

Inhaled Nitric Oxide Modifies Left Ventricular Diastolic Stress in the Presence of Vasoactive Agents in Heart Failure

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Nitric oxide (NO) inhalation therapy has been widely used in several diseases with pulmonary hypertension. However, application of NO inhalation therapy remains controversial in heart failure. Cardiovascular effects of inhaled NO (iNO) were evaluated in dogs before and after induction of heart failure with and without infusion of vasoactive agents. iNO did not affect the baseline left ventricular (LV) function or the response to isoproterenol in control conditions or heart failure induced by procainamide. Pulmonary vascular resistance was significantly decreased by iNO in heart failure with infusion of vasoactive agents. Unexpectedly, LV end-diastolic pressure was significantly elevated by iNO in heart failure in the presence of infusion of vasoactive agents independent of their types; either the vasodilating agents of acetylcholine and nitroglycerin or the vasoconstricting agents of norepinephrine and angiotensin-II. The end-diastolic LV dimension and wall stress were also significantly increased by iNO, however, those at end systole were not affected. These results suggested that NO inhalation therapy reduced pulmonary vascular resistance, whereas in the presence of additional stress of vasoactive agents, it increased LV preload and end-diastolic wall stress in heart failure.

Keywords: nitric oxide; heart failure; \dot{Q} ; hemodynamics; vasodilation

Nitric oxide (NO) regulates vascular tone and modulates myocardial function (1–6). The effect of inhaled NO (iNO) is believed to be limited to pulmonary vascular beds without significant effects on systemic circulation (7–9). NO inhalation therapy has been widely applied in various diseases such as persistent pulmonary hypertension in newborns (10, 11), primary pulmonary hypertension (12), adult respiratory distress syndrome (13), congenital (14) and valvular heart diseases (15), and transplanted hearts (16). In the treatment of heart failure, however, it is controversial whether NO inhalation therapy is effective (17–19) or potentially harmful (20, 21). Several papers have demonstrated NO inhalation therapy improves hemodynamics (17, 18) and exercise capacity (19) in heart failure. In contrast, some papers have warned that NO inhalation therapy potentially induces pulmonary edema or exacerbates cardiac dysfunction in heart failure (20, 21).

Previous studies have suggested that NO suppresses myocardial contractility and attenuates positive inotropic responses to β -adrenergic stimulation in myocytes (22, 23) and laboratory animals (24). The cardiac dysfunction of cardio-

myopathy (25) and sepsis (3, 26–28) is attributable to excessive production of NO. However, there are few reports demonstrating the direct effects of iNO on cardiac function (29, 30).

iNO potentially dilates pulmonary vascular beds, and in this sense, it must be effective in heart failure with pulmonary hypertension. However, efficacy of iNO may be invalid in heart failure without marked pulmonary hypertension. Accordingly, the current investigation aimed to determine the cardiovascular effects of iNO, particularly on the cardiac function in heart failure lacking pulmonary hypertension. To accomplish this goal, we used a dog model of procainamide-induced cardiac dysfunction (31), which shows serious cardiac dysfunction but does not accompany pulmonary hypertension. We studied the cardiovascular effects of iNO in the presence or absence of additional stress of vasoactive factors, which characterize clinical syndrome of heart failure. Enhanced sympathetic nervous system was represented by norepinephrine (NE) and isoproterenol (ISO) infusions and enhanced rennin angiotensin system by angiotensin-II (Ang-II) infusion. Using the stepwise infusion of these agents, we modified cardiac function and hemodynamics and studied the effects of iNO under the various conditions of left ventricular (LV) stress. We also investigated whether iNO affected responses to endothelial-dependent and endothelial-independent vasodilators of acetylcholine (ACh) and nitroglycerine (NTG), which have been reported as being attenuated in heart failure.

