INHALED NITRIC OXIDE IS NOT A MYOCARDIAL DEPRESSANT IN A PORCINE MODEL OF HEART FAILURE

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Background: **Inhaled nitric oxide has been shown to be a potent and selective pulmonary vasodilator. Reports of increases in left ventricular end-diastolic pressure and episodes of pulmonary edema during the clinical use of inhaled nitric oxide in patients with preexisting left ventricular dysfunction have raised concerns that this agent may have myocardial depressant effects. We therefore undertook a study of the effects of inhaled nitric oxide on myocardial contractility in a porcine model of ventricular failure and pulmonary hypertension.** ***Methods:*** **After inducing heart failure in 10 pigs by rapid ventricular pacing, hemodynamic measurements and pressure-volume diagrams (by the conductance method) were obtained in six animals at baseline and during administration of inhaled nitric oxide at concentrations of 20 and 40 ppm. Myocardial contractile state was assessed by the end-systolic pressure-volume relationship and preload-recruitable stroke work, whereas diastolic function was measured in terms of the end-diastolic pressure-volume relationship and the pressure decay time constant T.** ***Results:*** **Baseline hemodynamics reflected heart failure and pulmonary hypertension, and inhaled nitric oxide induced significant reductions in mean pulmonary artery pressure and pulmonary vascular resistance. Although left ventricular end-diastolic pressure increased during administration of inhaled nitric oxide, no changes were observed in measures of systolic or diastolic function.** ***Conclusions:*** **Inhaled nitric oxide reduced pulmonary vascular resistance but did not alter myocardial contractility or diastolic function. Increases in left ventricular end-diastolic pressure during inhaled nitric oxide therapy are therefore not due to myocardial depression and may be related to increases in volume delivery to the left side of the heart resulting from reduced pulmonary vascular resistance. (J Thorac Cardiovasc Surg 1998;115:700-8)**

Pulmonary vascular resistance (PVR) is often elevated in congestive heart failure. Although the precise mechanism of this form of secondary pulmonary hypertension is not known, chronic elevations in left atrial pressure and pulmonary venous congestion, as well as alterations in sympathetic tone, are thought to play a role.[1] Patients with heart failure and pulmonary hypertension, whether primary or secondary, are at increased risk of right ventricular failure after cardiac transplantation.[2] For this reason, demonstration that PVR can be decreased pharmacologically in such patients (i.e., that the pulmonary hypertension is not due to fixed vascular resistance) is generally a pretransplant requirement.[3] In patients receiving left ventricular (LV) assist devices for advanced heart failure, pulmonary hypertension often limits the adequacy of device filling and may require institution of biventricular mechanical support.[4]

Nitric oxide (NO), initially described as an endothelium-derived relaxation factor, has been implicated in a wide variety of physiologic and pathophysiologic processes. Inhaled NO has been shown to

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cause pulmonary vasodilatation in primary pulmonary hypertension,[5] in pulmonary hypertension resulting from congenital heart disease,[6] and in the adult respiratory distress syndrome.[7] Recently, inhaled NO has been used to selectively lower PVR in patients undergoing cardiac operations.[8]

A clinical report describing the development of pulmonary edema in patients with heart failure receiving inhaled NO therapy,[9] as well as subsequent investigations demonstrating reproducible elevations in LV filling pressures,[10, 11] have raised concerns about the use of inhaled NO in patients with heart failure. Although NO has been shown to exert negative inotropic effects in some settings,[12, 13] it is unclear whether observed elevations in left atrial pressure are related to direct myocardial effects of inhaled NO. Although NO is avidly bound and inactivated by a variety of substrates, including hemoglobin,[14] and is thought not to have effects beyond arterioles immediately subjacent to alveoli, evidence suggests that the binding of NO to hemoglobin may result in the formation of active nitrosothiol metabolites.[15] We therefore undertook a study of the effects of inhaled NO on myocardial contractility in a porcine model of ventricular failure and pulmonary hypertension, testing our hypothesis that inhaled NO, when administered at clinically relevant doses, does not exert negative effects on myocardial function.

Methods

Animal care. Animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the Institute of Laboratory Animal Resources and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH Publication No. 86-23, revised 1985). In addition, this study also conforms with the position of the American Heart Association on Research Animal Use.

