

## ORIGINAL ARTICLE

# Nitroprusside in Critically Ill Patients with Left Ventricular Dysfunction and Aortic Stenosis

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## ABSTRACT

**BACKGROUND**

Vasodilators are considered to be contraindicated in patients with severe aortic stenosis because of concern that they may precipitate life-threatening hypotension. However, vasodilators such as nitroprusside may improve myocardial performance if peripheral vasoconstriction is contributing to afterload.

**METHODS**

We determined the response to intravenous nitroprusside in 25 patients with severe aortic stenosis and left ventricular systolic dysfunction. Patients were included in the study if they had been admitted to the intensive care unit for invasive hemodynamic monitoring of heart failure and if they had a depressed ejection fraction ( $\leq 0.35$ ), severe aortic stenosis (aortic-valve area,  $\leq 1$  cm<sup>2</sup>), and a depressed cardiac index ( $\leq 2.2$  liters per minute per square meter). Patients were excluded if they had hypotension, defined as either the need for intravenous inotropic or pressor agents or a low mean systemic arterial pressure ( $< 60$  mm Hg). Patients were enrolled irrespective of other, coexisting valve disease or coronary artery disease.

**RESULTS**

At base line, the mean ( $\pm$ SD) ejection fraction was  $0.21 \pm 0.08$ ; the aortic-valve area was  $0.6 \pm 0.2$  cm<sup>2</sup>, with peak and mean gradients of  $65 \pm 37$  and  $39 \pm 23$  mm Hg, respectively; and the cardiac index was  $1.60 \pm 0.35$  liters per minute per square meter. After six hours of therapy with nitroprusside (at which time the dose had been increased to a mean of  $103 \pm 67$   $\mu$ g per minute), the cardiac index had increased to  $2.22 \pm 0.44$  liters per minute per square meter ( $P < 0.001$  for the comparison with base line). After 24 hours of nitroprusside infusion (dose,  $128 \pm 96$   $\mu$ g per minute), the cardiac index had increased further, to  $2.52 \pm 0.55$  liters per minute per square meter ( $P < 0.001$  for the comparison with base line). Nitroprusside was well tolerated and had minimal side effects.

**CONCLUSIONS**

Nitroprusside rapidly and markedly improves cardiac function in patients with decompensated heart failure due to severe left ventricular systolic dysfunction and severe aortic stenosis. It provides a safe and effective bridge to aortic-valve replacement or oral vasodilator therapy in these critically ill patients.

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**A**ORTIC STENOSIS IS ONE OF THE MOST common types of valvular heart disease worldwide. Concomitant left ventricular dysfunction is often present, typically a result of the aortic stenosis itself or of coexisting coronary artery disease. Congestive heart failure and left ventricular dysfunction in the setting of severe aortic stenosis are associated with a high mortality rate. Although Ross and Braunwald noted a median survival of 1.5 to 2.0 years in patients with severe aortic stenosis and symptomatic congestive heart failure,<sup>1</sup> more recent studies have indicated that patients with severe aortic stenosis and abnormal left ventricular function on echocardiography survive a mean of only 1 year.<sup>2</sup> In fact, abnormal left ventricular systolic function has been shown to be one of the most powerful predictors of death in patients with severe aortic stenosis.<sup>3</sup> Nevertheless, even in this population, surgical replacement of the aortic valve can lead to dramatic improvements in cardiac function and survival.<sup>4,5</sup>

Although the surgical mortality rate in patients with severe aortic stenosis and left ventricular dysfunction is generally considered acceptable, difficulties arise in the treatment of patients who present with severe decompensated heart failure. Proceeding directly to surgery is associated with a perioperative mortality rate as high as 30 to 50 percent in these patients, who are in unstable condition and who often have multiple coexisting diseases.<sup>6</sup> Balloon valvuloplasty has been recommended in this situation as a bridge to surgery or as palliative therapy in those deemed not to be candidates for surgery.<sup>7</sup> However, it is associated with a high rate of procedural complications and poor long-term results.<sup>8,9</sup> Furthermore, few physicians are adequately trained in this procedure; its use is therefore limited to major medical centers. For these reasons, an effective medical therapy to improve cardiac function in these critically ill patients is needed.

