

# Reflex Increase in Blood Pressure during the Intracoronary Administration of Adenosine in Man

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## Abstract

Infusion of adenosine (0.022–2.2 mg/min) into the left anterior descending (LAD) coronary artery of 26 patients produced a dose-dependent increase in blood pressure without a change in heart rate. At adenosine 2.2 mg/min, systolic pressure rose by  $21.0 \pm 2.2$  mmHg from  $134 \pm 4.3$  mmHg ( $P < 0.001$ ) and diastolic pressure increased by  $10.4 \pm 1.1$  mmHg from  $76 \pm 1.9$  mmHg ( $P < 0.001$ ). The rise in arterial pressure was associated with a  $22 \pm 3.4\%$  increase in systemic vascular resistance ( $P < 0.01$ ) and no change in cardiac output ( $-2.8 \pm 4.3\%$ ,  $P = \text{NS}$ ). Plasma norepinephrine levels rose by  $40 \pm 14\%$  from  $105 \pm 9$  pg/ml ( $P < 0.05$ ) and epinephrine levels by  $119 \pm 31\%$  from  $37 \pm 9$  pg/ml ( $P < 0.01$ ). Right atrial infusion of adenosine produced insignificant hemodynamic effects, suggesting that systemic spillover of adenosine was not responsible for the observed effects. In 20 cardiac transplant patients with denervated hearts, LAD infusion of adenosine (2.2 mg/min) produced no change in systolic pressure ( $-0.1 \pm 1.6$  mmHg from  $139 \pm 3.4$  mmHg,  $P = \text{NS}$ ) and a decrement in diastolic pressure ( $-4.7 \pm 1.2$  mmHg from  $98 \pm 2.5$  mmHg,  $P < 0.01$ ). Thus, infusion of adenosine into the LAD coronary artery causes a reflex increase in arterial pressure due to a rise in systemic vascular resistance, probably as a result of increased sympathetic discharge. This reflex pathway may be of importance in disease states such as myocardial ischemia, in which myocardial adenosine levels are elevated.

## Introduction

Adenosine is an agent whose direct effect is potent relaxation of vascular smooth muscle in vitro and in vivo (1–3). Systemic administration produces hypotension in conscious animals (4, 5) and in anesthetized humans (6). However, in initiating a study of coronary artery dilation in conscious patients we observed a hypertensive response elicited by the intracoronary administration of adenosine. This hypertensive response was of particular interest as increases in blood pressure are known to accompany myocardial ischemia (7), a condition in which myocardial adenosine accumulates (8). The purpose of this study was to describe the blood pressure rise elicited by the intracoronary administration of adenosine and to determine underlying mechanisms.

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## Methods

### Patients studied

**Innervated hearts.** 26 patients undergoing diagnostic cardiac catheterization for evaluation of chest pain syndromes were studied. 13 of these patients have been included in a preliminary report that describes the effects of adenosine on coronary blood flow (9). Patients with unstable angina, recent myocardial infarction, valvular heart disease, elevated left ventricular filling pressures, or impaired left ventricular systolic function were excluded. Patients with a focal left anterior descending (LAD)<sup>1</sup> coronary artery stenosis of 50% or greater diameter narrowing were not studied. Five patients had an angiographically documented stenosis of  $> 50\%$  in the right or left circumflex coronary artery, but none received angiographically evident collateral blood flow from the LAD. There were 20 men and 6 women ranging in age from 17 to 72 yr (mean 48 yr).

**Denervated hearts.** 20 cardiac transplant recipients undergoing a routine annual cardiac catheterization were studied between 1 and 3 yr posttransplantation. Patients with uncontrolled hypertension were excluded. There were 15 males and 5 females ranging in age from 19 to 62 yr (mean 44 yr). Written informed consent was obtained from all patients before the diagnostic catheterization, in accordance with guidelines established by the Committee for the Protection of Human Subjects at Brigham and Women's Hospital.

### Study design

All vasoactive medications were discontinued 18–24 h before cardiac catheterization, except for unrestricted use of sublingual nitroglycerin, which was withheld 1 h before catheterization. None of these patients were taking dipyridamole or methylxanthine medications before the study. No effort was made to control caffeine ingestion.

