Cardiovascular Effects of Inhaled Nitric Oxide in Patients With Left Ventricular Dysfunction

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Background Pulmonary vascular resistance (PVR) is frequently elevated in patients with advanced heart failure. Nitric oxide (NO), which contributes to the activity of endothelium-derived relaxing factor, causes relaxation of pulmonary arteries and veins in vitro. Inhalation of NO gas causes pulmonary vasodilation in patients with primary and secondary forms of pulmonary hypertension.

Methods and Results To test the hypothesis that inhalation of NO gas lowers PVR in patients with heart failure, we studied the hemodynamic effects of a 10-minute inhalation of NO (80 ppm) in 19 patients with New York Heart Association class III (n=5) and class IV (n=14) heart failure due to left ventricular (LV) dysfunction. Although inhalation of NO had no effect on pulmonary artery pressures, the PVR decreased by 31±7% ($P<.001$) due to a 23±7% increase ($P<.001$) in pulmonary artery wedge pressure and despite a 4±2% ($P<.05$) decrease in cardiac index. The magnitude of the decrease in PVR with inhaled NO was inversely related ($r=-.713$; $P<.001$) to the baseline PVR. Inhaled NO had no effect on heart rate, systemic arterial pressure, systemic vascular resistance, or LV peak +dP/dt or −dP/dt.

Conclusions In patients with heart failure due to LV dysfunction, inhalation of NO causes a decrease in the PVR associated with an increase in LV filling pressure. These findings predict that inhaled NO, if used alone at this dose (80 ppm), may have adverse effects in patients with LV failure. (***Circulation*.** 1994;90:2780-2785.)

Key words • nitric oxide • lung • heart failure • endothelium-derived factors

The endothelium plays an essential role in the dynamic regulation of vascular tone by synthesizing and releasing a variety of substances, one of which, endothelium-derived relaxing factor (EDRF), has the physicochemical properties of nitric oxide (NO) or a closely related substance.[1,2] Endogenous NO produced by endothelial cells diffuses into neighboring vascular smooth muscle cells, where it binds to the heme component of guanylyl cyclase, thereby activating the enzyme, resulting in increased cyclic GMP production and relaxation.[3,4] Arterial and venous endothelial cells in the pulmonary vasculature produce NO constitutively and in response to a variety of stimuli.[5-8] NO appears to be involved both in the regulation of basal pulmonary vascular resistance (PVR)[9,10] and in counterregulating the effects of vasoconstrictor substances.[11-15]

PVR is frequently increased in patients with advanced heart failure. The underlying mechanism for increased PVR in heart failure is not known, but it almost certainly involves activation of vasoconstrictor pathways by the sympathetic nervous system, the renin-angiotensin system, and/or endothelin.[16,17] Although there is evidence that endothelium-dependent vasodilation is impaired in the systemic vasculature of both animal models[18] and patients with heart failure,[19-22] it is not known whether this mechanism contributes to increased PVR.

Inhalation of NO gas causes pulmonary vasodilation in patients with primary pulmonary hypertension[23] and pulmonary hypertension secondary to congenital heart disease[24] and to adult respiratory distress syndrome.[25] These observations suggest that inhaled NO might ameliorate pulmonary vasoconstriction, and they led to our hypothesis that inhalation of NO would lower PVR in patients with heart failure. To test this hypothesis, we studied the hemodynamic effects of a 10-minute inhalation of NO (80 ppm) in 19 patients with moderate to severe heart failure secondary to LV dysfunction from idiopathic or ischemic dilated cardiomyopathy.

Methods

Study Population

Nineteen patients with New York Heart Association functional class III (n=5) or IV (n=14) heart failure were studied. All patients were receiving digitalis, diuretics, and angiotensin-converting enzyme inhibitors. There were 15 men and 4 women, with a mean age of 52±3 years. The cause of heart failure was ischemic cardiomyopathy in 10 patients and idiopathic dilated cardiomyopathy in 9. The peak VO$_2$ averaged 9.9±1.6 mL·kg^{-1}·min^{-1}. The study protocol was approved by the Committee for the Protection of Human Subjects from Research Risks at the Brigham and Women's Hospital, and written informed consent was obtained in all cases.