METHODS

Experimental Preparation

A total of 18 adult mongrel dogs of either sex, weighing 7.5 to 16.0 kg, were anesthetized with sodium pentobarbital (20–30 mg/kg, intravenously). Each dog was intubated and ventilated with oxygen-enriched air using a volume ventilator (model 683; Harvard, South Natick, MA), of which respiratory rate, V_T , and end-expiratory lung volume were adjusted to maintain arterial blood gas in a physiological range, and those conditions were kept constant throughout the experiment. Thoracotomy was performed in the left fifth intercostal space, and then heart was suspended in a pericardial cradle (Figure 1). The left anterior descending coronary artery was exposed and a Doppler flow probe was placed on it. Coronary blood flow velocity was measured with a 20 MHz pulsed ultrasonic Doppler velocimeter (VF1, Valpey-Fisher, Hopkinton, MA). A 7 F balloon-tipped catheter was inserted from jugular vein into the main pulmonary artery to measure pulmonary arterial pressure (Ppa). An electromagnetic flow probe was placed on the main pulmonary artery and connected to an electromagnetic flow meter (MFV-1100; Nihon Kohden). A 7 F catheter was placed in the left carotid artery to measure aortic pressure using a strain-gauge manometer (TP-200T transducer; Nihon Kohden). LV pressure, LV dP/dt, and the logistic time constant of isovolumic relaxation of LV (32, 33) were measured by a catheter-tipped transducer (PC-350; Miller, Houston,

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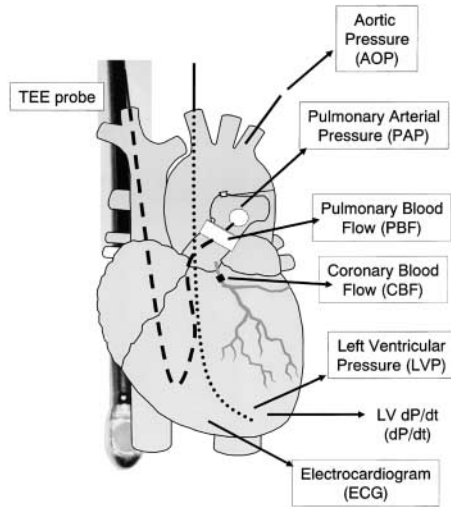


Figure 1. Schematic illustration of instrumentation used in assessing hemodynamics and left ventricular (LV) function. A 5-MHz transducer for transesophageal echocardiography was placed just behind LV to monitor changes in LV dimension.

TX) inserted from the right carotid artery into LV. ECG was continuously monitored and used to measure heart rate. A 5-MHz transducer for transesophageal echocardiography (SSD-830, UST-5234S-5; Aloka, Tokyo, Japan) was placed just behind LV to monitor changes in LV dimension. The study was reviewed and approved by the Committee of the Ethics on Animal Experiments in Asahikawa Medical College. The dogs were treated in accordance with the guideline of the Committee.

Experimental Protocol

We randomized the order of experiments with or without iNO; nine dogs underwent the experiment with iNO then without iNO, whereas the other 9 dogs underwent the reverse sequence (Figure 2). After the stable baseline hemodynamics were recorded, the dose response to each of the following five vasoactive agents was examined in a random order. Each infusion was continued for 3 minutes to obtain a stable hemodynamic change, and it was stepwisely increased up to the maximal dose. The maximal dose of each agent was determined to obtain 20 to 30% changes in the LV end-diastolic pressure (LVEDP) by preliminary experiments. Five vasoactive agents included ISO (Nikken Chemicals Co., LTD., Tokyo, Japan, 0.01, 0.02, 0.05 µg/kg/minute), Ach (Daiichi Pharmaceutical Co., LTD., Tokyo, Japan, 2.5, 5, 10 µg/kg/minute), NTG

(Nippon Kayaku Co., LTD., Tokyo, Japan, 5, 10, 20 µg/kg/minute), NE (Nikken Chemicals Co., 0.2, 0.5, 1.0 µg/kg/minute), and Ang-II (Sigma Chemicals Pty Ltd, Perth, Australia, 0.1 0.2, 0.5 µg/kg/minute). After the maximal dose was examined, dogs were allowed to recover to the baseline, and then the next agent was examined. When the control experiments were completed, procainamide was infused as described below, and we repeated the same protocol as control experiments with or without iNO. The application order of vasoactive agents was randomly determined but kept constant in each dog before and after heart failure with and without iNO.