Although vasodilator therapy has been increasingly used in the management of left ventricular dysfunction,<sup>10-12</sup> conventional teaching dictates that its use in patients with severe aortic stenosis is contraindicated.<sup>13-18</sup> Surprisingly, despite the widespread prevalence of this belief within the medical community, there are few data to support it. In fact, small studies have documented beneficial hemodynamic effects of vasodilatation in asymptomatic patients with severe aortic stenosis and normal or slightly depressed left ventricular function.<sup>19,20</sup> However, the effect of vasodilatation in symptomatic

patients with more severe ventricular dysfunction is unknown, since they have been excluded from these studies. We performed the Use of Nitroprusside in Left Ventricular Dysfunction and Obstructive Aortic Valve Disease (UNLOAD) Study to investigate the use of nitroprusside, a potent intravenous vasodilator, in critically ill patients with congestive heart failure and severe aortic stenosis.

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## METHODS

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### STUDY DESIGN

This prospective study was conducted in a cardiac intensive care unit at the Cleveland Clinic Foundation. We enrolled patients who met the following criteria for inclusion: admission to an intensive care unit for invasive hemodynamic monitoring of heart failure; depressed left ventricular function (ejection fraction,  $\leq 0.35$ ); severe aortic stenosis (aortic-valve area,  $\leq 1$  cm<sup>2</sup> on echocardiography<sup>21</sup>); and a depressed cardiac index ( $\leq 2.2$  liters per minute per square meter), determined by the Fick method. The only criterion for exclusion was hypotension, defined as either the need for intravenous inotropic or pressor agents (dobutamine, dopamine, epinephrine, milrinone, norepinephrine, or phenylephrine) or a mean systemic arterial pressure below 60 mm Hg. Our institutional review board approved the study, and all the patients provided written informed consent to participate.

### PROTOCOL

All the patients underwent continuous electrocardiographic and invasive hemodynamic monitoring involving the use of a pulmonary-artery catheter and arterial catheter. Heart rate, blood pressure, electrocardiographic findings, and cardiac hemodynamic variables were recorded at base line, before the initiation of nitroprusside administration. Patients then received intravenous nitroprusside in a dose titrated to produce a mean arterial pressure between 60 and 70 mm Hg; the exact dose was determined for each patient by his or her treating cardiologist. After approximately 6 and 24 hours of nitroprusside infusion, heart rate, blood pressure, and cardiac hemodynamic variables were recorded. Electrocardiography was repeated at 24 hours. The primary end point of the study was the change from base line in the cardiac index (as determined by the Fick method) during nitroprusside administration.

All echocardiographic data were obtained by an experienced sonographer and interpreted by an ex-

perienced staff echocardiographer who was blinded to the patients' participation in the study. The area of the aortic valve was calculated with the use of transthoracic echocardiography and the continuity equation<sup>22,23</sup> or with the use of transesophageal echocardiography by means of planimetry.<sup>24,25</sup> In a subgroup of patients, gradients across the aortic valve were measured both before the start of nitroprusside administration and again during its administration. These gradients were correlated with simultaneous measurements of cardiac output from a pulmonary-artery catheter. We also calculated the dimensionless index, which is the ratio of the velocity–time integral measured in the left ventricular outflow tract to the velocity–time integral measured in the aortic valve. A value of 0.25 or less is consistent with severe aortic stenosis (aortic valve area,  $\leq 0.75$  cm<sup>2</sup>) as measured by cardiac catheteriza-

tion.<sup>26</sup> In patients who underwent aortic-valve replacement, intraoperative transesophageal echocardiography was conducted. Cardiothoracic surgeons, who were also blinded to the patients' participation in the study, recorded findings at the time of surgery.

