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Adenosine Infusion for the Reversal of Pulmonary Vasoconstriction in Biventricular Failure

A Good Test but a Poor Therapy

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Background. Elevation of pulmonary vascular resistance is an important determinant of right ventricular function in patients with end-stage biventricular heart failure. Vasodilator drug therapy directed at the pulmonary vasculature is used in the hemodynamic assessment of patients for orthotopic heart transplantation, and therapy aimed at decreasing pulmonary vascular resistance and transpulmonary pressure gradient has been advocated in patients awaiting heart transplantation. Adenosine infusion has been shown to cause selective pulmonary vasodilatation in normal subjects and in patients with primary pulmonary hypertension but has not been assessed in patients with biventricular heart failure.

Methods and Results. Using two infusion doses, we studied the pulmonary and renal hemodynamic effects of adenosine on patients referred for heart transplantation ($n=21$) and compared it with sodium nitroprusside ($n=18$). Patients received 30% oxygen via face mask throughout the study. Adenosine at 100 μg/kg/min achieved the same percentage fall in pulmonary vascular resistance as nitroprusside ($41\pm6\%$ versus $42\pm4\%$) and a greater and more consistent fall in transpulmonary pressure gradient ($35\pm6\%$ versus $9\pm30\%$, $p<0.02$). The mean arterial blood pressure fell by 16 mm Hg with nitroprusside but was unchanged by adenosine, indicating that in contrast to nitroprusside, adenosine acted as a selective pulmonary vasodilator. Despite this, cardiac index showed only a modest increase with adenosine (1.73 ± 0.09 to 1.89 ± 0.16 l $\cdot$ m^{-2}, $p<0.05$), and there was a rise in pulmonary capillary wedge pressure from baseline at the higher dose (29.7 ± 2.5 to 33.4 ± 3.4 mm Hg, $p<0.05$). Renal blood flow was unchanged during adenosine infusion.

Conclusions. Adenosine is a potent selective pulmonary vasodilator in patients with biventricular heart failure and is preferable to sodium nitroprusside as a test for the reversibility of pulmonary vasoconstriction. However, its deleterious effects on left atrial pressure make it unsuitable as a therapeutic agent in patients awaiting heart transplantation. (*Circulation* 1992;86:896–902)

KEY WORDS • adenosine • circulation, pulmonary • circulation, renal • vasoconstriction

Pulmonary vascular resistance and the transpulmonary pressure gradient are often elevated in biventricular heart failure[1] and are of concern for two reasons: first, it has been demonstrated that pharmacologically irreversible elevation of pulmonary vascular resistance and transpulmonary gradient predicts an increased mortality at orthotopic heart transplantation,[2–6] and second, there may be deleterious effects from chronic elevation of pulmonary vascular resistance and transpulmonary gradient on right ventricular function. The right ventricle is particularly sensitive to increases in afterload, with small increases in pulmonary vascular resistance resulting in sharp decreases in right ventricular stroke volume.[7] The clinical importance of right ventricular afterload as a determinant of survival in patients with heart failure is demonstrated by the fact that elevated pulmonary artery pressure is an independent predictor of mortality.[8,9] The vulnerability of patients with biventricular heart failure to the development of clinically significant right heart failure may be particularly high in patients with ischemic heart disease. The ability of the right ventricle to respond to increased afterload is dependent upon increased right coronary artery perfusion,[10] and stenosis or occlusion of the right coronary artery may increase the risk of right ventricular decompensation. Some investigators have also noted that left ventricular ejection fraction fails to correlate with exercise capacity in patients with biventricular heart failure, but right ventricular ejection fraction does.[11] Similarly, right ventricular ejection fraction may be more predictive of survival than left ventricular ejection fraction in patients with ischemic heart disease.[12] Recently, the use of long-term therapeutic infusions of pharmacological agents intended to reduce pulmonary vascular resistance and transpulmonary gradient has been advocated,[13,14] but the hemodynamic consequences of selective

TABLE 1. Patient Characteristics

	Group 1, adenosine 50 μg/kg/min (n=10)	Group 2, adenosine 100 μg/kg/min (n=11)	Group 3, sodium nitroprusside 2.7±0.9 μg/kg/min (n=18)
Age (years)	48.6±3.5	51.6±1.6	49.7±2.2
Sex (male:female)	8:2	10:1	13:5
Etiology (ischemic heart disease:cardiomyopathy)	6:4	8:3	11:7
NYHA class III:IV	7:3	7:4	13:5
Drug therapy			
Loop diuretics	10/10	11/11	18/18
ACE inhibitors	9/10	9/11	15/18
Digoxin	3/10	2/11	7/18
Nitrates / calcium antagonists	4/10	3/11	6/18

Mean age±SEM, sex, etiology of heart failure, New York Heart Association (NYHA) heart failure class, and drug therapy of patients at the time of investigation.

pulmonary vasodilatation in biventricular heart failure have not been investigated.