Diagnostic right and left heart catheterization and coronary angiography were performed by a standard percutaneous femoral approach. After completion of the diagnostic catheterization, an additional 5,000 U of heparin was given intravenously and an 8F guiding catheter was positioned at the ostium of the left coronary artery. A 20-mHz pulsed Doppler crystal mounted on the tip of a 2.5F catheter (Millar Instruments, Inc., Houston, TX) was advanced through the guiding catheter into the proximal or middle segment of the LAD. The use of this device to assess intracoronary blood flow velocity has been described in detail (10). The Doppler catheter was connected to a photographic multi-channel oscillographic recorder (model VR16; Electronics for Medicine, Pleasantville, NY) to display phasic and mean velocity waveforms. Before beginning the experimental protocol, the position of the Doppler flow velocity catheter and the range gate control were adjusted to optimize the audio flow velocity signal and the phasic flow velocity waveform. The Doppler catheter position and the range gate control were not changed thereafter.

Serial 2-min intracoronary infusions were administered via the central lumen of the Doppler catheter in the following sequence: control (0.9% sodium chloride); three concentrations of adenosine (0.022, 0.22, and 2.2 mg/min); and repeat control (0.9% sodium chloride for 5 min). Assuming a baseline blood flow in the LAD of 80 ml/min (11), these doses of adenosine would give final blood concentrations of  $10^{-6}$ ,  $10^{-5}$ , and  $10^{-4}$  M, but with the increase in blood flow at higher doses

1. Abbreviations used in this paper: ANOVA, analysis of variance; LAD, left anterior descending coronary artery.

the actual concentrations would be proportionately lower. At the end of each infusion, coronary arteriography was performed in biplane orthogonal views with the use of a power injection of nonionic contrast medium, iohexol (Omnipaque; Winthrop-Breon, New York, NY). Throughout each infusion the heart rate, arterial pressure, coronary blood flow velocity, and electrocardiogram (lead I) were monitored continuously. Adenosine (Sigma Chemical Co., St. Louis, MO) was dissolved in 0.9% sodium chloride and cold-filtered under sterile conditions. The purity was confirmed by HPLC.

In six patients with innervated hearts, arterial blood samples for blood gas measurements were drawn under control conditions and just before the end of the infusion of the peak dose (2.2 mg/min) of intracoronary adenosine.

In five patients with innervated hearts, a model 7F Swan-Ganz catheter was advanced to the pulmonary artery to allow collection of arterial and mixed venous blood samples for determination of cardiac output by the Fick technique. Samples for cardiac output determinations were obtained under control conditions and just before the end of the peak dose (2.2 mg/min) of intracoronary adenosine.

**Paired LAD and right atrial infusions of adenosine.** In five patients with innervated hearts, a Swan-Ganz catheter was positioned in the right atrium for a 2-min infusion of adenosine at 2.2 mg/min with continuous recording of heart rate, arterial pressure, and electrocardiogram (lead I). After a 5-min recovery period each of these patients received infusions into the LAD of three doses of adenosine (0.022, 0.22, and 2.2 mg/min) as described above, to allow paired comparisons of the responses to right atrial and intracoronary infusions.

**Intracoronary acetylcholine.** In five patients acetylcholine was infused for 2 min at 15 mcg/min into the LAD via a Doppler catheter to increase coronary blood flow. The coronary blood flow and arterial pressure responses of five patients who exhibited epicardial coronary artery dilation or minimal constriction without a flow-limiting narrowing were analyzed.

**Plasma catecholamines.** In nine patients with innervated hearts and seven patients with denervated transplanted hearts, samples of blood for plasma catecholamine determinations were obtained from a femoral artery under control conditions and just before the end of the peak dose (2.2 mg/min) of intracoronary adenosine. Blood for catecholamines was collected into iced tubes containing EGTA and reduced glutathione and assayed radioenzymatically (12).

**Quantitative coronary angiography.** Analysis of LAD dimensions at the Doppler catheter tip was performed by quantitative coronary angiography in all patients with suitable measurements of coronary flow velocity. The technique has been described previously in detail (13). In six patients with innervated hearts, the dimensions of a left circumflex epicardial arterial segment were analyzed during the LAD infusion of adenosine at 2.2 mg/min.

**Estimates of coronary blood flow changes.** Estimates of relative changes in coronary blood flow were made by correcting relative changes in mean coronary blood flow velocity, as measured directly by the Doppler catheter for changes from control in estimated vessel cross-sectional area at the catheter tip, as determined from the change in diameter measured by quantitative angiography in the optimal single plane view. This is a modification of the technique previously described (13).