Hemodynamic Measurements

Vasodilators, converting enzyme inhibitors, digitalis, and diuretics were withheld on the morning of the catheterization. A 7F Swan-Ganz catheter (Arrow International, Inc) was placed in the pulmonary artery. Femoral artery pressure was monitored via an 8F side-arm sheath (Cordis Laboratories). In 10 patients, a 7F micromanometer-tipped pigtail catheter

TABLE 1. Hemodynamic Effects of Inhaled NO in Patients With Congestive Heart Failure (n=19)

	Room Air	NO	P
HR, bpm	90±3	93±3	NS
MAP, mm Hg	79±3	81±3	NS
SVR, dyne · s · cm^{-5}	1102±104	1041±97	NS
PA, mm Hg	35±4	37±4	NS
PAWP, mm Hg	25±3	31±4	<.001
LVEDP, mm Hg; n=10	28±4	34±5	.02
PVR, dyne · s · cm^{-5}	226±30	119±13	<.001
PA−PAWP, mm Hg	11±1	6±0.5	<.001
SVI, mL/m^2	26±2	24±2	.03
CI, L · min^{-1} · m^{-2}	2.3±0.2	2.1±0.2	.03

HR indicates heart rate; bpm, beats per minute; MAP, mean arterial pressure; SVR, systemic vascular resistance; PA, mean pulmonary artery measure; PAWP, pulmonary artery wedge pressure; LVEDP, left ventricular end-diastolic pressure; PVR, pulmonary vascular resistance; SVI, stroke volume index; and CI, cardiac index.

(Millar Industries) was placed in the left ventricle (LV), allowing for simultaneous dP/dt and right heart pressure measurements. The ECG, femoral artery pressure, pulmonary artery pressure, and LV pressure were recorded on a strip chart recorder (Electronics for Medicine, PPG Biomedical Systems Division). Cardiac output was determined by the Fick method, based on the measured oxygen uptake (model MRM 2B, Waters Instruments, Inc) and oxygen content in the pulmonary and femoral arteries.[26] Oxygen content was calculated from the blood hemoglobin and oxygen saturation by standard methods.[26] Blood oxygen saturation was determined in duplicate samples on a Ciba-Corning model 270 Co-oximeter. LV peak +dP/dt (+dP/dt) and peak −dP/dt (−dP/dt) were computed on-line by an Electronics for Medicine amplifier (model 220A). Values for heart rate, arterial pressure, pulmonary arterial pressure, pulmonary artery wedge pressure, LV systolic pressure, LV end-diastolic pressure
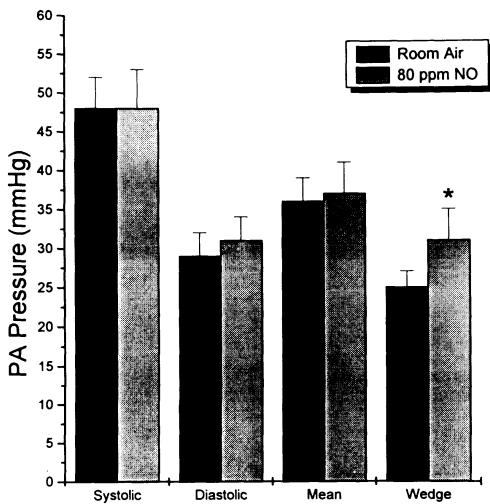