Drugs in current use for pulmonary vasodilatation lack selectivity for the pulmonary vasculature, and there is therefore a tendency for systemic hypotension to limit the doses that can be administered.

Adenosine, as an intravenous infusion, has shown promise as a selective pulmonary vasodilator in normal subjects[15–17] and in patients with primary pulmonary hypertension.[18] However, two factors potentially limit the use of adenosine in patients with severe heart failure, namely, the dysphoric side effects experienced by conscious normal subjects at rapid rates of infusion and renal vasoconstriction. A renal vasoconstrictor response was first reported by Drury and Szent-Györgyi in 1929[19] and was subsequently shown to be augmented in sodium-retaining[20] and high–angiotensin II[21] states. Most investigators have found this to be a transient response with renal blood flow returning to baseline or even increased levels over 1–4 minutes of infusion.[22,23] However, there is evidence in dogs that, in the presence of frusemide, renal vasoconstriction is sustained.[24]

The purpose of this study was to assess the effects of adenosine on renal blood flow and its clinical potential as a selective pulmonary vasodilator in patients with severe biventricular heart failure both in testing for the reversibility of elevated pulmonary vascular resistance and as a therapeutic agent. For comparison, the hemodynamic effects of sodium nitroprusside, the vasodilator most frequently used in current clinical practice, were assessed in the same patient population.

Subjects

Thirty-four consecutive patients requiring right heart catheterization for measurement of pulmonary vascular resistance as part of their assessment for cardiac transplantation were studied. Twenty-nine of the patients were infused with a single drug, and five patients received both drugs with infusion of adenosine followed 30 minutes later by sodium nitroprusside. Three consecutive subgroups were analyzed: group 1 (n=10; age, 47.5±3.9 years) received adenosine 50 μg·kg^{-1}·min^{-1}, group 2 (n=11; age, 51.6±1.6 years) received adenosine 100 μg·kg^{-1}·min^{-1}, and group 3 (n=18; age, 49.1±2.4 years) received sodium nitroprusside 2.7±0.9 μg·kg^{-1}·min^{-1}.

Patients had all been established on optimal drug therapy for at least 48 hours before the study period. Patient medication is shown in Table 1. Three patients were in atrial fibrillation, one in each group. Patients receiving phosphodiesterase inhibitors were excluded, as these are known to antagonize the pharmacological effects of adenosine.[25,26] All patients gave informed signed consent, and the study was approved by the hospital's ethics committee.

Methods

All patients received 30% oxygen via face mask throughout the study. Arterial oxygen saturations were measured at baseline and during drug infusions. Diamorphine 2.5 mg and diazemuls 2.5–5 mg were given intravenously to relax without markedly sedating the patient before right heart catheterization.

Pulmonary and Systemic Hemodynamics

A venous infusion port 7.5F flow-directed pulmonary artery thermodilution catheter (model 93A-831-7.5F, Baxter Healthcare Corporation, Irvine, Calif.) was introduced, and cardiac output measurements were made by taking the mean of at least three measurements recorded by a cardiac output computer (model COM-1RS, American Edwards Laboratories, Irvine, Calif.). Cardiac output was measured in liters per minute. A 20-gauge femoral arterial cannula was inserted for monitoring of systemic arterial pressure. Arterial and intracardiac pressures were measured by Baxter pressure transducers (model 43-260, Baxter Healthcare Corporation) and recorded on a chart recorder (Mingograf 7, Siemens-Elema, Sweden). Pressures are stated as millimeters of mercury (mm Hg). Pulmonary vascular resistance was calculated from the mean pulmonary artery pressure minus the mean wedge pressure, both recorded during end expiration and divided by the cardiac output. Systemic vascular resistance was measured from mean arterial pressure minus the mean right atrial pressure divided by the cardiac output. Both values were expressed as dyne/sec/cm^{-5} by multiplying the values obtained by a factor of 80. The ECG was continuously monitored.