### Statistical analysis

Dose response data were analyzed by analysis of variance (ANOVA), and Bonferroni *t* tests were applied to determine which values were different from baseline. Statistical significance of linear regression analyses was assessed by ANOVA. Parameters that were measured at only one dose of adenosine (cardiac output, systemic vascular resistance, plasma catecholamines levels, and arterial blood gas measurements) were analyzed by paired *t* tests. Data that were not normally distributed were analyzed by the Wilcoxon signed rank test. Group differences were analyzed by unpaired *t* tests. All null hypotheses were two tailed and the criterion of significance was  $P < 0.05$ . The data are presented as mean  $\pm$  SEM.

## Results

**Hemodynamic effects of intracoronary adenosine in patients with innervated hearts.** Infusion of adenosine over the range 0.022 to 2.2 mg/min into the LAD of patients with innervated hearts produced a dose-dependent increase in systolic and diastolic arterial pressure without a significant change in heart rate (Figs. 1 and 2). At the highest dose of adenosine (2.2 mg/min) systolic arterial pressure rose by  $21.0 \pm 2.2$  mmHg from  $134 \pm 4.3$  mmHg ( $P < 0.001$ ) and diastolic pressure increased by  $10.4 \pm 1.1$  mmHg from  $76 \pm 1.9$  mmHg ( $P < 0.001$ ), while heart rate did not change ( $1.3 \pm 1.1$  from  $67 \pm 1.7$  beats/min,  $P = \text{NS}$ ). Each of these parameters returned to baseline ( $P = \text{NS}$ ) during the recontrol measurement 5 min after discontinuing the last adenosine infusion. In the five patients with measurements of cardiac output, adenosine (2.2 mg/min) produced a  $22 \pm 3.4\%$  increase ( $P < 0.01$ ) in systemic vascular resistance from  $1,045 \pm 131$  dyn  $\cdot$  s  $\cdot$  cm $^{-5}$  without a change in cardiac output ( $-2.8 \pm 4.3\%$  from  $7.4 \pm 0.8$  liters/min,  $P = \text{NS}$ ).

**Paired LAD and right atrial infusions of adenosine.** Five patients with innervated hearts received infusions of adenosine into the LAD (2.2 mg/min) and into the right atrium (2.2 mg/min) (Fig. 3). Systolic arterial pressure rose to a greater extent ( $P < 0.05$ ) with LAD infusion ( $20.4 \pm 4.8$  mmHg) than with right atrial infusion ( $2.0 \pm 2.8$  mmHg). There was also a greater increase ( $P < 0.05$ ) in diastolic pressure with LAD infusion ( $9.4 \pm 2.0$  mmHg) than with right atrial infusion ( $2.8 \pm 0.8$  mmHg).

**Hemodynamic effects of intracoronary adenosine in patients with denervated hearts.** In marked contrast to patients with innervated hearts was the response observed in cardiac transplant patients with denervated hearts (Fig. 4), in whom adenosine (2.2 mg/min) produced no change in systolic arterial pressure ( $-0.1 \pm 1.6$  mmHg from  $139 \pm 3.4$  mmHg,  $P = \text{NS}$ ) and a decrement in diastolic pressure ( $-4.7 \pm 1.2$  mmHg from  $98 \pm 2.5$  mmHg,  $P < 0.01$ ) with no change in heart rate ( $-0.2 \pm 0.8$  from  $86 \pm 2.5$  beats/min,  $P = \text{NS}$ ).