Induction of heart failure. The protocol[16] was carried out in 10 conditioned female Yorkshire pigs weighing 45 to 50 kg. After induction of anesthesia with ketamine (20 mg/kg) and thiamylal sodium (4.5 mg/kg) and maintenance with isoflurane (1.5 to 2.0%) in 30% oxygen, the trachea was intubated and the lungs were mechanically ventilated. A longitudinal subxiphoid incision and partial inferior pericardiotomy were performed, and a unipolar pacemaker lead was sutured to the LV apex. Next, a subcutaneous tunnel and pocket were created, and a pacemaker (modified Medtronic Model Minix 8340, Medtronic, Inc., Minneapolis, Minn.) was inserted. After recovery from anesthesia, the animal was transferred to a chronic care area. One day after implantation, the pacemaker was activated at a rate of 230 beats/min with an external programming device. The animals were monitored daily and given a 3-day regimen of intravenous cefazolin and a standard diet with free access to water.

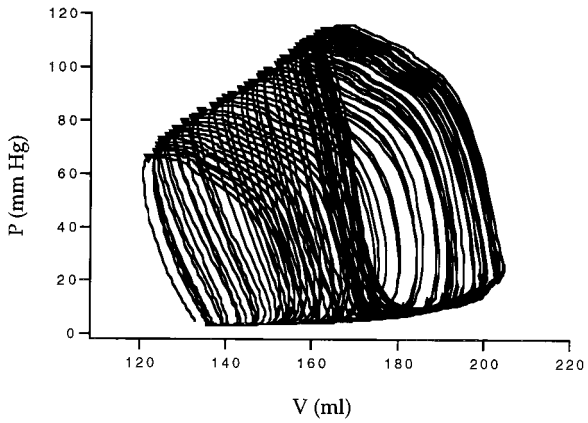

Fig. 1. Representative preload-varying pressure-volume diagram. *P*, Pressure; *V*, volume.

Experimental preparation. After 8 days of rapid pacing, the pacemakers were inactivated and animals were anesthetized with acepromazine maleate (0.5 mg/kg intramuscular), fentanyl (100 μg/kg), and atropine (1 to 2 mg intramuscularly). The lungs were mechanically ventilated, and ventilatory parameters were adjusted to maintain normocarbia as determined by frequent blood gas analyses. Normothermia was maintained by the use of two warming blankets and a heating lamp when necessary. Anesthesia was maintained with isoflurane (1.5% to 2.0%) in 30% oxygen. Through midline sternotomy and longitudinal pericardiotomy, the inferior vena cava, pulmonary artery (PA), and ascending aorta were isolated with snares. Two 5F micromanometer-tipped catheters (Millar Instruments, Houston, Tex.) were placed in the right atrium and PA through purse-string sutures for continuous pressure monitoring. A 16 mm perivascular flow probe (Transonics, Ithaca, N.Y.) was placed around the main PA. This flow probe was connected to an ultrasonic flowmeter that provided a continuous display of cardiac output. A 5F Millar micromanometer was placed in the right external carotid artery and advanced into the ascending aorta to monitor aortic pressure. A 12-electrode (1.0 cm interelectrode spacing) 6F micromanometer-tipped conductance catheter (Sentron, Federal Way, Wash.) was inserted through the LV apex and advanced through the aortic valve into the aortic outflow tract to measure LV volume and pressure. This catheter was connected to a signal conditioner (Leycom 5 Cardiodynamics, The Netherlands) that provides the conductance signal used for assessing LV volume. This device also measures blood resistivity, which is necessary for the estimation of volume. Blood resistivity was measured in each animal before the start of the experimental protocol. To ensure proper positioning of the conductance catheter, echocardiography was used and only segmental volume signals that corresponded to segments residing in the ventricular chamber were used for generation of the total

Table I. *Hemodynamics at baseline and at increasing concentrations of inhaled NO*