#### ADVERSE EVENTS AND SUBSEQUENT OUTCOMES

Any adverse events occurring during the administration of nitroprusside, such as hypotension (systolic arterial pressure,  $<60$  mm Hg), angina, evidence of ischemia on electrocardiography, acute renal failure, dyspnea, or arrhythmias, were recorded. The ultimate therapy (medical or surgical) and the ultimate outcome were noted.

#### STATISTICAL ANALYSIS

Continuous variables are expressed as means  $\pm$  SD and categorical variables as percentages. Wilcoxon's signed-rank test was used to analyze paired differences, and Wilcoxon's rank-sum test was used to analyze differences between subgroups. All statistical tests were performed with two-sided alternatives and a type I error of 0.05 and with the use of SAS software (version 8.2).

## RESULTS

#### CHARACTERISTICS OF THE PATIENTS

From August 1, 2000, to May 15, 2002, 29 consecutive patients met the inclusion criteria. Four of these patients had hypotension and therefore did not receive nitroprusside and were excluded from the study: three had a mean systemic arterial pressure below 60 mm Hg, and one required intravenous inotropic or pressor agents. The base-line characteristics of the remaining 25 patients are given in Table 1. One patient underwent aortic-valve replacement before the 24-hour time point and was included in all the analyses except the 24-hour subgroup analyses.

#### RESPONSE TO NITROPRUSSIDE

Nitroprusside was started at a mean dose of  $14 \pm 10$   $\mu$ g per minute, and the dose was increased to a mean of  $103 \pm 67$   $\mu$ g per minute at 6 hours and  $128 \pm 96$   $\mu$ g per minute at 24 hours. The effect of nitroprusside on the primary end point, the cardiac index, is shown in Figure 1. Six hours after base line, the cardiac index had increased to  $2.22 \pm 0.44$  liters per minute per square meter ( $P < 0.001$ ). After 24 hours, the cardiac index had increased further, to  $2.52 \pm 0.55$  liters per minute per square meter ( $P < 0.001$  for the

**Table 1. Base-Line Characteristics of the 25 Patients.\***

Characteristic	Value
Age — yr	73 $\pm$ 15
Male sex — no. (%)	16 (64)
Myocardial infarction $>7$ days earlier — no. (%)	17 (68)
History of coronary-artery bypass grafting — no. (%)	9 (36)
Recent unstable angina or myocardial infarction — no. (%) <sup>†</sup>	10 (40)
Unstable angina	2 (8)
Myocardial infarction without ST-segment elevation	6 (24)
Myocardial infarction with ST-segment elevation	2 (8)
Serum creatinine $>2.0$ mg/dl ( $>177$ $\mu$ mol/liter) — no. (%)	8 (32)
Ejection fraction	0.21 $\pm$ 0.08
Aortic-valve area — cm <sup>2</sup>	0.6 $\pm$ 0.2
Dimensionless index	0.19 $\pm$ 0.08
Dimensionless index $\leq 0.25$ — no. (%)	21 (88) <sup>‡</sup>
Aortic-valve pressure gradient — mm Hg	
Mean	39 $\pm$ 23
Peak	65 $\pm$ 37
Mitral regurgitation $\geq 3+$ — no. (%) <sup>§</sup>	5 (20)
Aortic regurgitation $\geq 3+$ — no. (%) <sup>§</sup>	3 (12)
Cardiac index — liters/min/m <sup>2</sup>	1.60 $\pm$ 0.35

\* Plus-minus values are means  $\pm$  SD.

<sup>†</sup> Occurrence within the previous seven days was considered recent.

<sup>‡</sup> In 1 of the 25 patients, only a transesophageal study was performed; gradients could not be determined, and the dimensionless index could not be calculated.