TABLE 2.   Hemodynamic Values at Baseline and During Drug Infusion for the Three Treatment Groups

	Mean arterial blood pressure (mm Hg)	Cardiac index (l/min)	Mean pulmonary artery pressure (mm Hg)	Wedge pressure (mm Hg)	Right atrial pressure (mm Hg)	PVR (dyne · sec · cm^{-5})
Group 1 baseline	84±4.7	1.96±0.15	37.9±3.9	27.5±3.6	13±3	261±46
Adenosine 50 μg/kg/min	87±5.2††	2.06±0.18*†††	38.0±4.4	29.6±4.4†	13±3	197±35**
Group 2 baseline	78±3.3	1.73±0.09	39.5±3.0	29.7±2.5	15±2	278±60
Adenosine 100 μg/kg/min	79±3.6††	1.89±0.16*†††	39.5±3.6†	33.4±3.4*††	15±2††	168±46**†
Group 3 baseline	84±3.5	1.73±0.09	40.4±2.7	27.1±2.4	12±2	371±38‖
Nitroprusside	68±2.1***	2.74±0.11***	30.2±2.5***	18.4±2.6***	8±1**	209±24***

Values given as mean±SEM. Pulmonary vascular resistance (PVR)/systemic vascular resistance (SVR) equals percentage ratio of PVR to SVR.

*Significant change within the group from baseline to infusion measurements at *$p<0.05$, **$p<0.01$, and ***$p<0.001$ levels.

†Significant difference between measurements during nitroprusside and adenosine infusions at †$p<0.05$, ††$p<0.01$, and †††$p<0.001$ levels.

§Significant difference between percentage change in response to adenosine infusion between the low- and high-dose infusion rates ($p<0.05$).

‖ Significant difference between the baseline value in the nitroprusside group and the baseline value in the adenosine groups ($p<0.05$).

Renal Blood Flow

A 7F coronary sinus thermodilution catheter (CCS Regional Pepine 2E, Webster Laboratories Inc., Baldwin Park, Calif.) was guided by flouroscopy from the femoral vein to the left renal vein for the measurement of left renal blood flow by continuous renal vein thermodilution[27]; the mean of the values derived from three injections of room-temperature normal saline was taken. Renal venous pressure was transduced from the central lumen of the catheter and renal vascular resistance calculated from the difference between mean arterial and renal venous pressures divided by the renal blood flow. This value was multiplied by 40 to give an estimate of total renal vascular resistance in both kidneys in dyne · sec^{-1} · cm^{-5}. Renal blood flow measurements were made during the measurement of systemic and pulmonary blood pressures.

When hemodynamic parameters had remained stable over a period of 15 minutes, the drug infusion was administered via a fourth lumen in the pulmonary flotation catheter so that the drug was delivered into the right atrium. Hemodynamic measurements were repeated between 5 and 10 minutes after the start of the infusion, when steady-state hemodynamics had been reached. The duration of the adenosine infusion was between 10 and 15 minutes. Nitroprusside was infused in incremental doses until the systolic arterial blood pressure had been reduced by 20 mm Hg or until a value of 80 mm Hg was reached. Patients were asked to report any symptoms they experienced during the adenosine infusion.

Statistical Analysis

The data was analyzed using the Wilcoxon signed rank test to evaluate changes from baseline to infusion in patients within each group. The two-tailed Mann-Whitney U test was used to compare results between the three groups. Results are presented as mean±SEM.

Results

The characteristics of the patients in the three infusion groups are shown in Table 1. There was no significant difference in mean age or baseline hemodynamic measurements, with the exception of pulmonary vascular resistance, which was higher in the nitroprusside group than in the groups given adenosine (371±38 dyne · sec · cm^{-5} versus 278±60, group 2, 100 μg/kg/min, and 261±46, group 1, 50 μg/kg/min, $p<0.05$) (Table 2). In both adenosine groups, there was a small but significant rise in cardiac index in response to adenosine infusion ($p<0.05$); the values for peak cardiac index did not differ significantly between the two infusion rates. The increase in flow was associated with an increase in pulmonary capillary wedge pressure but no increase in mean pulmonary artery pressure, reflecting a significant fall in the pulmonary vascular resistance at both infusion rates ($p<0.005$). The percentage of fall in pulmonary vascular resistance was greater in response to 100 μg/kg/min than to 50 μg/kg/min (41±6% versus 22±5%, $p<0.05$). There was, however, no significant effect of adenosine infusion on the systemic mean arterial pressure that did not fall in either group (Figure 1). This selective pulmonary vasodilatation was illustrated by the fall in the pulmonary vascular resistance/systemic vascular resistance percentage ratio ($p<0.005$ at both infusion rates). The fall in transpulmonary gradient in the group who received adenosine 100 μg/kg/min was greater than in those who received the lower dose of adenosine ($p<0.05$) and also than in those who received nitroprusside ($p<0.02$) (Figure 2).