Hemodynamic parameter (units)	*Baseline*		*NO 20 ppm*		*NO 40 ppm*	
	Mean	*SEM*	*Mean*	*SEM*	*Mean*	*SEM*
HR (beats/min)	91.2	5.7	87.0	5.4	85.9	6.6
Mean ABP (mm Hg)	87.9	6.2	94.1	5.7	93.4	5.7
CVP (mm Hg)	11.8	2.4	10.4	1.8	10.2	2.1
Mean PAP (mm Hg)	34.7	3.1	29.5*	2.2	29.0*	2.3
CO (L/min)	2.9	0.6	2.7	0.7	2.4	0.5
CO/kg (L/min-kg)	0.060	0.012	0.056	0.013	0.051	0.012
EDV (ml)	122.4	33.1	125.0	34.0	127.6	33.8
EDP (mm Hg)	16.8	3.5	18.1	3.1	19.1‡	3.4
PVR (Woods units)	6.8	1.7	4.5†	1.0	3.9*	1.2
SVR (Woods units)	32.1	6.6	42.3	11.0	40.4	6.9
EF (%)	25.0	5.4	22.5	4.6	21.2	2.9

NO, Nitric oxide; *HR,* heart rate; *ABP,* arterial blood pressure; *CVP,* central venous pressure; *PAP,* pulmonary artery pressure; *CO,* cardiac output; *EDV,* end-diastolic volume; *EDP,* end-diastolic pressure; *PVR,* pulmonary vascular resistance; *SVR,* systemic vascular resistance; *EF,* ejection fraction; *SEM,* standard error of the mean.

*$p = 0.02$; †$p = 0.04$; ‡0.01.

volume signal. The total conductance signal is not only affected by the conductivity of blood in the chamber in which the catheter is situated but also by conductive structures that surround the chamber. The contribution to the total conductance signal from these surrounding structures is termed parallel conductance (Vpc). We determined Vpc by the hypertonic saline technique rapidly injecting 5 ml of 5% saline into the PA. Vpc was determined before each set of measurements, correcting for changes between NO dose administrations.

NO administration. After endotracheal intubation, animals received a mixture of oxygen and nitrogen to achieve an inspired fraction of oxygen (Fio_2) of 35%. NO gas (800 ppm in N_2) (Airco, Riverton, N.J.) was randomly delivered at concentrations of 20 and 40 ppm by titrating the amount of N_2 downward and the level of NO upward so as to maintain a constant Fio_2 and total gas flow rate of 8 L/min. The inspired concentration of NO was measured by an NO analyzer (Drager, Chantilly, Va.).

Study protocol. Animals were studied at baseline and during administration of two doses (20 and 40 ppm) of inhaled NO. Data collected in each condition consisted of standard hemodynamic measurements and a series of LV pressure-volume loops measured before and during inferior vena caval occlusion (IVCO). The IVCO was limited to 10 seconds to avoid reflex responses and was repeated if arrhythmias occurred. Mechanical ventilation was suspended during the period of data collection. Measurements were made 5 minutes after reaching a steady-state concentration of NO at each dose.

Data analysis. All analog signals were digitized at 200 Hz using a 12 bit A-D board (AD Instruments, Milford, Mass.) and stored on a removable hard drive for subsequent analysis using IGOR analysis software (WaveMetrics, Inc., Lake Oswego, Ore.). Pressures, flow, and volume data were subjected to a 5-point binomial smooth (gaussian filtering). End-diastolic pressure (EDP) was identified as the point just preceding the upstroke of the LV pressure wave, and end-diastolic volumes (EDV) were determined from the lower right-hand corner of the pressure-volume loop. PVR and systemic vascular resistance (SVR) were calculated using standard formulas. T, the time constant of active isovolumic relaxation,[17] was calculated using the zero-asymptote method. All steady-state data represent the average of five consecutive cardiac cycles.

Three relations derived from the pressure-volume diagram (Fig. 1) were examined during IVCO; at least seven cardiac cycles free of arrhythmias were used for each analysis:

1. End-systolic pressure-volume relationship (ESPVR). The slope, E_{ES}, and volume-axis intercept, V_O, of the ESPVR were determined as in previous studies. Briefly, V_O was initially assumed to be 0 ml, and values for end-systolic pressure (ESP) and volume (ESV) were determined for each cardiac cycle by identifying the point at which the value of $P(t)/(V(t) - V_O)$ reached a maximum. Regression analysis of these ESP and ESV points provided an improved estimate of V_O. This updated V_O value was then substituted into the above equation and new values for ESP and ESV were obtained. Subsequent iterations were performed until the value of V_0 changed by less than 2 ml.

2. Stroke work-end-diastolic volume relationship (preload-recruitable stroke work, PRSW). Stroke work was determined for each cardiac cycle by calculating the area within the respective pressure-volume loop. PRSW was defined by the relationship between stroke work and EDV and characterized by the slope (M_W) and volume intercept (V_W) of this relationship.