Procainamide-induced Heart Failure

We used the procainamide-induced heart failure model (31), which was characterized by cardiac dysfunction without pulmonary hypertension. This model allowed us to evaluate the cardiovascular effects of iNO with minimizing the potential effects of pulmonary vasodilation on cardiac function. Procainamide (Daiichi Pharmaceutical Co.) was continuously infused at a variable dose of 5 to 10 mg/kg/minute to maintain the LV dP/dt by 30 to 40% of the baseline level.

NO Administration

NO gas, stored in nitrogen at the concentration of 800 ppm, was mixed into the inspiration limb of a respirator circuit. The inspired concentration of NO was continuously monitored at the point just proximal to the endotracheal tube using a chemiluminescence analyzer (NOA 270B, Severs, CO). NO gas was delivered at the concentration of 70 ppm by titrating the amount of nitrogen. Exhaled gas was scavenged through an absorption column.

Data Analysis and Statistics

Hemodynamic data were monitored on a direct-writing oscillograph and recorded on a multichannel recorder (polygraph system RM 6200; Nihon Kohden) and continuously digitized and recorded on a personal computer throughout the experiment using a physiological data analyzing system (MacLab; ADInstruments Pty Ltd, NSW, Australia). The logistic time constant of isovolumic relaxation of LV was used as an index of LV diastolic function (32, 33). LV end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD), LV wall thickness at end systole (WTes) and end diastole (WTed) were measured by M-mode transesophageal echocardiography. LV fractional shortening was calculated as $([LVEDD] - [LVESD])/[LVEDD] \times 100$. LV end-diastolic and end-systolic meridional wall stress, WSed and WSes, were calculated as follows (34):

$$WSed = 0.334 \times LVEDP \times LVEDD / WTed / (1 + WTed / LVEDD).$$

$$WSes = 0.334 \times LVESP \times LVESD / WTes / (1 + WTes / LVESD).$$

The data were stored and analyzed using a personal computer. All values were reported as mean ± SEM. Differences between baseline measurements and subsequent values were assessed by repeated-measures analysis of variance. If an overall difference was found, compari-

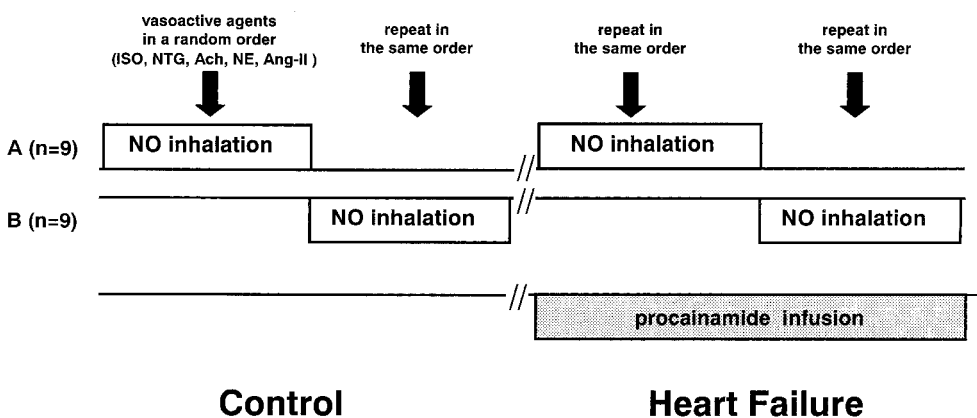


Figure 2. Experimental protocols. Dogs were randomly divided into A or B groups, and underwent control protocol after heart failure protocol by procainamide infusion. A group (n = 9) underwent the experiments with inhaled nitric oxide (iNO) then without iNO, whereas B group (n = 9) underwent the reverse sequence. Vasoactive agents of isoproterenol (ISO), nitroglycerine (NTG), acetylcholine (Ach), norepinephrine (NE), and angiotensin-II (Ang-II) in three doses each were applied in a random order at the first arrow, and repeated in the same order with or without iNO in control conditions and heart failure conditions.