Arterial oxygen saturations were maintained at a high level throughout, with unchanged mean values in response to adenosine 50 μg/kg/min (95±0.6% at baseline and 95±0.6% on adenosine, NS) and adenosine 100 μg/kg/min (97±0.5% at baseline and 95±0.4% on adenosine, NS) and a slight fall in response to sodium nitroprusside (96±0.6% at baseline and 95±0.9% on nitroprusside, $p<0.01$).

Renal blood flow and renal vascular resistance were not significantly affected by either rate of adenosine infusion.

In contrast to the minor effects of adenosine on the systemic and renal circulations, sodium nitroprusside caused highly significant falls in mean arterial blood pressure ($p<0.001$), systemic vascular resistance ($p<0.001$), and renal vascular resistance ($p<0.001$). There was only a modest increase in renal blood flow because of the fall in renal perfusion pressure. Sodium

TABLE 2. Continued

SVR (dyne · sec · cm⁻⁵)	PVR/SVR	Fall in PVR (%)	Transpulmonary gradient (mm Hg)	Fall in TPG (%)	Heart rate (beats per minute)	Left renal blood flow (ml/min)	Renal vascular resistance (dyne · sec · cm⁻⁵)
1,669±130	15±2.4		10±1.5		84±7	204±29	17,480±3,120
1,674±159†††	11±1.7**††	22±5††	8±1.1**	16±5	83±6	195±29	17,480±2,000††
1,709±261	15±1.7		10±1.2		89±7	224±25	12,040±1,200
1,709±267†††	9±1.1**†††	41±6§	6±0.9**	35±6§††	90±7	245±28	11,360±1,240
1,978±155§	19±1.3		13±0.9		91±5	207±26	16,080±5,760
1,027±64***	21±1.9	42±4	12±0.9	9±30	96±5**	261±35*	10,360±1,160**

nitroprusside also resulted in a much greater increase in cardiac output than adenosine ($p<0.001$ at both infusion rates) and reductions in both mean pulmonary artery pressure and pulmonary capillary wedge pressure. The percentage fall in pulmonary vascular resistance in response to sodium nitroprusside was similar to the higher infusion rate of adenosine (sodium nitroprusside, 42±4% versus adenosine, 41±6%, NS) but was greater than the fall caused by the lower infusion rate of adenosine (22±5%, $p<0.01$). In contrast to the heart rate rise observed in normal subjects in response to adenosine infusion at either 50 or 100 μg/kg/min,[17,28] we saw no significant rise in heart rate in response to adenosine in these patients with biventricular heart failure. There was a small but highly significant reflex increase in heart rate in response to sodium nitroprusside infusion ($p<0.01$).

No patients experienced chest pain, dysphoric symptoms, or episodes of atrioventricular block or bradycardia during the drug infusions.

Discussion

Effects of Adenosine and Nitroprusside on the Pulmonary and Systemic Circulations

Adenosine causes relaxation of vascular smooth muscle in sections of human large and small pulmonary arteries in vitro.[29] In clinical studies, pulmonary vasoconstriction cannot be observed directly and it is therefore necessary to obtain information on pulmonary vascular tone from measurements of the pressure gradient and the flow of blood across the pulmonary vasculature. This allows calculation of the pulmonary vascular resistance from the equation $R=Q/P$, where R is the resistance, P is the pressure gradient across the system, and Q is the cardiac output (which is equal to the blood flow through the pulmonary vasculature excluding beat-to-beat variation).[30] Pulmonary vascular resistance calculated from this equation is an approximation to the actual resistance because the pulmonary vasculature is not a rigid tube, flow is pulsatile, and pulmonary vascular impedance therefore contributes to total resistance, and no allowance is made for the recruitment of additional capillaries at higher pressures.[30] Some authors have therefore advocated the use of the simpler, directly measurable variable of transpulmonary pressure gradient, the difference in pressure between the mean pulmonary arterial blood pressure and the pulmonary capillary wedge pressure.[4,31]