3. End-diastolic pressure-volume relationship (EDPVR). End-diastolic points were identified from each pressure-volume loop during the IVCO, and the resulting points were fit to an exponential equation: $EDP = Ae^{B \cdot EDV}$, where A and B are the nonlinear regression coefficients. In addition, this equation was used to calculate the predicted EDV at pressure equal to 10 mm Hg (V_O), allowing direct comparison of EDV at a common EDP between different conditions.[18]

Statistical analysis. Statistical analyses were performed with InStat for Macintosh (GraphPad Software, Los Angeles, Calif.). Linear relations (ESPVR, PRSW)

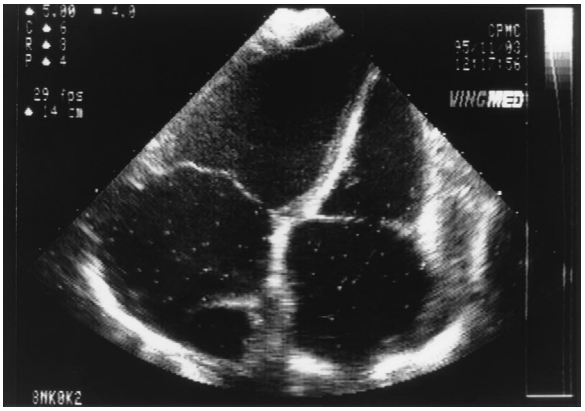

Fig. 2. Echocardiogram demonstrating four-chamber dilatation.

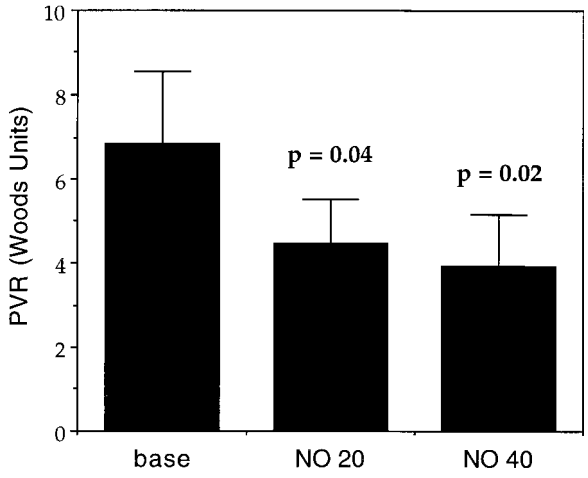

Fig. 3. Effects of inhaled nitric oxide *(NO)* on pulmonary vascular resistance *(PVR)*.

were described by a slope (m) and a volume-axis intercept (V_O) obtained from linear regression analysis, whereas exponential equations were expressed in terms of constants A and B. The effect of NO dose on the slope and V_O values of ESPVR and PRSW, the coefficients of the EDPVR, and hemodynamic parameters was assessed by a two-way analysis of variance with subsequent comparisons of individual groups to the baseline group by the Dunnett post-test. A p value < 0.05 was considered significant.

Results

Hemodynamics. Ten pigs underwent successful induction of heart failure by use of the described pacing protocol. During preparation of the experimental setup, one animal (animal 5) died from ventricular fibrillation on induction of anesthesia and two others (animals 2 and 10) died from ventricular fibrillation during median sternotomy. A fourth animal (animal 3) did not complete the experimental protocol because of excessive hemorrhage and early hemodynamic deterioration. Baseline measurements in the six remaining animals reflected biventricular failure and pulmonary hypertension, with reduced cardiac output and elevated mean PA pressure, PVR, and LVEDP (Table I). In addition, all animals exhibited clinical manifestations of heart failure, including ascites and pleural effusions, and echocardiograms performed for purposes of conductance catheter positioning demonstrated severe chamber dilatation (Fig. 2).

Administration of inhaled NO at concentrations of 20 and 40 ppm caused no changes in heart rate, mean systemic arterial pressure, central venous pressure, SVR, or cardiac output but led to dramatic reductions in PA pressure and PVR and elevations in LVEDP (Table I, Figs. 3 and 4).

Contractile state. A representative pressure-volume diagram is shown in Fig. 1, and representative ESPVR and PRSW plots under the three study conditions (baseline and inhaled NO at 20 and 40 ppm) are depicted in Figs. 5 and 6. Notice that the two relations that describe the ventricular contractile state appear to be unaffected by the administration of inhaled NO. The mean values for all animals are presented in Table II, demonstrating no significant differences in the slopes or volume intercepts of either contractile condition under any study condition.

