 years old male was transplanted 3 years ago due to intractable heart failure on the basis of congestive cardiomyopathy. He had experienced four rejections that were successfully treated. Current medication was cyclosporine and dipyridamole, and at the time of investigation he was in New York Heart Association functional class I-II. No dipyridamole was taken the last 24 hours before the investigation, which was made in connection with routine endomyocardial biopsy and selective coronary angiography. The study was accepted by the Ethic´s committee and the patient was fully informed.

A Wilton-Webster coronary sinus flow catheter was introduced into the coronary sinus under fluoroscopic control, and the position was tested by injection of contrast medium. The coronary sinus blood flow was

determined by the thermodilution technique (5). A pacing electrode was introduced via the left femoral vein into the apical region of the right ventricle. The electrode was connected with an external pacemaker with an on demand rate of 60/minute.

After diagnostic coronary angiography, adenosine was given with a 7 F coronary-catheter in two arterial positions, first in the left coronary orifice, secondly in the descending aorta at the level of the diaphragm. The patient was unaware of which site of injection was used. Adenosine dilutions were made from a standard solution of 5.0 mg/ml in saline, prepared by the hospital pharmacy. Adenosine was given in 3.0 ml in doses of 0.1, 1.0, 2.5, 5.0 and 10 mg. A constant injection time of 10 seconds was chosen in order to make the results comparable with those of intravenous injection of adenosine. After the intraarterial injections, adenosine was given as a bolus into an antebrachial vein in doses of 2.5, 5.0, 7.5 and 10 mg; the vein was thereafter flushed with 5 ml of saline. In each dose-response series an injection of saline alone was included, single-blind. At onset of pain the patient raised his left hand. When the maximum pain began to subside the hand was lowered half way, and when the pain had disappeared the hand was lowered to the supine position. These time instants were noted on the online recordings of coronary sinus flow and of ECG (chest leads), the speed of which was 25 mm/sec. The magnitude of maximal pain was rated according to the CR-10 scale designed by Borg (2). The patient was also asked to describe the location and the character of the pain. Before the next dose the patient was asked whether any pain or discomfort remained. If the patient did not wish to proceed further, the last dose given was taken as the maximum tolerable. Heart rate was calculated before injection and at the highest rate after injection. When there was no obvious increase in heart rate the calculations were made 30-40 seconds after injection or at least 10 seconds after any sinus or AV block.

In a reference group coronary angiography was performed in 7 male patients with angina pectoris. This group has been examined principally in the same way, as previously described for 6 of the 7 patients (7).

Statistics

Changes were compared to previously (7) reported reference values. A value

differing more than 2 S.D. away from the reference material was considered statistical significant.

Table 1. Pain, coronary sinus blood flow and heart rate response after injection of adenosine in the heart transplanted patient compared to a reference group (mean ± S.D.).

	observed	reference group
Pain threshold (mg adenosine)		
Intracoronary injection	10.0	2.7 ±3.3
Intraaortic injection	1.0	1.3 ±0.9
Intravenous injection	no pain	3.6 ±1.3
Pain threshold ratio		
Intracoronary/Intraaortic	10	2.1 ± 2.5
Time(sec) to start of pain (mean of all doses that gave pain)		
Intracoronary injection	16,2	19.7 ± 5.8
Intraaortic injection	14.3 ± 2.8	15.9 ± 4.2
Intravenous injection	-	18,7 ± 4.5
Time(sec) to start of coronary sinus blood flow increase (mean of all adenosine injections)		
Intracoronary injection	2.8 ± 1.2	1.8 ± 1.8
Intravenous injection	22.0 ± 5.7	13.2 ± 5.3
Coronary sinus blood flow increase in %		
Intracoronary injection(1mg)	165	113 ± 80
Intravenous injection (5mg)	112	211 ± 109
Increase in heart rate in % (mean of all adenosine injections)		
Intracoronary injection	3±2	26 ±28
Intraaortic injection	5±4	31 ±19
Intravenous injection	2±4	42 ±24
Time to maximum heart rate (sec) (mean of all adenosine injections)		
Intracoronary injection	56±24	40 ±17
Intraaortic injection	35±7	24 ± 4
Intravenous injection	41±8	40 ± 7

RESULTS

Provocation of pain

When given intracoronary adenosine provoked chest pain only at the highest dose (10 mg) as opposed to the reference group where pain was induced at 2.7±3.3 mg (mean± S.D.). Injection of adenosine into the aorta at the diaphragmal level followed the same dose-response relation as in the reference group and the pain was located to the chest and the diaphragmal area. The lowest dose of adenosine that gave pain (pain threshold) when injected into the aorta was of the same magnitude as in the reference group. When the pain thresholds (in mg of adenosine) between intracoronary and intraaortic injections were compared , the difference was more than 3 S.D. higher as when compared to the correspondingly ratio of the reference group.When the ratio of the score of pain induced by intracoronary and intraaortic injections in patient was compared to the corresponding ratio of the reference group the difference was more than 3 S.D..