TABLE 1. EFFECTS OF INHALED NITRIC OXIDE ON THE BASELINE HEMODYNAMICS AND CARDIAC FUNCTION BEFORE AND AFTER ADMINISTRATION OF PROCAINAMIDE

	Control Experiment			Procainamide (+)		
	iNO(-)	iNO(+)	p Value	iNO(-)	iNO(+)	p Value
Heart rate, bpm	161 ± 8	158 ± 7	NS	103 ± 7**	99 ± 7 [†]	NS
Mean AOP, mm Hg	84 ± 3	84 ± 3	NS	51 ± 4**	51 ± 4 [†]	NS
LVP, mm Hg	143 ± 5	144 ± 6	NS	92 ± 5**	92 ± 4 [†]	NS
dP/dt, mm Hg/s	2976 ± 257	2849 ± 186	NS	1222 ± 88**	1195 ± 95 [†]	NS
-dP/dt, mm Hg/s	-3989 ± 341	-3931 ± 373	NS	-1626 ± 151**	-1538 ± 133 [†]	NS
Mean Ppa, mm Hg	13.7 ± 0.7	13.7 ± 0.7	NS	13.3 ± 0.8*	12.9 ± 0.9 [†]	NS
Mean PBF, L/min	0.46 ± 0.1	0.45 ± 0.1	NS	0.34 ± 0.1**	0.33 ± 0.1 [†]	NS
Mean CBF, Hz	0.80 ± 0.1	0.83 ± 0.1	NS	0.49 ± 0.1**	0.51 ± 0.1 [†]	NS
LVEDP, mm Hg	5.4 ± 0.8	5.7 ± 0.6	NS	7.5 ± 0.6*	8.0 ± 1.0 [†]	NS
τ_L , m	22 ± 2	23 ± 2	NS	40 ± 4**	40 ± 4 [†]	NS
LVEDD, mm	30 ± 2	31 ± 2	NS	29 ± 1**	29 ± 1 [†]	NS
LVESD, mm	24 ± 2	24 ± 2	NS	25 ± 1 ^{NS}	25 ± 1 ^{NS}	NS
LVEF, %	49 ± 6	50 ± 6	NS	36 ± 4**	34 ± 4 [†]	NS

Definition of abbreviations: AOP = aortic pressure; CBF = coronary blood flow; dP/dt = first derivative of LV pressure; HR = heart rate; iNO(+) = condition with inhaled nitric oxide; iNO(-) = condition without inhaled nitric oxide; LVEDD = left ventricular end-diastolic dimension; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension; NS = not significant; PBF = pulmonary blood flow; Ppa = pulmonary arterial pressure; procainamide(+) = after administration of procainamide; τ_L = time constant of isovolumic relaxation of left ventricle.

Values are mean ± SE, n = 18.

p Value: iNO(-) versus iNO(+) in the control experiment and after administration of procainamide(+).

* p < 0.05.

** p < 0.01 versus iNO(-) in the control experiment; [†] p < 0.01, [‡] p < 0.05 versus iNO(+) in control experiment.

sons were performed with two-tailed Student's *t* test for unpaired data. Data were considered to be significantly different at a p value of 0.05 or less.