Mean values for parameters that describe the EDPVR are listed in Table III. No significant changes were observed in either coefficient A or B. Consistent with this, the mean volume at a pressure of 10 mm Hg (V_O) was not significantly affected by either dose of inhaled NO (Fig. 7). In addition, no evidence of impaired active relaxation was observed because the pressure decay constant T was unaffected by inhaled NO.

Discussion

The results of this study demonstrate that in a porcine model of congestive heart failure and pulmonary hypertension, inhaled NO therapy is not associated with depression of LV contractile state or alteration of diastolic properties. Consistent with clinical reports of NO-induced elevations in pulmonary capillary wedge pressure, we found dose-de-

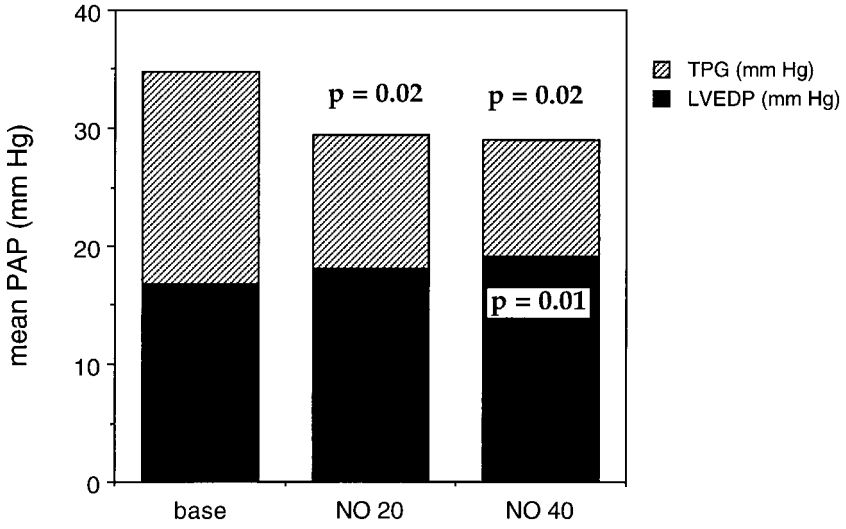

Fig. 4. Effects of inhaled nitric oxide *(NO)* on pulmonary artery pressure *(PAP)* pressure, left ventricular end-diastolic pressure *(LVEDP)*, and transpulmonary gradient *(TPG)*.

pendent rises in LV EDPs. Thus the acute elevations in LV filling pressures were not due to a direct myocardial effect of inhaled NO.

Pulmonary hypertension is a common consequence of long-standing congestive heart failure.[11] Although mechanisms responsible for this process are poorly understood,[2] chronic elevations in left atrial pressure, pulmonary venous congestion, intravascular volume expansion, and alterations in sympathetic tone are thought to play a role.[1] Interestingly, recent evidence suggests that pulmonary hypertension may in fact result from impairments in the release of NO by the pulmonary vascular endothelium[19, 20] and that cardiopulmonary bypass–related endothelial dysfunction may be responsible for further perioperative elevations in PVR.[21] Finally, the effects of NO on platelet function during cardiopulmonary bypass cannot be ignored.[22]

Whatever the mechanism, secondary elevations in PVR are initially reactive in nature and are usually reversible if underlying pathologic processes (e.g., congestive heart failure, hypoxia) are corrected early in their course.[23] Persistent elevations in pulmonary arterial pressures, however, lead to structural vascular changes, resulting in a fixed, irreversible form of pulmonary hypertension, the presence of which is associated with an increased risk of right heart failure and death after cardiac transplantation.[3] Accordingly, reversibility of pulmonary hypertension with vasodilators such as nitroprusside, and most recently by inhaled NO,[11] is generally considered to be a requirement in the selection of cardiac transplant recipients.

Recent reports of left atrial pressure elevations[10, 11] and the development of pulmonary edema[9] during inhaled NO therapy have raised concerns about the safe use of this new agent in patients with ventricular dysfunction. Given the potential for inhaled NO to lower PVR in patients with chronic reactive pulmonary hypertension, to counteract the pulmonary vasoconstrictive effects of cardiopulmonary bypass, and to evaluate the reversibility of pulmonary hypertension in cardiac transplant candidates, it is clear that patients with heart failure stand to benefit greatly from the clinical use of this new agent. For this reason, an understanding of the mechanism by which inhaled NO causes elevations in left atrial pressures is clinically important.