<sup>§</sup> Regurgitation was scored by color Doppler and semiquantitative methods, with a score of 0 denoting no regurgitation, 1+ mild regurgitation, 2+ moderate regurgitation, 3+ moderately severe regurgitation, and 4+ severe regurgitation.

comparison with base line). The effect of nitroprusside at 6 and 24 hours on the heart rate, mean arterial pressure, pulmonary-capillary wedge pressure, systemic vascular resistance, and stroke volume is also shown in Figure 1.

At 24 hours, the pulmonary vascular resistance had declined significantly (from  $370 \pm 177$  to  $199 \pm 102$  dyn·sec·cm<sup>-5</sup> [P<0.001 for the comparison with base line]), as had the pulmonary-artery systolic pressure (from  $59 \pm 14$  to  $52 \pm 11$  mm Hg

[P<0.001 for the comparison with base line]). At 24 hours, the increase in cardiac index in the 4 patients without coronary artery disease (from  $1.86 \pm 0.33$  liters per minute per square meter at base line to  $3.03 \pm 0.59$  liters per minute per square meter) was similar to that in the 20 patients with coronary artery disease (from  $1.54 \pm 0.34$  liters per minute per square meter at base line to  $2.42 \pm 0.49$  liters per minute per square meter; P=0.30 for the comparison between the two subgroups). Likewise, the in-

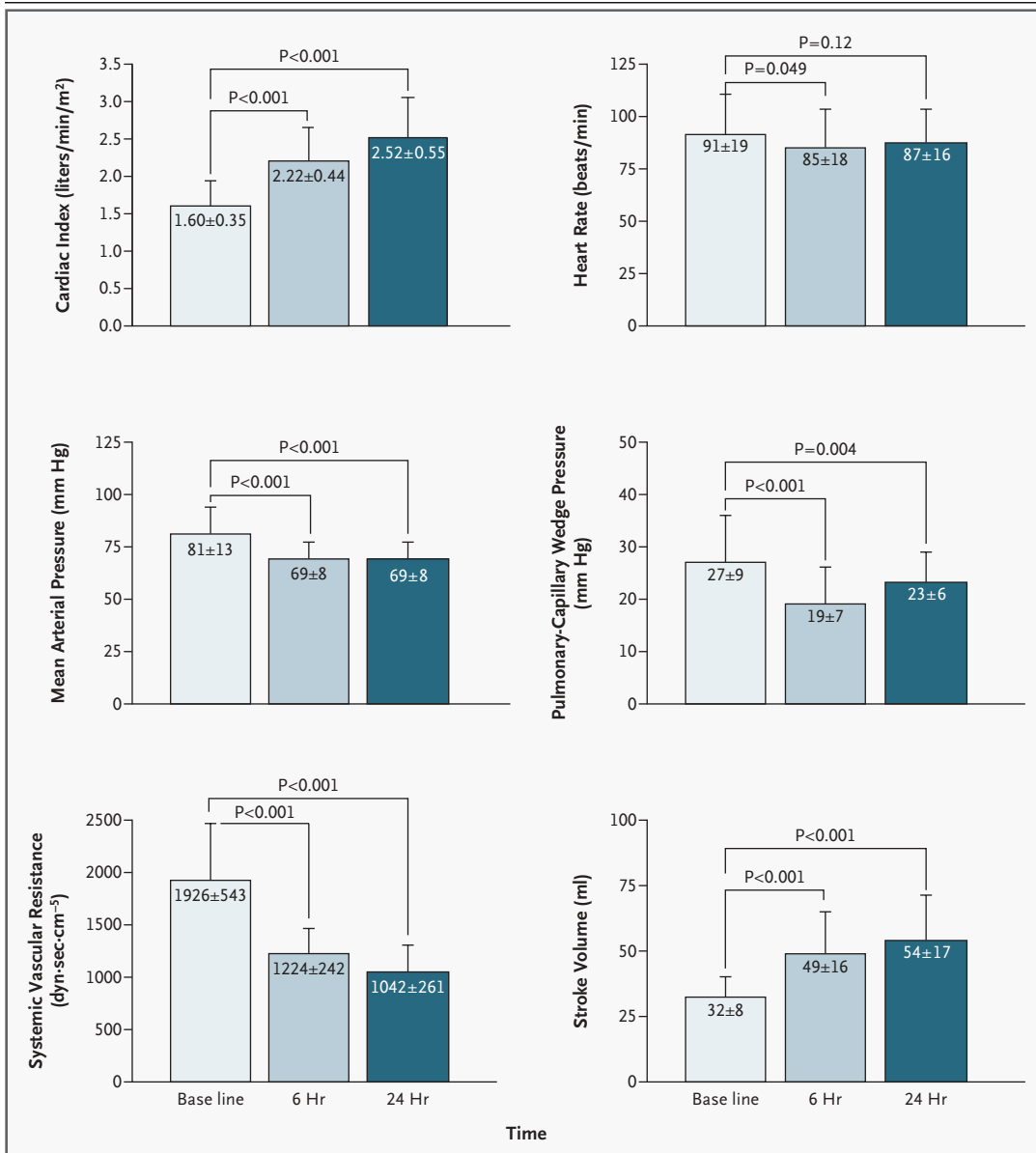
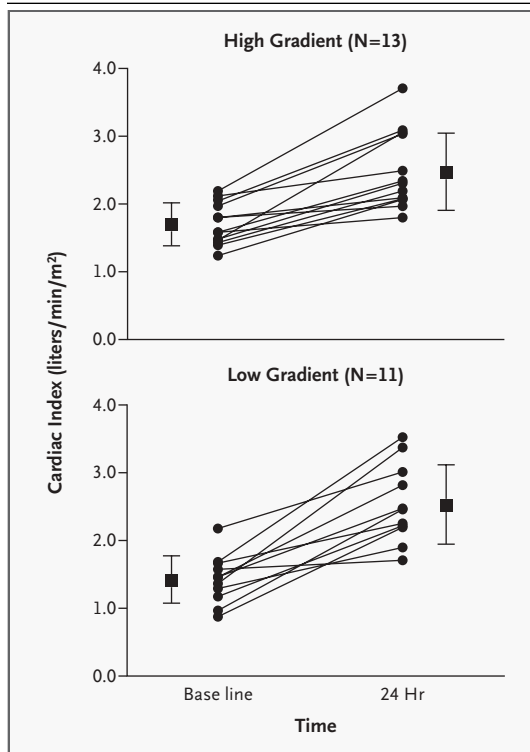