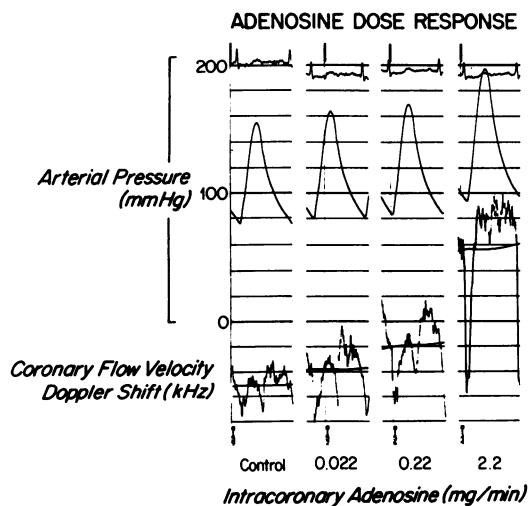
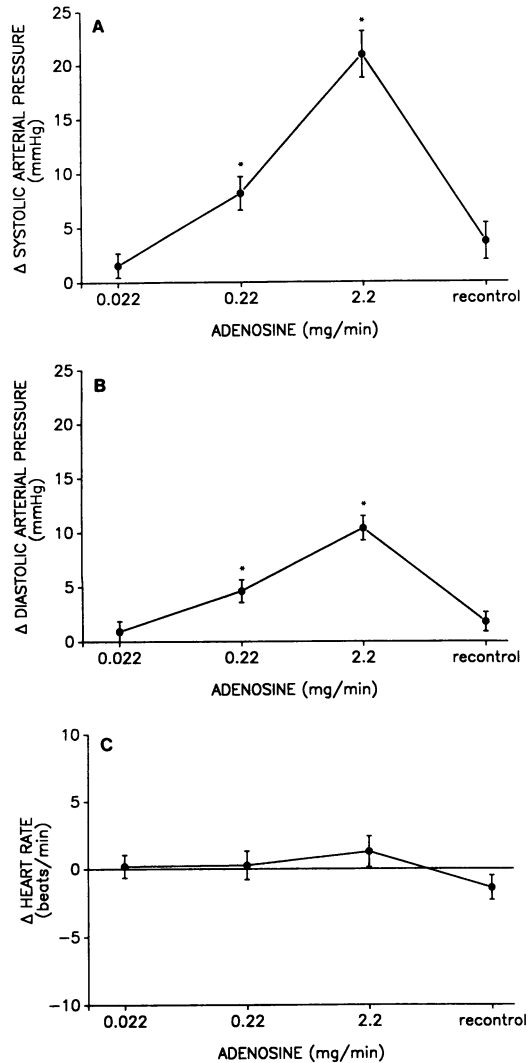


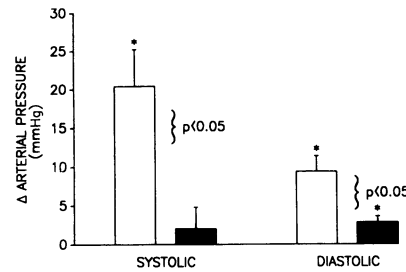
Figure 1. Typical hemodynamic response to graded intracoronary infusions of adenosine. The upper waveforms represent arterial blood pressure and the lower waveforms represent phasic and mean coronary flow velocity. There is a dose-related increase in systolic and diastolic pressures and in coronary flow velocity in response to adenosine (0.022–2.2 mg/min).



**Figure 2.** Dose-response relationship for the effects of intracoronary adenosine on (A) systolic blood pressure, (B) diastolic blood pressure, and (C) heart rate in 26 patients with innervated hearts. Heart rate did not change over this dose range. Systolic and diastolic pressures increased significantly from baseline at 0.22 mg/min and increased further at 2.2 mg/min. The *P* values shown are from ANOVA. \*Significant differences from baseline (Bonferroni correction).

**Plasma catecholamine response to intracoronary adenosine.** In the nine patients with innervated hearts who had determination of plasma catecholamine responses to intracoronary adenosine, norepinephrine levels rose by  $40 \pm 14\%$  from  $105 \pm 9$  pg/ml ( $P < 0.05$ ) and epinephrine levels rose by  $119 \pm 31\%$  from  $37 \pm 9$  pg/ml ( $P < 0.01$ ), while dopamine levels did not change ( $5 \pm 7\%$  from  $71 \pm 14$  pg/ml,  $P = \text{NS}$ ). In the seven posttransplant patients with denervated hearts in whom plasma catecholamine levels were determined, intracoronary adenosine infusion was not associated with a significant change in norepinephrine levels ( $7 \pm 4\%$  from  $145 \pm 25$  pg/ml), epinephrine levels ( $33 \pm 27\%$  from  $31 \pm 7$  pg/ml), or dopamine levels ( $1 \pm 6\%$  from  $123 \pm 14$  pg/ml).

**Effect of increased coronary blood flow on systemic hemodynamics.** In the 20 subjects with innervated hearts with measurement of coronary blood flow, LAD infusion of adenosine (2.2 mg/min) produced a  $334 \pm 35\%$  increase in estimated coro-



**Figure 3.** Comparison of hemodynamic responses to intracoronary and right atrial adenosine infusions (2.2 mg/min) in five patients with innervated hearts. Right atrial infusion produced no change in systolic pressure and a slight increase in diastolic pressure in contrast to the striking increases in systolic and diastolic pressures observed with intracoronary infusion. Open bars, intracoronary infusion; solid bars, right atrial infusion. \*Different from control,  $P < 0.05$ .