Because of the complex interactions between the ventricles and pulmonary and systemic vascular beds, identification of the dominant mechanism underlying an observed hemodynamic effect can be difficult. Theoretically, left atrial pressure may be influenced, either independently or in combination, by changes in systolic function, end-diastolic LV compliance, active relaxation, or extracardiac parameters, such as total body volume status, vascular resistance, and venous tone. Because inhaled NO is inactivated by hemoglobin,[24] it should not have direct myocardial effects[14] but might influence ventricular performance indirectly by its actions on the pulmonary vasculature or through a stable metabolite or carrier molecule.[11, 15]

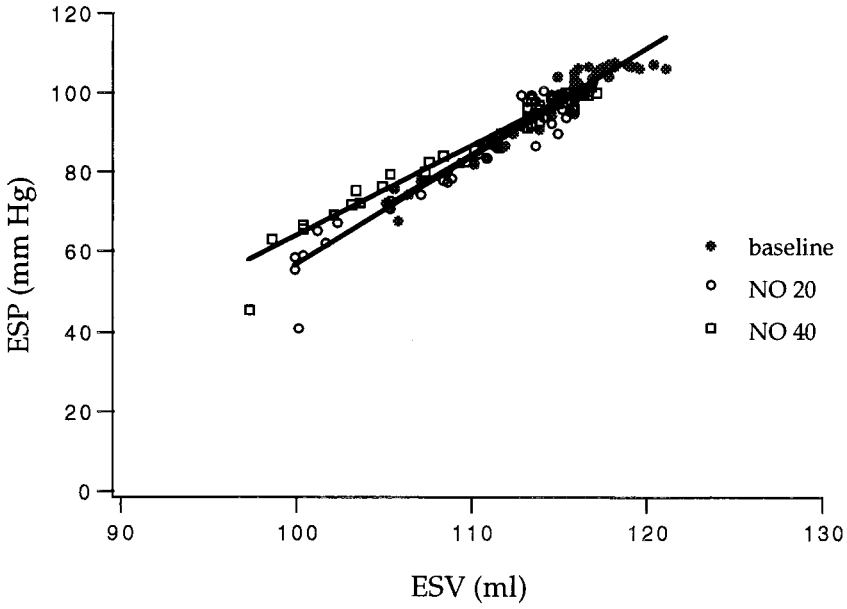

Fig. 5. Representative end-systolic pressure-volume relationship plot. *ESP,* End-systolic pressure; *ESV,* end-systolic volume; *NO*, nitric oxide.

It has been suggested that elevations in left atrial pressure are a direct consequence of decreases in LV contractile state induced by inhaled NO.[11] In support of this hypothesis, endogenous NO has been shown to exert negative inotropic effects under certain conditions; it was implicated in the myocardial depression induced by endotoxemia and in response to a variety of cytokines.[25, 26] In this study, although inhaled NO administered at therapeutic doses caused significant elevations in LVEDP, there was no effect on ESPVR or PRSW, indicating that changes in left atrial pressures were not a result of depressions in contractility.

It has also been hypothesized that elevations in LVEDP might be related to adverse effects of inhaled NO on diastolic relaxation, compliance, or both,[11] the latter effect potentially mediated by NO-induced coronary vasodilatation.[27] The effects on diastolic function of the NO donor sodium nitroprusside have been studied in isolated heart preparations and humans,[28] revealing changes in early but not late (isovolumic) relaxation and increases in diastolic distensibility. In our study neither the isovolumic pressure decay constant (T) nor the end-diastolic pressure volume relation were affected by the administration of inhaled NO.