Effects on transpulmonary gradient and pulmonary vascular resistance. In this study, the agent that resulted in the greatest fall in transpulmonary pressure gradient was adenosine 100 μg/kg/min. This fall (35%) occurred as a result of a rise in pulmonary capillary wedge pressure that was not transmitted back across the pulmonary vasculature to result in an equivalent rise in mean pulmonary artery pressure. The mean value for pulmonary artery pressure was unchanged by the infusion of adenosine 100 μg/kg/min. However, there was
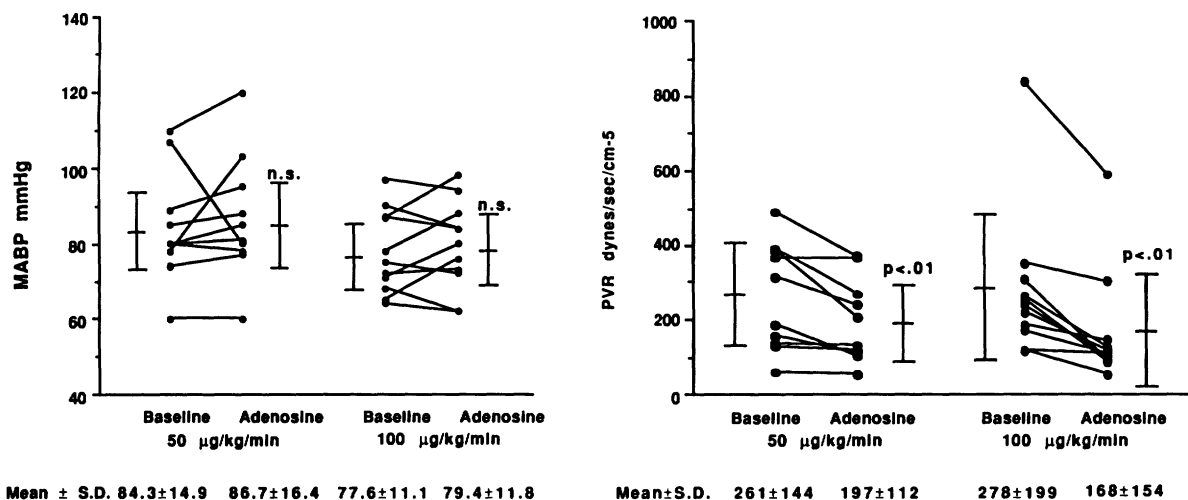

FIGURE 1. *Plots show changes in mean arterial blood pressure (MABP, mm Hg) and pulmonary vascular resistance (dyne/sec/cm⁻⁵) in individual patients given adenosine.*
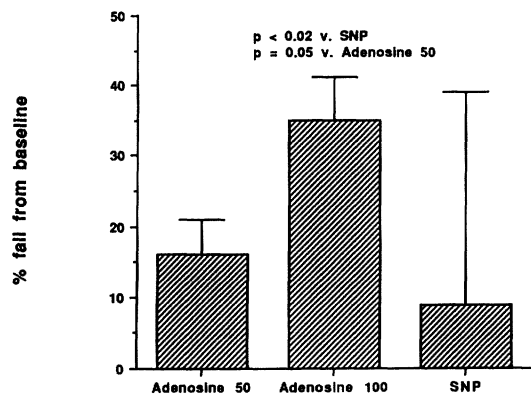
FIGURE 2. *Bar graph shows percentage fall in transpulmonary gradient (mm Hg) in each group. Differences between the group receiving adenosine 100 µg/kg/min and the other two groups are indicated. SNP, sodium nitroprusside.*

only a small increase in the blood flow through the pulmonary vasculature with adenosine but a large increase with nitroprusside. The percentage fall in pulmonary vascular resistance, which takes into account the rise in flow as well as the change in pressure gradient across the pulmonary circulation, was therefore similar in the group given adenosine 100 µg/kg/min and the group who received nitroprusside (41% versus 42%, NS).

Pulmonary selectivity. The absence of a fall in the systemic mean arterial blood pressure and the decrease in the pulmonary vascular resistance/systemic vascular resistance percentage ratio in response to adenosine infusion demonstrated that the drug caused selective pulmonary vasodilatation in these patients. In contrast, there was a 16–mm Hg fall in mean arterial pressure and an increase in the pulmonary vascular resistance/systemic vascular resistance percentage ratio during nitroprusside infusion, demonstrating that the vasodilating effect of nitroprusside lacks any selectivity for the pulmonary vasculature.

The mechanism by which intravenously infused adenosine acts selectively on the pulmonary circulation in these patients is not clear. The most likely explanation is that the very short half-life of adenosine ($\approx$10 sec)[32–34] and the delayed transit time through the pulmonary circulation in patients with low cardiac index results in little adenosine reaching the systemic circulation. Alternatively, systemic adenosine receptors may be downregulated in biventricular heart failure. The absence of changes in the systemic circulation was accompanied by a failure to observe the usual reflex rise in heart rate observed with these rates of intravenous adenosine infusion in normal subjects[35] and the absence of symptoms of chest discomfort and dyspnea, which are very frequent when 100 µg/kg/min of adenosine is infused into normal subjects.[17]

Effects on cardiac output. Despite significant pulmonary vasodilatation and the maintenance of right ventricular filling pressures, the ability of adenosine to increase the cardiac output was limited. There are two possible explanations for this. It may be that the beneficial vasodilating effects of A_2-receptor agonism in the pulmonary vasculature are balanced by antagonism of the inotropic effects of circulating and locally released catecholamines via A_1-receptor agonism in the ventric-

ular myocardium and at prejunctional receptors on cardiac sympathetic nerve endings.[36,37] Alternatively, changes in the resistance to outflow from the right ventricle may not exert an important influence on overall cardiac output. The principle factor determining cardiac output in patients with biventricular heart failure may be the resistance to outflow from the left ventricle, indicated by the systemic vascular resistance, which was unchanged at the higher dose of adenosine.