RESULTS

Baseline Hemodynamics and Cardiac Function

There were no significant differences in the baseline hemodynamics and cardiac function with and without iNO in the control experiments (Table 1). After the continuous infusion of procainamide, heart rate, LV pressure, LV dP/dt, aortic pressure, and Ppa were significantly decreased, whereas LVEDP and logistic time constant of isovolumic relaxation of LV were significantly increased (Table 1). LVEDD significantly decreased without significant change in LVESD, resulted in approximately -26% reduction in LV ejection fraction with procainamide (p < 0.01). However, iNO affected neither LV function nor hemodynamics at the baseline even in heart failure.

Responses to ISO

ISO significantly increased LV dP/dt from 2,975.6 ± 211.8 to 4,037.7 ± 345.0 mm Hg/second and heart rate from 161.3 ± 6.6 to 203.6 ± 9.0 bpm in a dose-dependent fashion in the control experiments. In heart failure, the baseline LV dP/dt and heart rate were significantly decreased, however, the dose response to ISO was well preserved (Figure 3). More importantly, iNO did not significantly affect these positive inotropic and chronotropic responses to ISO even in heart failure.

Cardiovascular Effects of Vasoactive Agents in Control Experiments

Vasodilating agents, both Ach and NTG significantly decreased aortic pressure and LV pressure. NTG significantly decreased pulmonary blood flow (PBF) and Ppa. In contrast, Ach significantly increased both PBF and Ppa. As a result, pulmonary vascular resistance (PVR) was significantly increased with NTG, (e.g., from 22.6 ± 3.1 to 24.5 ± 3.4 mm Hg/L/minute with 20

μg/kg/minute NTG [p < 0.01]), in contrast, PVR was slightly decreased with Ach (Figure 4A). LVEDP was significantly decreased dose-dependently with NTG (from 4.7 ± 0.6 to 3.0 ± 0.5 mm Hg with 20 μg/kg/minute NTG [p < 0.01]); however, it was not significantly affected with Ach. LVEDD and LVESD were slightly decreased, and fractional shortening was slightly increased with both agents. Despite these differences in Ach and NTG, iNO did not significantly affect their hemodynamic changes in the control experiments.

Vasoconstricting agents, both NE and Ang-II significantly increased aortic pressure, LV pressure, LVEDP, and dP/dt. Coronary blood flow and PBF were significantly increased, however, Ppa was not significantly changed with NE. PVR was significantly decreased with NE (e.g., from 23.8 ± 2.5 to 17.4 ± 2.2 mm Hg/L/minute with 1 μg/kg/minute NE [p < 0.05]). In contrast, Ppa and LVEDP were significantly increased, PBF was significantly decreased, and thus PVR was not significantly changed with Ang-II. LVEDD was slightly increased, but LVESD was slightly decreased, accordingly fractional shortening was significantly increased with NE. In contrast, LVEDD, LVESD, and fractional shortening were slightly increased with Ang-II. Despite these hemodynamic differences in NE and Ang-II, iNO did not significantly affect their hemodynamic responses in the control experiments.

Cardiovascular Effects of Vasoactive Agents in Heart Failure

In contrast to the control experiments, PVR (mm Hg/L/minute) was significantly decreased with iNO in heart failure independent of types of vasoactive agents (Figure 4A); 24.2 ± 3.4 to 18.9 ± 2.6 by NTG 20 μg/kg/minute, p value less than 0.05; 26.7 ± 4.5 to 23.0 ± 4.1 by Ach 10 μg/kg/minute, p value less than 0.05; 25.0 ± 3.3 to 22.0 ± 3.5 by NE 1 μg/kg/minute, p value less than 0.05; 28.2 ± 2.0 to 24.2 ± 2.0 by Ang-II 0.5 μg/kg/minute, p value less than 0.05. LVEDP (mm Hg) was significantly increased with iNO in heart failure independent of types of vasoactive agents (Figure 4B); 4.6 ± 1.1 to 5.7 ± 1.1 by NTG 20 μg/kg/minute, p value less than 0.05; 6.1 ± 1.4 to 7.4 ± 1.7 by Ach 10