If the LVEDP elevations observed during inhaled NO therapy are not due to alterations of systolic or diastolic function, extracardiac mechanisms must be invoked. In a previous theoretical analysis[29] it was demonstrated in the setting of preexistent LV dysfunction, volume loading, and pulmonary hypertension that pulmonary vasodilation, by causing shifts of blood between pulmonary arterial and pulmonary venous compartments, could by itself account for elevations of pulmonary venous pressure. This study concluded that in the presence of significant ventricular dysfunction these pulmonary venous pressure elevations could increase LVEDP, especially in the setting of high baseline PVR and volume status. In this study inhaled NO did not lead to alterations in systolic or diastolic function. These findings support the results of the previous theoretical analyses and indicate that elevations in LV filling pressures observed during inhaled NO therapy are not due to any measurable direct myocardial effects. Interestingly, in previous experiments in animals with normal ventricular function, inhaled NO reversed thromboxane-induced elevations in pulmonary arterial pressures and PVR but did not cause increases in LVEDP.[30]

If, as we propose, volume shifts associated with pulmonary vasodilatation are responsible for increases in LVEDP, one might expect to observe increases in LVEDV. Although a slight increase was observed in mean LVEDV after inhaled NO administration, this difference did not approach statistical significance. One explanation for this observation,

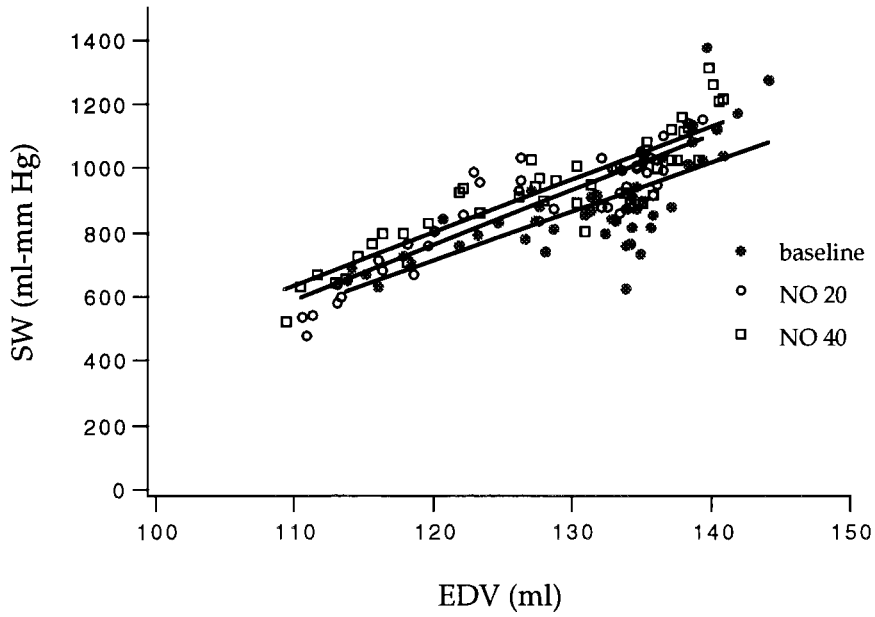

Fig. 6. Representative preload-recruitable stroke work plot. *SW,* Stroke work; *EDV,* end-diastolic volume; *NO,* nitric oxide.

Table II. *Mean parameters of the ESPVR (E_{es}, V_o) and the PRSW (M_w, V_o)*

	Baseline		*NO 20 ppm*		*NO 40 ppm*	
Parameter	*Mean*	*SEM*	*Mean*	*SEM*	*Mean*	*SEM*
E_{ES} (mm Hg/ml)	5.7	2.1	5.9	2.1	5.6	2.3
ESPVR V_o (ml)	38.7	13.2	47.3	11.9	46.8	13.6
M_w (mm Hg)	45.6	13.2	43.8	11.8	37.4	8.6
PRSW V_o (ml)	57.1	11.6	60.5	11.1	59.7	15.5

NO, Nitric oxide; E_{ES}, slope; *ESPVR,* end-systolic pressure-volume relationship; M_w, slope; *PRSW,* preload-recruitable stroke work; *SEM,* standard error of the mean.

as suggested by Loh and colleagues[10] and confirmed by our analysis, is that because the high baseline EDV corresponded with the steep portion of the EDPVR, small increases in LVEDV resulted in proportionately greater changes in LVEDP, allowing the latter but not the former to reach statistical significance.