FIG 1. Bar graph showing effect of inhalation of NO gas (80 ppm, 10 minutes) on pulmonary artery (PA) pressures in 19 patients with heart failure secondary to left ventricular dysfunction. Measurements were made after the patients inhaled room air (shaded bars) or NO (solid bars) from a face mask for 10 minutes. *P<.001 vs room air.
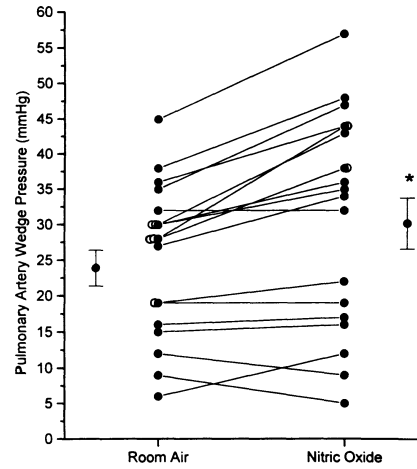

FIG 2. Graph showing pulmonary artery wedge pressure before and after a 10-minute inhalation of room air or NO. *P<.001 vs room air.

(LVEDP), and LV +dP/dt and −dP/dt were calculated by averaging at least 50 consecutive beats under each experimental condition.

Inhalation of Nitric Oxide

NO gas (800 ppm) and N$_2$ (Airco) were mixed by use of a standard low-flow blender (Low Flow MicroBlender, Bird Products Corp) before introduction into the inspiratory limb of a closed breathing circuit attached to a face mask. The inhaled concentrations of NO and oxygen were regulated separately. The inhaled O$_2$ concentration was measured directly with an on-line oximeter (Ohmeda Oximeter). The inhaled concentrations of NO, nitrogen dioxide (NO$_2$), and the higher oxides of nitrogen (NO$_x$) were measured continuously by a chemiluminescence technique (Chemiluminescent NO$_x$-NO$_2$ Analyzer, Thermo Environmental Instruments, Inc). The exhaled gases were scavenged by a vacuum system.

To establish baseline conditions, patients inhaled room air (FIO$_2$, 21%; N$_2$, 79%) via the closed face mask system for 10 minutes before the baseline hemodynamic measurements. Patients then inhaled NO at 80 ppm (FIO$_2$, 21%; N$_2$, 79%) via
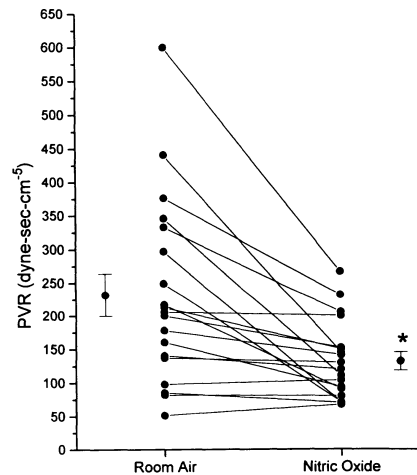

FIG 3. Graph showing effect of NO inhalation on pulmonary vascular resistance (PVR). *P<.001 vs room air.

face mask for 10 minutes, and hemodynamic measurements were repeated.

Statistical Methods

All data are presented as the mean±SEM. Differences between two observations for one variable within the same group were determined by two-tailed paired *t* test. Differences between groups were determined by two-tailed unpaired *t* test. Differences were considered significant if the null hypothesis could be rejected at the .05 probability level.

Results

Hemodynamic Effect of Inhaled NO

Baseline measurements during inhalation of room air revealed moderate LV failure with elevation of the LVEDP and mean pulmonary artery wedge pressure, and reduced stroke volume and cardiac indexes (Table 1). There was moderate reactive pulmonary hypertension, with an average PVR of 226±30 dyne · sec · cm^{-5}.

Inhalation of NO caused no change in heart rate, mean systemic arterial pressure, systemic vascular resistance, or pulmonary artery pressure (systolic, diastolic, or mean) but caused a 23±7% increase in the mean pulmonary artery wedge pressure (Table 1, Figs 1 and 2) associated with 4±2% and 7±2% decreases in cardiac index and stroke volume index, respectively (Table 1). The mean transpulmonary pressure gradient decreased by 35±7% (Table 1), and the PVR decreased by 31±7% (Table 1 and Fig 3).