Effects on pulmonary capillary wedge pressure. These two possible explanations for the lack of a major increase in cardiac output in response to adenosine infusion also provide possible mechanisms for the rise in pulmonary capillary wedge pressure observed during the adenosine infusion. A negative inotropic effect would exacerbate the elevation of left atrial pressure resulting from the diminished contractility of the failing left ventricle, but a decrease in the resistance to outflow from a right ventricle that was more vigorous than the left ventricle would allow the right ventricle to drive the pulmonary capillary wedge pressure up. If the latter explanation is correct, it would be appropriate to regard the elevation of pulmonary vascular resistance in these patients as a mechanism protecting against high left atrial pressures and reducing the tendency toward pulmonary edema, a concept that draws into question the therapeutic value of attempting selectively to decrease pulmonary vascular resistance in patients with biventricular failure. It may well be that both the negative inotropic effects of adenosine A_1-receptor activation and the disparate effects on the relations between afterload and ventricular function on the two sides of the heart both play a part in determining the overall hemodynamic response to adenosine infusion.

Systemic effects of sodium nitroprusside. In contrast, sodium nitroprusside achieved a marked improvement in cardiac output in relation to ventricular filling pressures; however, mean arterial pressure fell below 60 mm Hg in 22% of the patients, putting the cerebral and coronary circulations at risk. Thus, its potential therapeutic value is limited by its hypotensive effects.

Effects of Adenosine and Nitroprusside on Renal Perfusion

Adenosine. This study is the first to report the effects of intravenous adenosine on renal blood flow in patients with heart failure. Animal studies have shown that adenosine administered to the kidney results in a dose-related reduction in renal blood flow of 1–4 minutes' duration followed by a return to baseline or slightly elevated levels of blood flow.[22,23,38] One study of the effect of adenosine infusion on human effective renal plasma flow has been reported.[39] This was performed in patients undergoing cerebral aneurysm surgery. Sodium para-aminohippurate clearance was used to measure effective renal plasma flow, but renal vein cannulation was not performed, and the para-aminohippurate extraction fraction was not measured. Adenosine is known to affect afferent arteriolar tone[38] and to have differential effects on the vascular tone of the deep cortex and medulla.[40] Both of these effects are likely to alter para-aminohippurate extraction fraction.[41,42] The effects of adenosine on renal blood flow cannot, therefore, be determined from the change in effective renal plasma flow observed in this study.

Use of the continuous thermodilution technique in the renal vein[27] avoids these methodological difficulties by measuring the renal venous outflow from the whole kidney rather than the effective renal plasma flow. Our results from measurements taken 5–10 minutes after the start of intravenous adenosine infusion showed no significant reduction in total renal blood flow. As discussed above, we are unable to be certain that a significant dose of adenosine was reaching the kidney: It is possible that most of the adenosine had been metabolized before reaching the renal circulation. However, whether the absence of sustained renal vasoconstriction is secondary to a very low dose of adenosine reaching the kidney or to rapid restoration of renal perfusion after only transient reduction, it seems clear that intravenous adenosine infusions up to 100 μg/kg/min fail to decrease total renal perfusion in patients with end-stage heart failure on conventional therapy.

Nitroprusside. The results of previous studies of the effect of intravenous infusions of sodium nitroprusside on renal blood flow in patients with heart failure are also subject to the methodological limitations discussed above. However, sodium nitroprusside is not known to have a differential vasodilator effect on renal arterioles in the deep cortex and medulla in the same way as adenosine,[40] and major changes in paraamino hippurate extraction fraction are therefore less likely. Our results are similar to those of Leier and coworkers,[43] who found a marked decrease in mean renal perfusion pressure but no overall change in renal blood flow in response to nitroprusside infusion, such that calculated renal vascular resistance fell considerably. In our study, there was a modest increase in renal blood flow, which just reached significance ($p<0.05$).