Limitations of the conductance technique for measuring LV volume are described in detail elsewhere[31, 32] and predominantly affect the relationship between conductance and absolute ventricular volume. To minimize error, we confirmed proper catheter positioning by echocardiography, and gain and offset values were determined by measurement of blood resistivity and by the parallel conductance technique.[31, 32] Comparison of the stroke volume derived from PA flow and by the conductance technique resulted in considerable variations in gain (alpha) values among different animals, ranging from 0.6 to 1.4, but showed no appreciable intraanimal variability. Therefore although conductance volumes were not strictly equivalent to actual volumes and the value of the correction factor alpha varied between animals, alpha was relatively consistent between individual measurements within the same animal, allowing valid comparisons to be made between study conditions because each animal served as its own control. In addition, general anesthesia may be considered a confounding factor because isofluorane is known to induce vasodilatation and may decrease contractility. However, because each animal acted as its own control, without alteration of the inhaled concentration of anesthetic during the course of the experiment, these effects

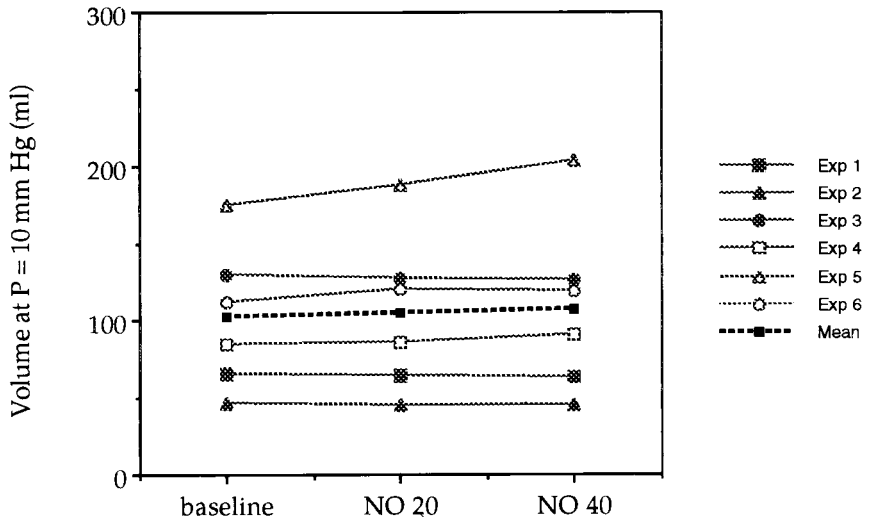

Fig. 7. Comparison of V_{10} values derived from the end-diastolic pulmonary vascular resistance. *NO,* Nitric oxide.

Table III. *Mean values for coefficients of the EDPVR (A, B) and V_{10}*

	Baseline		*NO 20 ppm*		*NO 40 ppm*	
Parameter	*Mean*	*SEM*	*Mean*	*SEM*	*Mean*	*SEM*
A	0.437	0.216	0.191	0.131	0.118	0.083
B	0.049	0.011	0.061	0.014	0.064	0.015
V_{10} (ml)	102.2	19.2	105.0	21.0	107.8	22.9
T (msec)	57.7	5.9	60.1	4.5	59.4	5.9

EDPVR, End-diastolic pressure-volume relationship; *NO,* nitric oxide; *T,* pressure decoy constant; V_{10}, volume at P = 10 mm Hg; *SEM,* standard error of the mean.

are not expected to influence the results of the study. Finally, the animal model of heart failure used in this study[16] was extremely reproducible, effecting biventricular dilatation, depression of ejection fraction, and decreased cardiac output in all animals tested.

In conclusion, we have reproduced, in a porcine model of heart failure and pulmonary hypertension, the constellation of clinically observed hemodynamic responses to inhaled NO therapy, including dose-dependent decreases in pulmonary arterial pressure and PVR and increases in LVEDP. Furthermore, determination of the ESPVR, PRSW, EDPVR, and T in these animals has demonstrated no effect of inhaled NO on myocardial contractility or relaxation. An alternative explanation that has been proposed on theoretical grounds is that volume shifts caused by pulmonary vasodilatation are responsible for clinically observed elevations in left atrial pressure and may also explain why patients with preexisting ventricular dysfunction are at greatest risk for these pressure elevations. Although clinical validation of our findings in humans is necessary and is the subject of current investigations, an understanding of this mechanism may lead to strategies allowing the safe use of inhaled NO in heart failure, perhaps by adjunctive vasodilator therapy. Considering that increases in LVEDP do not accompany PVR reductions induced by nonspecific vasodilators (i.e., agents that cause both systemic and pulmonary vasodilation), the importance of increasing systemic vascular capacity in this population during inhaled NO therapy is underscored.

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