After intravenous injection of adenosine no chest pain was provoked, but after the two highest dosages our patient reported pain in the forehead. The patient experienced respiratory stimulation at all dosages also in accordance with previous findings (1,12).

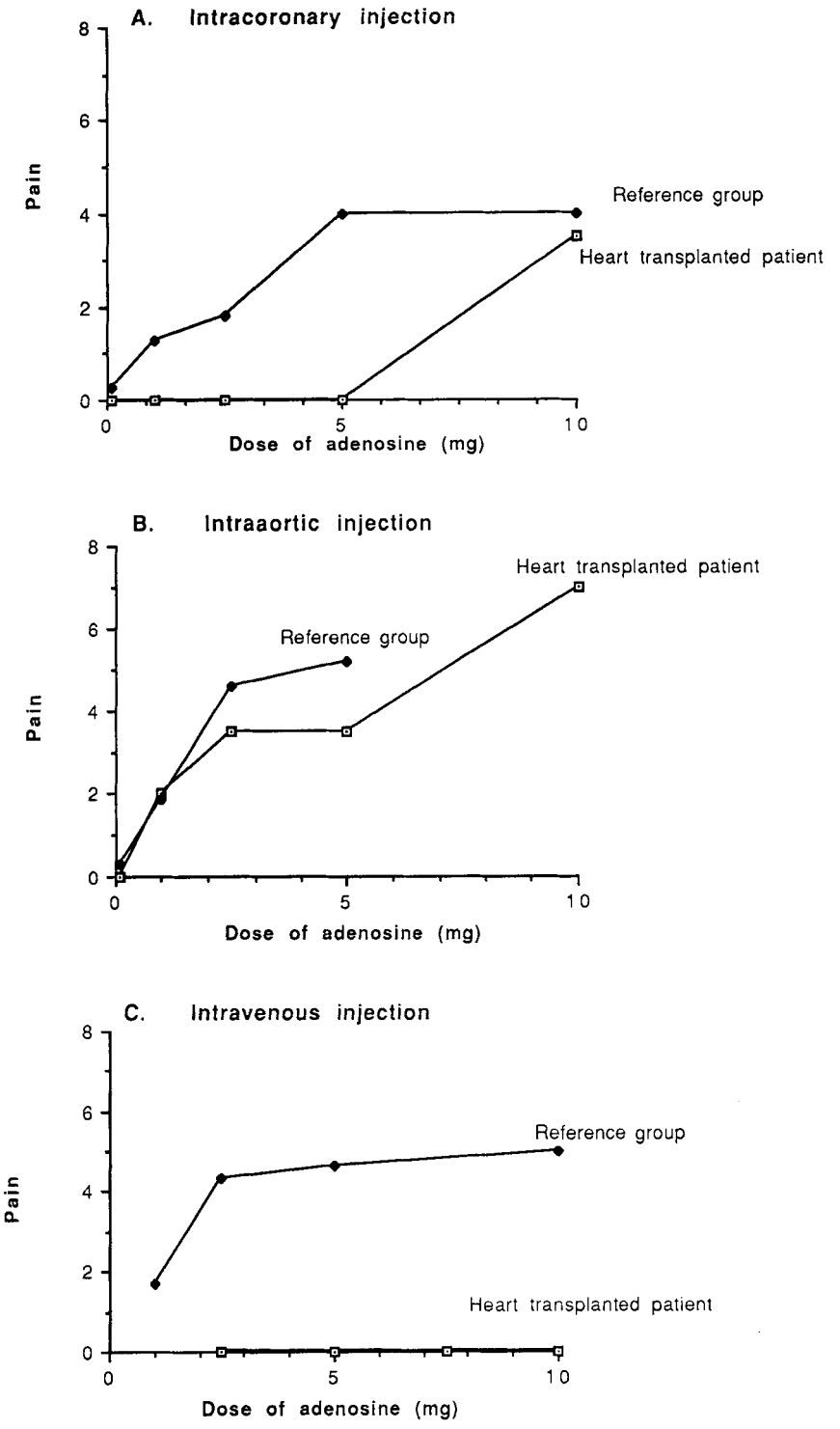
Coronary flow.