The decrease in PVR was due to the increase in pulmonary artery wedge pressure, as shown by the correlation (*r*=−.848, *P*=.0001) between the changes in PVR and pulmonary artery wedge pressure (Fig 4A) and lack of correlation with changes in pulmonary artery pressure (Fig 4B; *r*=.13) or cardiac index (Fig 4C; *r*=.04). The increase in mean pulmonary artery wedge pressure was due to an increase in LV filling pressure, as shown by the correlation (*r*=.939, *P*<.0001) between the changes in LV end-diastolic pressure and pulmonary artery wedge pressure with inhaled NO (Fig 5).

TABLE 2. Hemodynamic Characteristics of Patients With a Change in Pulmonary Artery Wedge Pressure Above or Below the Median With Inhalation of NO

	% PAWP <0.26 (n=9)	% PAWP >0.26 (n=10)	*P*
HR, bpm	87±4	94±3	NS
MAP, mm Hg	75±3	84±3	.02
SVR, dyne · s · cm^{-5}	987±153	1218±148	NS
PA, mm Hg	29±5	42±5	.02
PAWP, mm Hg	21±4	28±4	.02
SVI, mL/m^2	30±2	21±2	.004
CI, L · min^{-1} · m^{-2}	2.6±0.2	1.9±0.2	.01
PVR, dyne · s · cm^{-5}	138±23	295±40	.002
LVEDD, cm	6.2±0.4	7.1±0.3	.04
V̇O$_2$	9.6±0.1	11.7±0.8	NS

LVEDD indicates left ventricular end-diastolic dimension; V̇O$_2$, peak oxygen consumption. Other abbreviations as in Table 1. n=19 for all parameters except EDD (n=16) and V̇O$_2$ (n=17).

Hemodynamic Determinants of an Increase in Pulmonary Artery Wedge Pressure With Inhaled NO

The most prominent hemodynamic effect of NO inhalation was the increase in pulmonary artery wedge pressure (median increase, 26%). In the 10 patients with an increase in pulmonary artery wedge pressure of ≥26% (mean increase, 33±7%), the baseline pulmonary artery pressure, pulmonary vascular resistance, and LV end-diastolic dimension (by M-mode echocardiography; n=16) were higher and the cardiac index and stroke volume index were lower than in the 9 patients with an increase of <26% (Table 2). Thus, more severe LV dysfunction (as evidenced by higher left heart filling pressures, lower stroke volume, and larger LV cavity size) was present in the patients who had the largest increases in pulmonary artery wedge pressure with inhaled NO.
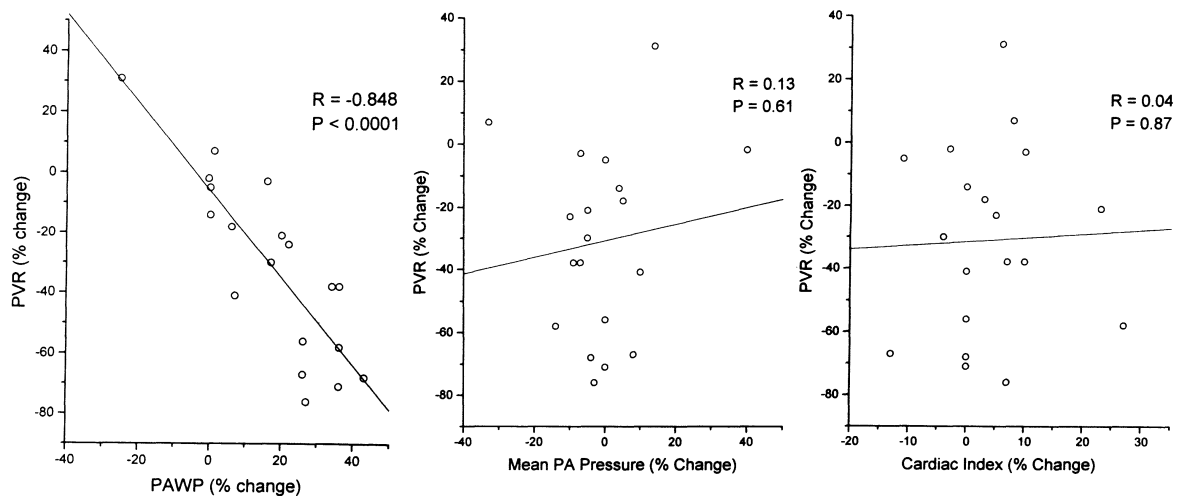