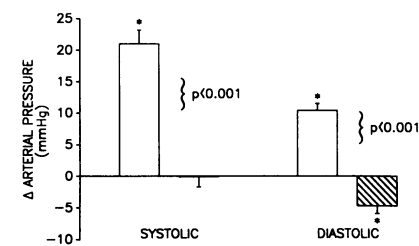
stolic pressure in contrast to the striking increases in systolic and diastolic pressures observed with intracoronary infusion. Open bars, intracoronary infusion; solid bars, right atrial infusion. \*Different from control,  $P < 0.05$ .

nary blood flow ( $P < 0.001$ ) while increasing systolic arterial pressure by  $20.4 \pm 2.5$  mmHg ( $P < 0.001$ ) and diastolic blood pressure by  $10.3 \pm 1.3$  mmHg ( $P < 0.001$ ). In five patients with innervated hearts, infusion of acetylcholine (15 mcg/min) into the LAD produced a  $254 \pm 37\%$  increase in estimated coronary blood flow ( $P < 0.01$ ), but did not significantly increase systolic ( $0.4 \pm 5.2$  mmHg) or diastolic ( $2.0 \pm 2.7$  mmHg) arterial pressures.

**Effect of adenosine on the tone of contralateral coronary artery.** In six patients with innervated hearts, the effect of LAD infusion of adenosine (2.2 mg/min) on the tone of the epicardial circumflex coronary artery was examined. In these patients adenosine produced a  $20.3 \pm 4.1$  mmHg ( $16 \pm 3\%$ ) increase in systolic arterial pressure and a  $10.3 \pm 3.6$  mmHg ( $16 \pm 6\%$ ) increase in diastolic pressure. A slight reduction in diameter of the left circumflex coronary artery segments of  $-5.1 \pm 0.6\%$  ( $P < 0.05$ ) was observed in these patients despite the increase in distending pressure.

**Respiratory effects of intracoronary adenosine.** In the seven patients with innervated hearts who had arterial blood gas measurements, LAD infusion of adenosine (2.2 mg/min) produced a possible small increase in  $\text{PO}_2$  ( $6.7 \pm 2.5$  mmHg from  $71 \pm 3.1$  mmHg,  $P < 0.10$ ), a small decrease in  $\text{PCO}_2$  ( $-3.4 \pm 1.0$  mmHg from  $43 \pm 0.8$  mmHg,  $P < 0.05$ ), and a possible small increment in pH ( $0.021 \pm 0.007$  from  $7.37 \pm 0.01$ ,  $P < 0.06$ ).

**Side effects of intracoronary adenosine.** Among the patients with innervated hearts two experienced flushing, one developed mild dyspnea, and two experienced mild chest fullness. These symptoms abated  $< 1$  min after discontinuation of the adenosine infusion. None of the cardiac transplant patients reported any symptoms.



**Figure 4.** Hemodynamic responses to intracoronary infusion of adenosine (2.2 mg/min) in patients with innervated hearts ( $n = 26$ ) and cardiac transplant patients with denervated hearts ( $n = 20$ ). Systolic and diastolic

pressures rose significantly in patients with innervated hearts, while systolic pressure did not change and diastolic pressure fell in patients with denervated hearts. Open bars, innervated hearts; hatched bars, denervated hearts. \*Different from control,  $P < 0.01$ .

## Discussion

The results of this study indicate that intracoronary administration of adenosine in conscious humans produces a dose-dependent increase in systolic and diastolic arterial pressure due to an increase in systemic vascular resistance. Intracoronary infusion of adenosine produced a much greater pressor response than an infusion of the same dose into the right atrium, indicating that systemic spillover from the coronary sinus was not responsible for the effects of the intracoronary infusion. The increase in blood pressure was associated with an elevation of plasma catecholamine levels. In addition, an increase in arterial pressure was not observed in cardiac transplant patients with denervated hearts, demonstrating the cardiac origin of this reflex and providing additional evidence that systemic effects of adenosine did not cause the blood pressure rise. The increase in coronary blood flow induced by intracoronary adenosine is not the stimulus for the pressor response since intracoronary infusions of acetylcholine sufficient to produce similar increases in coronary blood flow did not elicit an increase in arterial pressure.