Figure 1. Mean (±SD) Hemodynamic Values at Base Line and 6 and 24 Hours after the Start of Nitroprusside Infusion.



**Figure 2.** Change in the Cardiac Index 24 Hours after the Start of the Nitroprusside Infusion in Subgroups of Patients, According to the Mean Aortic-Valve Pressure Gradient at Base Line.

No significant difference was observed between those with low-gradient stenosis and those with high-gradient stenosis in the response to nitroprusside ( $P=0.20$ ). A low gradient in pressure across the aortic valve was defined as less than or equal to 30 mm Hg, and a high gradient as greater than 30 mm Hg. The squares and error bars represent means  $\pm$ SD.

crease from base line in the cardiac index at 24 hours was similar in the 19 patients without mitral regurgitation (from  $1.65\pm 0.37$  to  $2.60\pm 0.59$  liters per minute per square meter) and the 5 with clinically significant mitral regurgitation (a score of  $\geq 3+$  on a scale from 0 to 4+) (from  $1.39\pm 0.16$  to  $2.20\pm 0.12$  liters per minute per square meter;  $P=0.62$  for the comparison between the two subgroups). The improvement in the cardiac index occurred both in patients with low-gradient aortic stenosis (mean aortic-valve pressure gradient,  $\leq 30$  mm Hg)<sup>27</sup> and in those with high-gradient aortic stenosis (mean gradient,  $>30$  mm Hg) (Fig. 2). In none of the patients did the cardiac index decrease during nitroprusside administration (Fig. 2).