FIG 4. Scatterplots of regression analyses depicting the relation between the change in pulmonary vascular resistance (PVR) with NO (vs room air) and the change in pulmonary artery wedge pressure (PAWP) (left), mean PA pressure (middle), or cardiac index (right) in 19 patients.

The baseline PVR was more than twofold higher in the group that had the largest increases in pulmonary artery wedge pressure with inhaled NO (Table 2), suggesting that resting PVR might be a determinant or predictor of the response to inhaled NO. Consistent with this view, there was a strong correlation ($r=-.713$, $P<.001$) between the baseline PVR and the decrease in PVR with inhaled NO (Fig 6).

As an alternative approach to this issue, we identified a subgroup of 5 patients who had "compensated" LV failure, as defined by a pulmonary artery wedge pressure ≤ 18 mm Hg (mean, 12 ± 2 mm Hg) and a cardiac index ≥ 2.5 $L\cdot min^{-1}\cdot m^{-2}$ (mean, 2.8 ± 0.3 $L\cdot min^{-1}\cdot m^{-2}$). In these patients, inhalation of NO has no effect on pulmonary artery wedge pressure ($+7\pm3\%$) or PVR ($+5\pm13\%$). In the remaining 14 patients with "decompensated" LV failure (mean pulmonary artery wedge pressure, 30 ± 2 mm Hg; mean cardiac index, 1.9 ± 0.1 $L\cdot min^{-1}\cdot m^{-2}$), inhalation of NO increased the pulmonary artery wedge pressure by $27\pm3\%$ ($P<.001$) and decreased the PVR by $43\pm7\%$ ($P<.001$).

Effects of Inhaled NO on LV Function

Since it has been suggested that NO can depress the contractile function of isolated cardiac myocytes,[27] we considered the possibility that inhaled NO exerted a negative inotropic effect on the LV. A negative inotropic effect of inhaled NO was suggested by a decrease in stroke volume index despite an increase in pulmonary artery wedge pressure (Fig 7A). However, in the 10 patients in whom it was measured, inhaled NO had no effect on LV peak $+dP/dt$, despite increasing LVEDP by 8 ± 1 mm Hg (Fig 7B). LV peak $-dP/dt$, which reflects isovolumic relaxation in the absence of changes in loading conditions or heart rate,[28,29] was also not affected by inhaled NO (baseline, 807 ± 140 mm Hg/s; NO, 800 ± 139 mm Hg/s; $P=NS$; n=10).

Discussion

The major finding of this study is that in patients with reactive pulmonary arterial hypertension secondary to LV failure, inhalation of NO causes reciprocal changes in the PVR (decrease) and LV filling pressure (increase). In patients with primary pulmonary hypertension, inhalation of NO causes a decrease in pulmonary artery pressure.[23] In contrast, in patients with LV failure, we found that inhalation of NO is associated not with a decrease in pulmonary artery pressure, but rather, with an increase in LV filling pressure that accounts for the decrease in PVR. Preliminary reports from two other groups[30,31] also indicate a similar effect of inhaled NO on LV filling pressure in patients with LV failure.

The observed decrease in transpulmonary artery pressure gradient, particularly in the setting of no change or a small decrease in cardiac output, indicates that inhaled NO caused pulmonary vasodilation. NO diffuses readily through tissues, and therefore inhalation of NO may increase the concentration of NO in the vicinity of vascular smooth muscle cells in pulmonary resistance vessels, thereby exerting a direct vasodilator effect.