For many years it has been appreciated that adenosine produces potent relaxation of isolated arteries *in vitro* (1) and marked vasodilation with local administration in experimental animals (3). Systemic administration in conscious animals consistently results in a hypotensive response (4, 5). Adenosine has been infused systemically as a hypotensive agent in anesthetized patients undergoing surgery, producing a pronounced decrease in systemic vascular resistance (6). In contrast, Biaggioni et al. (14, 15) found that intravenous infusion of adenosine in conscious humans in doses that were larger than we used in the present study increases systolic arterial pressure significantly. This pressor response was not observed in patients with severe autonomic failure, suggesting a reflex autonomic mechanism. Infusion of adenosine also produced profound respiratory stimulation, suggesting that chemoreceptor activation may play a role in the observed hemodynamic response to systemic administration.

In the present study we observed an increase in systolic and diastolic arterial pressure with infusion of adenosine into the LAD. The increase in arterial pressure was due to an increase in systemic vascular resistance without an increase in cardiac output. These findings indicate that the pressor response is not due to a direct positive inotropic effect of adenosine, nor is it due to a release from efferent nerve endings of neurotransmitters with positive inotropic actions. Although this result suggests a reflex mechanism, it does not necessarily indicate that the heart is the source of the afferent limb of the reflex. For this reason we compared the hemodynamic responses of paired right atrial and LAD infusions to exclude the possibility that the observed response was due to spillover of adenosine from the coronary sinus. Right atrial infusion produced minimal hemodynamic effects, in contrast to the striking pressor response with LAD infusions. These findings are consistent with the heart being the source of the afferent limb. Further evidence in support of a reflex mechanism initiated by stimulation of cardiac afferents is the absence of the pressor response with intracoronary infusion of adenosine in the denervated hearts of cardiac transplant patients, since afferent mechanisms in extracardiac sites are preserved in these patients. It is probable that these adenosine-sensitive cardiac afferents are

different from those that mediate chest pain since most of the patients did not find the infusions painful.

Based on our observation of increases in norepinephrine and epinephrine levels with intracoronary infusion of adenosine, it is likely that at least a major component of the efferent limb of this pressor response is increased sympathetic discharge. It is of interest that we observed no change in heart rate or cardiac output with this response, suggesting that this excitatory reflex does not increase sympathetic outflow to the sinoatrial node or the myocardium. Alternatively, it is possible that this reflex in fact does stimulate heart rate but this effect is offset by the baroreceptor reflex. While the constrictor effect was prominent in the systemic vasculature, a modest degree of constriction was also detected in a contralateral coronary artery, suggesting that at least some cardiac efferents are also stimulated. Although it is likely that adenosine exerts its effects primarily by activation of a hypertensive pathway, as evidenced by an increase in serum catecholamine concentrations, we cannot exclude the possibility that it also raises blood pressure by the inhibition of a tonic hypotensive pathway.

The most apparent physiologic implication of this reflex concerns states in which endogenous myocardial adenosine levels are elevated, such as in myocardial ischemia (8). A hypertensive response elicited by adenosine could be beneficial in impending cardiogenic shock by helping to maintain adequate arterial pressure and increasing diastolic coronary perfusion pressure. It could also be deleterious by increasing myocardial oxygen demand. Concentrations of adenosine in the interstitial fluid during ischemia have been estimated at  $10^{-6}$  M (16). In our study, infusion of the highest dose of adenosine (2.2 mg/min) would produce a final blood concentration of  $10^{-4}$  M with a resting blood flow of 80 ml/min (11), but with the attendant increase in blood flow induced by adenosine and the estimate that 90% of infused adenosine is taken up by endothelial cells (17, 18) it is likely the interstitial fluid concentrations of adenosine achieved are within the relevant range. An additional support for this concept is suggested by the observation that the doses of adenosine required to elevate systemic blood pressure and the doses required to increase coronary blood flow were similar in most patients (Fig. 1).

Given the regional differences in the autonomic innervation of the anterior and inferior wall, it would be of interest to determine whether a pressor response to adenosine would also occur with infusion of adenosine to the inferior wall. However, because adenosine has potent effects in suppressing sinoatrial node automaticity and depressing atrioventricular nodal conduction (19), we did not administer adenosine into a right or circumflex coronary artery because of our concern for patient safety.

In conclusion, the intracoronary infusion of adenosine in conscious man elicits a reflex that leads to an increase in systemic blood pressure.

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