Adenosine administration in the coronary artery and the antebrachial vein,but not into the aorta, resulted in increased coronary sinus blood flow with onset shortly after the onset of injection. The response did not differ from the reference values (table 1). The flow responses shown in table 1 are after intracoronary and intravenous injection of 1 mg respectively 5 mg adenosine. These doses were choosen because they were given to all of the tested subjects.

Sinus and AV nodal conduction and heart rate response.

Intra aortic injection did not induce any conduction defects even at the highest dose given. After intracoronary injection of adenosine, except at the lowest dose (0.1 mg), SA arrest/blocks were seen. The duration of

Figure 1:Pain responses of different doses of adenosine. Pain response is graded according to the CR-10 Borg scale



bradycardia was proportional to the dose given and amounted to 32 seconds after 1,0 mg adenosine and to 73 seconds at the highest dose (10 mg).
Intravenous injection did not provoked SA arrest/block but resulted in AV block II-III with longer duration being 23 seconds at maximum dose and a dose dependent delay of onset (table 2). In the reference group no SA arrest/block developed, and only 2 out of 7 developed AV block after intravenous injection of adenosine, both at higher dosages, 10 and 15 mg and both with a duration of the block less than 5 seconds.
The mean heart rate before each injection was for the transplanted patient 92.9±5.6 m^{-1} and for the reference group 62.4±10.0 m^{-1}

Table 2. AV block after intravenous injection and SA arrest/block after intracoronary injection of adenosine.in to the heart transplanted patient

Adenosine dose (mg)	time after injection to block (sec)	Duration of block (sec)
Intravenous:		
2.5	20	3
5.0	21	12
7.5	18	17
10.0	15	23
Intracornary:		
0.1	-	0
1.0	5	33
2.5	3	44
5.0	1	65
10.0	0.5	74

After the disappearance of sinus and AV block the heart rate returned to the baseline (table 1).

DISCUSSION

The main finding in this case report on a heart transplanted patient is that higher doses of intracoronary adenosine were needed to produce pain comparable to the reference group. In contrast, intraaortic administration provoked similar degrees of pain in our patient compared to the reference group. This was expected because the neurons responsible for the pain, when adenosine was given into the aorta at the diaphragmal level, should not be influenced by the transplantation operation itself. Although the provocation of pain was greatly attenuated when given intracoronarily,

even at the highest dose of intracoronary adenosine only a moderate pain was reported and located to the chest. This pain is less likely to have originated from the pulmonary vascular bed as no pain was reported after intravenous injection. The most probable explanation is that the pain originates from the residual atrial tissue with intact original innervation. Another possibility for pain induction could be recirculation of adenosine through Thebesian veins and subsequent activation of mediastinal neurons. An alternative possibility is activation of cardiac neurons shown to grow into a canine experimental heart transplant model (9). Furthermore, about 5 % of patients with transplanted hearts experienced chest pain in association with acute myocardial infarction (6). Our observations therefore strongly corroborate adenosine as a messenger between myocardial ischaemia and chest pain.

Coronary sinus flow increased to the same degree as in the reference group both after intracoronary and intravenous injections. Also the early onset of flow increase was similar to the reference group. These observations indicate that adenosine induced increase of coronary flow is independent of coronary vascular innervation and in keeping with a direct effect of adenosine on the vascular tone (4).
The normally seen increase in heart rate of about 25 % following intravenous and intracoronary injections of adenosine were absent in this transplanted patient. This observation indicate that the increased heart rate is mediated via cardiac innervation. This heart rate response was previously reported to be associated with both increased systolic and diastolic blood pressures (8). These observations could possibly relate to the paradoxical increase of heart rate and blood pressure in anterior acute myocardial infarction that consequently could be mediated by ischaemically released adenosine which in its turn sensitizes sympathetic cardiac nerves resulting in a sympatho-adrenergic response.

ACKNOWLEDGEMENTS

This study was supported by the Swedish Heart and Lung Foundation, the Groschinsky Foundation and Söderbergs Foundations

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