We believe that the NO-induced increase in LV filling pressure is due to a small increase in LV volume that
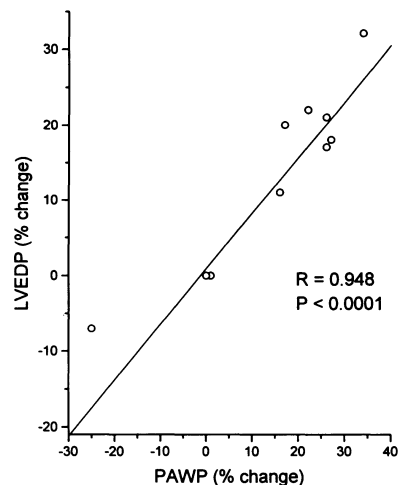

FIG 5. Scatterplot showing relation between the percent changes in pulmonary artery wedge pressure (PAWP) and left ventricular end-diastolic pressure (LVEDP) with inhaled NO in 10 patients.

occurred secondary to an increase in pulmonary venous return to the LV. For a given pulmonary artery pressure, a decrease in PVR will result in an increase in the net driving force for LV filling. Although an increase in LV volume would result in increases in ejection fraction and stroke volume in a normal LV, in our patients LV function was severely depressed and may have been on the flat portion of the Starling relation. In addition, an NO-induced increase in LV volume may have increased the magnitude of functional mitral regurgitation that is present in the majority of such hearts.[32,33] Thus, an NO-induced redistribution of blood from the right ventricle to the LV may occur with no increase, or even a small decrease, in stroke volume. Since the failing LV often operates on the steep portion of the diastolic pressure/volume relation, a substantial increase in LV filling pressure might reflect only a small NO-induced increase in LV volume.
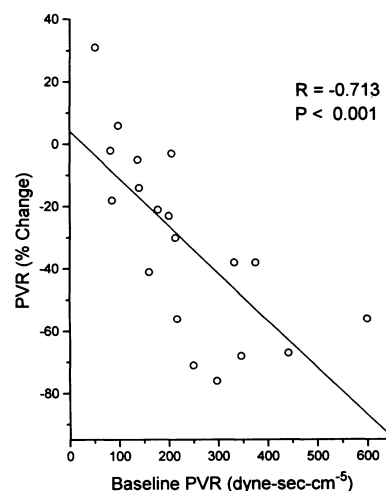

FIG 6. Scatterplot showing relation between the baseline pulmonary vascular resistance (PVR) and the percent change in PVR after inhalation of NO in 19 patients.
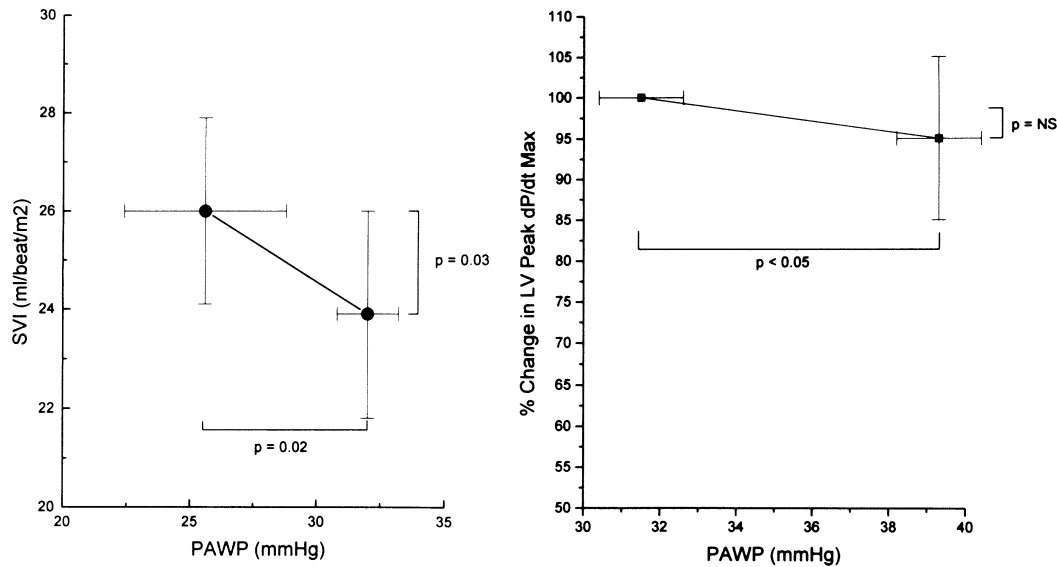
FIG 7.   Graphs showing (left) effect of inhaled NO on the relation between stroke volume index (SVI) and mean pulmonary artery wedge pressure (PAWP) and (right) effect of inhaled NO on the relation between left ventricular (LV) peak +dP/dt and PAWP.