The results of echocardiography before and after the start of nitroprusside administration in a subgroup of six patients are shown in Figure 3. Nitroprusside increased the mean and peak gradients across the valve, with no change in aortic-valve area.

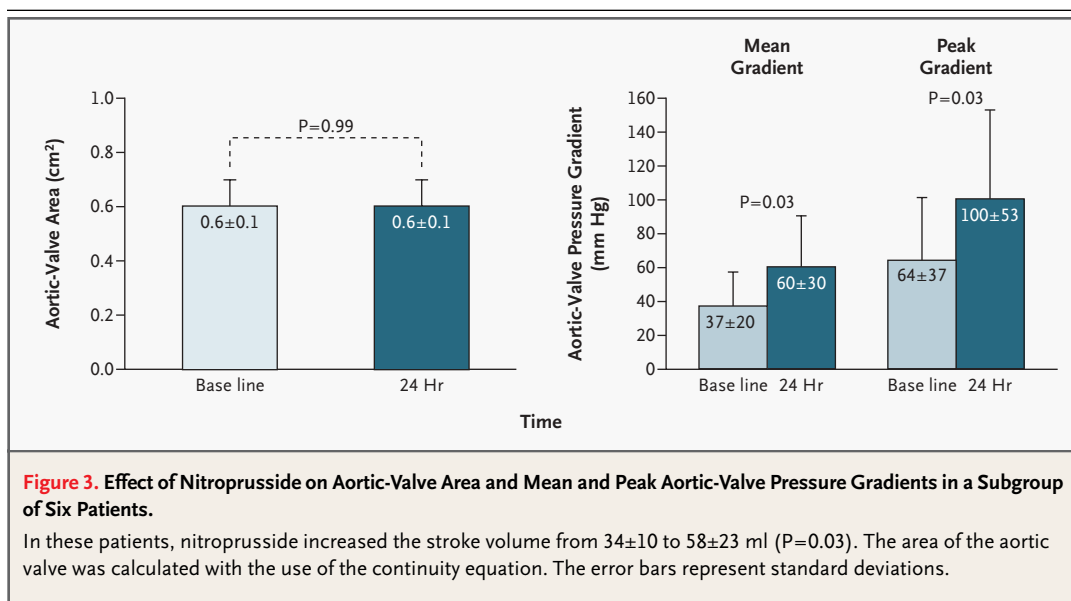
#### RESULTS OF SURGERY AND VALVULOPLASTY

Fourteen patients underwent open-heart surgery. The presence of severe aortic stenosis was confirmed by intraoperative transesophageal echocardiography and by surgical inspection in all 14 patients. Another patient, who was found to have peak and mean aortic-valve pressure gradients of 73 and 55 mm Hg, respectively, with an aortic-valve area of  $0.4\text{ cm}^2$  at the time of cardiac catheterization, underwent balloon valvuloplasty because of severe emphysema.

#### ADVERSE EVENTS AND SUBSEQUENT OUTCOMES

Nitroprusside was well tolerated. The base-line serum creatinine level,  $1.8\pm 0.9$  mg per deciliter ( $159\pm 80\ \mu\text{mol}$  per liter), decreased to  $1.6\pm 0.9$  mg per deciliter ( $141\pm 80\ \mu\text{mol}$  per liter) after 24 hours ( $P=0.04$ ). There was one episode of chest pain during the 24-hour infusion period; it occurred in a patient who had diffuse three-vessel coronary disease and had previously undergone coronary-artery bypass grafting; the pain was managed with nitroglycerin and beta-blockers. In one patient, acute renal failure developed as a result of intravenous-contrast nephropathy. There were no episodes of dyspnea, ischemic electrocardiographic changes, arrhythmias, or hypotension.