Summary

As the principle hemodynamic goals of therapy in biventricular heart failure are to shift the ventricular function curves upward and to the left, increasing cardiac output and decreasing cardiac filling pressures, adenosine appears to be a much less attractive therapeutic agent in these patients than its capacity for selective pulmonary vasodilatation would suggest. It is, however, a potent pulmonary vasodilator and achieves this without compromising mean arterial blood pressure. It is very fast acting and rapidly cleared, was well tolerated by all patients, and did not produce renal vasoconstriction or the adverse side effects that we anticipated might have been limitations to its use. It would therefore appear that infusion of adenosine is superior to sodium nitroprusside as a test for the reversibility of pulmonary vasoconstriction in patients undergoing hemodynamic assessment for orthotopic heart transplantation, but it is unlikely to be of value as a therapeutic strategy in patients with biventricular heart failure.

Acknowledgments

References

1. Grossman W, Braunwald E: Pulmonary hypertension, in Braunwald E (ed): *Heart Disease.* Philadelphia, WB Saunders Co, 1988, p 799
2. Griepp R, Stinson E, Dong E, Clark D, Shumway N: Determinants of operative risk in human heart transplantation. *Am J Surg* 1971; 122:192–197
3. Kirklin J, Naftel D, McGiffin D, McVay R, Blackstone E, Karp R: Analysis of morbid events and risk factors for death after cardiac transplantation. *J Am Coll Cardiol* 1988;11:917–924
4. Erickson K, Costanzo-Nordin M, O'Sulivan J, Johnson MR, Zucker MJ, Pifarre R, Lawless CE, Robinson JA, Scanlon PJ: Influence of preoperative transpulmonary gradient on late mortality after orthotopic heart transplantation. *J Heart Transplant* 1990; 9:526–537
5. Addonizio L, Gersony W, Robbins R, Drusin RE, Smith CR, Reison DS, Reemtsma K, Rose EA: Elevated pulmonary vascular resistance and cardiac transplantation. *Circulation* 1987;76(suppl V):V-52–V-55
6. Costard A, Hill I, Schroeder J, Fowler M: Response to nitroprusside: Predictor of early transplant mortality. (abstract) *J Am Coll Cardiol* 1989;13:62A
7. McFadden E, Braunwald E: Cor pulmonale, in Braunwald E (ed): *Heart Disease.* Philadelphia, WB Saunders Co, 1988, p 1598
8. Romeo F, Pelliccia F, Cianfrocca C, Gallo P, Barilla F, Cristofani R, Reale A: Determinants of end-stage idiopathic dilated cardiomyopathy: A multivariate analysis of 104 patients. *Clin Cardiol* 1989;12:387–392
9. Komajda M, Jais JP, Reeves F, Goldfarb B, Bouhour JB, Juillieres Y, Lanfranchi J, Peycelon P, Geslin P, Carrie D, Grosgogeat Y: Factors predicting mortality in idiopathic dilated cardiomyopathy. *Eur Heart J* 1990;11:824–831
10. Brooks H, Kirk E, Vokonas P, Urschel C, Sonnenblick E: Performance of the right ventricle under stress: Relation to right coronary flow. *J Clin Invest* 1971;50:2176–2183
11. Franciosa J, Baker B, Seth L: Pulmonary versus systemic hemodynamics in determining exercise capacity of patients with chronic left ventricular failure. *Am Heart J* 1985;110:807–813
12. Polak J, Holman L, Wynne J, Colucci W: Right ventricular ejection fraction: An indicator of increased mortality in patients with congestive heart failure associated with coronary artery disease. *J Am Coll Cardiol* 1983;2:217–224
13. Bolling S, Deeb G, Crowley D, Badellino M, Bove E: Prolonged amrinone therapy prior to orthotopic cardiac transplantation in patients with pulmonary hypertension. *Transplant Proc* 1988;20: 757–766
14. Gheorghiade M, Sueta C, Adams K, Bourge RC, Murali S, Uretsky BF, Pritzker MR, McGoon MD, Starling RC, Butman SM, Grossman S: Multicenter randomized trial of Epoprostenol in patients with severe heart failure. *J Am Coll Cardiol* (in press)
15. Bush A, Busst CM, Clarke B, Barnes PJ: Effect of infused adenosine on cardiac output and systemic resistance in normal subjects. *Br J Clin Pharmacol* 1989;27:165–171
16. Edlund A, Sollevi A, Linde B: Hemodynamic and metabolic effects of infused adenosine in man. *Clin Sci* 1990;79:131–138
17. Reid PG, Fraser A, Watt A, Henderson A, Routlege P: Acute hemodynamic effects of intravenous infusion of adenosine in conscious man. *Eur Heart J* 1990;11:1018–1028
18. Morgan J, McCormack D, Griffiths M, Morgan C, Barnes P, Evans T: Adenosine as a vasodilator in primary pulmonary hypertension. *Circulation* 1991;84:1145–1149
19. Drury A, Szent-Györgyi A: The physiological activity of adenine compounds with special reference to their action upon the mammalian heart. *J Physiol* (Lond) 1929;68:213–237
20. Thurau K: Renal hemodynamics. *Am J Med* 1964;36:689–719
21. Hall J, Granger J, Hester R: Interactions between adenosine and angiotensin II in controlling glomerular filtration. *Am J Physiol* 1985;248:F340–F346
22. Osswald H, Spielman W, Knox F: Mechanism of adenosine-mediated decreases in glomerular filtration rate in dogs. *Circ Res* 1978;43:465–469
23. Tagawa H, Vander A: Effects of adenosine compounds on renal function and renin secretion in dogs. *Circ Res* 1970;26:327–338
24. Osswald H, Sacher R, Lesser K: Conversion of adenosine into a pure renal vasoconstrictor by frusemide. Athens, *Int Soc Nephrology* 1981;20:HE-038
25. Ther L, Mushawek R, Hergott J: Antagonismus zwischen adenosin und methyl-xanthinen am reizleitungssystem des herzens. *Arch Exp Pathol Pharmacol* 1957;231:586–590
26. Osswald H: Renal effects of adenosine and their inhibition by theophylline. *Naunyn Schmiedebergs Arch Pharmacol* 1975;288: 79–86
27. Haywood G, Stewart J, Counihan P, Sneddon JF, Tighe D, Bennett ED, McKenna WJ: Validation of bedside measurements of