The NO-induced changes in LV filling pressure and PVR correlated with both the baseline PVR (see Fig 6) and the severity of hemodynamic compromise (see Table 2). It was previously observed that inhaled NO has no hemodynamic effects in control subjects who have a normal PVR.[34] Since the degree of reactive pulmonary hypertension is generally related to the severity of hemodynamic compromise in patients with LV failure, it might be anticipated that patients with more severe heart failure will have a more marked hemodynamic response to inhaled NO. To examine this prediction further, we compared the effects of inhaled NO in a subset of 5 patients with relatively compensated hemodynamics ("compensated group," defined by a pulmonary artery wedge pressure ≤ 18 mm Hg and a cardiac index ≥ 2.5 L·m^{-1}·m^{-2}) and those of the re-maining 14 patients ("decompensated group," defined by a pulmonary artery wedge pressure ≥ 18 mm Hg and/or a cardiac index <2.5 L·m^{-1}·m^{-2}). Although the LV ejection fractions were comparable in the two groups, the baseline PVR was higher in the decompen-sated group (Table 2). As predicted by our hypothesis, the NO-induced fall in PVR (43% versus 7%) and increase in LV filling pressure (27% versus 0%) were larger in the decompensated group. Taken together, these observations suggest that the greater effect of inhaled NO in patients with decompensated LV failure is due to the greater degree of reactive pulmonary hypertension present in such patients.

A second potential explanation for the decrease in transpulmonary gradient is that inhaled NO exerts a direct negative inotropic effect on the LV, resulting in a primary increase in LV filling pressure. In this scenario, passive pulmonary vasodilation might occur because of recruitment of precapillary vessels, an effect that has been demonstrated in animals.[35] However, we feel that a direct negative inotropic effect of inhaled NO is less likely, for several reasons. First, NO is rapidly inacti-vated by hemoglobin[1] and might not be expected to reach the coronary circulation under these conditions.

Second, we observed no decrease in LV +dP/dt, a highly sensitive measure of changes in contractile state. Third, it has been shown that in humans, the intracor-onary infusion of nitroprusside, to donate NO to the myocardium, has no effect on +dP/dt and, contrary to our findings with inhaled NO, caused a decrease in LV filling pressure apparently due to an increase in ventric-ular distensibility.[36]

An interesting corollary of these observations is that selective pulmonary vasodilation, in the absence of systemic vasodilation, may not be desirable in patients with severe LV failure. Clearly, inhaled NO, adminis-tered alone at the dose used in this study (80 ppm), may have adverse effects in such patients. Nevertheless, the ability of inhaled NO to reduce PVR selectively (ie, without causing systemic vasodilation), resulted in a unique physiological situation and thus provided the basis for these novel observations. Finally, on the basis of these observations, it is intriguing to speculate that an elevation in PVR may play an important adaptive role in patients with LV failure by limiting LV filling and thereby "protecting" the LV from excessive dilation, albeit at the expense of increased right ventricular work.

References

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