All the patients continued to receive nitroprusside until surgery, conversion to maintenance medical therapy, or death. There were five in-hospital deaths. In two of the patients who died, supportive care was withdrawn in the hospital; in one, multi-organ failure had developed, and the other had had refractory unstable angina that was not amenable to revascularization. A third patient died of a pulmonary embolus on the fifth hospital day, while awaiting a decision regarding candidacy for surgery. A fourth patient presented with acute renal failure (serum creatinine level, 3.8 mg per deciliter [ $336\ \mu\text{mol}$  per liter]), which progressed despite an improvement in cardiac function with nitroprusside administration; therapy was switched to comfort measures, according to his family's wishes, and he later died of septic shock. Ultimate therapy in the other 21 patients (including the 5th patient who died, perioperatively) consisted of aortic-valve replace-



ment in 13, coronary-artery bypass grafting without aortic-valve replacement in 1 (who did not receive a prosthetic valve because of the small size of her aortic annulus), balloon valvuloplasty in 1, and medical therapy in the remaining 6. Medical therapy consisted of conventional oral therapy for heart failure (angiotensin-converting-enzyme inhibitors, isosorbide dinitrate combined with hydralazine, beta-blockers, or a combination of these drugs) in five patients and palliative intravenous dobutamine in one patient. An additional patient died after discharge from the hospital. At 30 days, the overall rate of survival was 76 percent.

#### DISCUSSION

In critically ill patients with severe aortic stenosis and severe left ventricular systolic dysfunction, nitroprusside leads to rapid, marked, and consistent improvements in cardiac output. Our patients were exceedingly ill; nevertheless, after 24 hours of nitroprusside infusion, the cardiac index had become normal. In fact, all the patients who met the simple inclusion criteria benefited from nitroprusside administration.

An important concern regarding our study is whether our patients truly had severe aortic stenosis or whether they had “pseudostenosis” resulting from low cardiac output — a condition that would be expected to improve with nitroprusside.<sup>17</sup> We believe that they did, in fact, have severe aortic ste-

nosis, for a number of reasons. Many of the patients had substantially elevated gradients in pressure across the aortic valve, even in the face of low cardiac output, indicating that they had severe stenosis. Calculation of the dimensionless index allowed us to determine the severity of aortic stenosis independently of cardiac function. All but three patients had a dimensionless-index value of 0.25 or less, a level consistent with the presence of severe aortic stenosis.<sup>26</sup> In addition, echocardiography before and after nitroprusside administration showed significant increases in the mean and peak gradients, without a significant change in aortic-valve area, again indicating the presence of true aortic stenosis. Finally, intraoperative transesophageal echocardiography and surgical findings confirmed the presence of severe aortic stenosis in all the patients who underwent open-heart surgery.

The use of vasodilators is traditionally considered to be contraindicated in patients with severe aortic stenosis because, it is believed, cardiac output is fixed across the narrowed valve — that is, only a small amount of blood can actually leave the heart because the valve is so stenotic.<sup>13-18</sup> In this scenario, vasodilatation would potentially be catastrophic because it would reduce systemic vascular resistance without any compensatory increase in cardiac output, and severe hypotension would ensue. This concept, however, is an oversimplification of the cardiac hemodynamics involved, especially in patients with left ventricular dysfunction. Resistance across the

aortic valve, though essentially fixed, is not the only factor that determines the effective afterload of the left ventricle. Since resistances in a series are additive, the total resistance seen by the left ventricle is the sum of the resistance across the aortic valve and the systemic vascular resistance. Therefore, increasing or decreasing systemic vascular resistance directly leads to proportional changes in the effective afterload of the left ventricle, even when there is severe aortic stenosis.<sup>19,28</sup> Since the failing heart is exquisitely sensitive to afterload,<sup>29</sup> a reduction in afterload with nitroprusside administration leads to proportional increases in cardiac output, preventing the development of hypotension.<sup>30</sup>