absolute human renal blood flow by a continuous thermodilution technique. *Crit Care Med* 1992;20:659–644

28. Conradson TB, Clarke B, Dixon CM, Dalton RN, Barnes PJ: Effects of adenosine on autonomic control of heart rate in man. *Acta Physiol Scand* 1987;131:525–531

29. McCormack D, Clarke B, Barnes P: Characterisation of adenosine receptors in human pulmonary arteries. *Am J Physiol* 1989;25: H41–H46

30. Milnor W: Pulmonary circulation, in *Cardiovascular Physiology.* Oxford, Oxford University Press, 1990, pp 357–382

31. Murali S, Uretsky B, Reddy P, Tokarczyk T, Betschart A: Reversibility of pulmonary hypertension in congestive heart failure patients evaluated for cardiac transplantation: Comparative effects of various pharmacologic agents. *Am Heart J* 1991;122:1375–1381

32. Catravas J: Removal of adenosine from the rabbit pulmonary circulation in vivo and in vitro. *Circ Res* 1984;54:603–611

33. Fuller R, Maxwell D, Conradson T, Dixon C, Barnes P: Circulatory and respiratory effects of infused adenosine in conscious man. *Br J Clin Pharmacol* 1987;24:309–317

34. Williams M: Adenosine receptors as drug targets: Fulfilling the promise? *J R Coll Physicians Lond,* IBC Technical Services Ltd, 1989

35. Conradson TB, Dixon CM, Clarke B, Barnes PJ: Cardiovascular effects of infused adenosine in man: Potentiation by dipyridamole. *Acta Physiol Scand* 1987;129:387–391

36. Burnstock G: Vascular control by purines with emphasis on the coronary system. *Eur Heart J* 1989;10:F15–F21

37. Collis M: Purines and the heart. *J R Coll Physicians Lond,* IBC Technical Services Ltd, 1989

38. Stein J: Regulation of the renal circulation. *Kidney Int* 1990;38: 571–576

39. Zall S, Eden E, Winso I, Volkmann R, Sollevi A, Ricksten SE: Controlled hypotension with adenosine or sodium nitroprusside during cerebral aneurysm surgery: Effects on renal hemodynamics, excretory function, and renin release. *Anesth Analg* 1990;71: 631–636

40. Spielman W, Britton S, Fiksen-Olsen M: Effect of adenosine on the distribution of renal blood flow in dogs. *Circ Res* 1980;46: 449–456

41. Velasquez M, Notargiacomo A, Cohn J: Influence of cortical plasma transit time on *p*-aminohippurate extraction during induced renal vasodilatation in anesthetized dogs. *Clin Sci* 1972; 43:401–411

42. Reubi F: *Clearance Tests in Clinical Medicine.* Springfield, Ill, Charles C Thomas, 1963, p 23

43. Leier C, Bambach D, Thompson M, Cattaneo S, Goldberg R, Unverferth D: Central and regional hemodynamic effects of intravenous isosorbide dinitrate, nitroglycerin and nitroprusside in patients with congestive heart failure. *Am J Cardiol* 1981;48: 1115–1123