Increased afterload is not synonymous with systolic hypertension. In fact, nearly all our patients would have been considered normotensive, if not frankly hypotensive, if systolic blood pressure alone had been examined. However, systolic arterial pressure, in contrast to mean systemic arterial pressure, is a poor measure of afterload in patients such as these, since their reduced stroke volume leads to a narrowed pulse pressure.<sup>31</sup> To determine afterload, therefore, it is essential to obtain an accurate measurement of mean arterial pressure, a primary determinant of systemic vascular resistance. Depending on the cardiac output, elevated systemic vascular resistance can be evident even when the mean arterial pressure is as low as 60 mm Hg.

Alternative strategies in these critically ill patients include balloon valvuloplasty and intravenous inotropic therapy. Clearly, balloon valvuloplasty can improve the area of the aortic valve and reduce the transvalvular gradient, but the resulting improvement in cardiac output is limited, even in patients with cardiogenic shock.<sup>9,32</sup> This limited improvement, in addition to the high rate of complications and the need for highly specialized physicians and facilities, precludes the widespread use of this procedure. Dobutamine has been studied during stress echocardiography in patients with severe aortic stenosis and reduced ejection fraction and is considered safe in patients without coronary artery disease. However, in patients who do have coronary artery disease (such as the majority of the patients in our study), there is an increased rate of complications, including arrhythmias and provocation of myocardial ischemia.<sup>33</sup> Thus, we believe that dobutamine is relatively contraindicated in many of these patients. Other agents, such as milrinone, have not been used in this setting and also can be quite expensive (approximately \$400 per day).<sup>34</sup> In contrast,

nitroprusside is a safe, inexpensive (about \$4 per day),<sup>34</sup> and highly effective treatment, and the only hemodynamic monitoring equipment that it requires is widely available.

We believe that nitroprusside has two important clinical applications in this population of patients. In severely ill patients who are candidates for surgery, it can allow optimization of cardiac function before valve replacement. In patients who are not candidates for surgery or in those who choose not to undergo surgery, nitroprusside may serve as a bridge to an effective regimen of oral vasodilators—namely, angiotensin-converting-enzyme inhibitors or isosorbide dinitrate combined with hydralazine; these therapies have been convincingly shown to decrease morbidity and mortality in patients with congestive heart failure alone.<sup>11,35,36</sup>

Our results should not be considered applicable to patients with severe aortic stenosis who have normal left ventricular function. Since the normal ventricle is much less sensitive to afterload than the failing ventricle, the potential benefits of nitroprusside may be lessened and the risks may be increased. However, the validity of this concern is unclear because invasive hemodynamic studies have suggested that nitroprusside is well tolerated even in such patients.<sup>19,20</sup>

The results of our study are clinically relevant because it was a “real-life” study. The only exclusion criterion was hypotension, which precludes the administration of nitroprusside. There were no restrictions on the cause of the left ventricular dysfunction, on the nature of the coexisting valvular heart disease, or on any aspect of coronary artery disease, including myocardial infarction. Thus, we believe that our results can be safely applied to virtually all patients without hypotension who meet the criteria used for inclusion in the study.

Much attention has focused on the treatment of the stenotic valve in patients with severe aortic stenosis and congestive heart failure; however, our results indicate that ventricular dysfunction plays an important part in decompensation in these patients. We believe that our study provides evidence supporting a reexamination of conventional thinking about the use of vasodilators in patients with severe aortic stenosis and depressed ventricular function. Specifically, our results indicate that the administration of nitroprusside to patients with severe aortic stenosis and severe left ventricular systolic dysfunction dramatically improves cardiac output and has minimal side effects. Given this improvement in cardiac

function, these critically ill patients can eventually undergo aortic-valve replacement or receive effective oral vasodilator therapy.

Dr. Mills reports having received lecture fees from Scios.

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