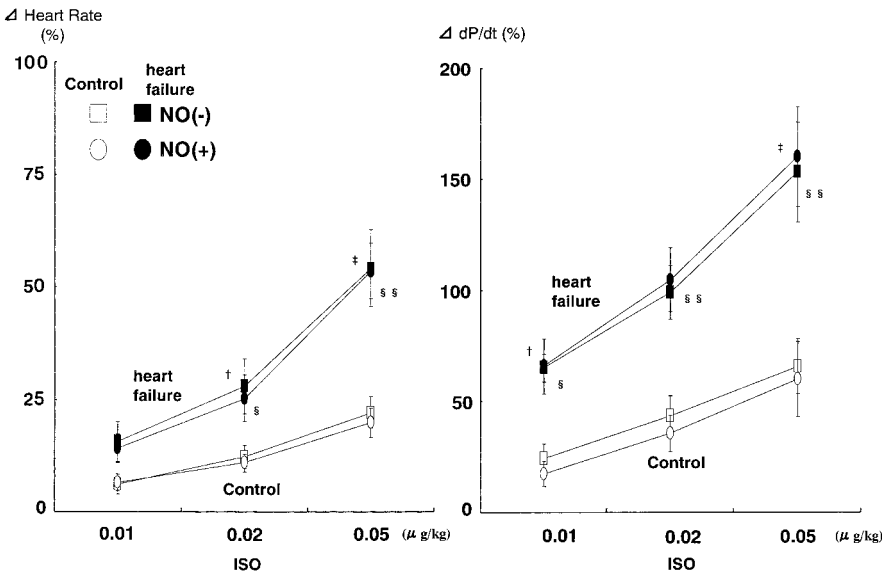


Figure 3. Dose responses to ISO in heart rate (HR) (right panel) and LV dp/dt (left panel) with (open circle) and without (open square) iNO in control experiments, and with (filled circle) and without (filled square) iNO in heart failure. ISO increased HR and LV dp/dt dose-dependently. There were no significant differences in the responses of HR and LV dp/dt to ISO with and without iNO. Data are means \pm SEM. †p Value less than 0.05, ‡p value less than 0.01 versus NO(-) baseline, §p value less than 0.05, §§p value less than 0.01 versus NO(+) baseline, n = 18.

$\mu\text{g/kg/minute}$, p value less than 0.05; 11.0 ± 2.4 to 12.9 ± 2.4 by NE $1 \mu\text{g/kg/minute}$, p value less than 0.05; 11.8 ± 2.4 to 13.1 ± 2.7 by Ang-II $0.5 \mu\text{g/kg/minute}$, p value less than 0.05.

Table 2 shows the changes in LVEDD and fractional shortening at the maximum dose of each vasoactive agent compared with the control experiments. In contrast to the control experiments, iNO increased LVEDD significantly in heart failure independent of types of vasoactive agents (Table 2).

The WSed (10^3 dyn/cm^2), but not WSes, was significantly increased with iNO in heart failure (Figure 5); 2.73 ± 0.54 to 3.45 ± 0.69 by NTG $20 \mu\text{g/kg/minute}$, p value less than 0.05; 4.67 ± 0.57 to 5.69 ± 0.38 by Ach $10 \mu\text{g/kg/minute}$, p value less than 0.05; 6.78 ± 1.02 to 8.25 ± 1.37 by NE $1 \mu\text{g/kg/minute}$, p

value less than 0.05; 11.24 ± 1.43 to 13.67 ± 1.57 by Ang-II $0.5 \mu\text{g/kg/minute}$, p value less than 0.05.

The remaining hemodynamic parameters were not significantly affected by iNO.

DISCUSSION

The major findings of the current investigation are as follows: (1) iNO does not influence cardiac function or hemodynamics at baseline in the control conditions or heart failure conditions, (2) the positive inotropic and chronotropic actions of β -adrenergic stimulation are not affected by iNO in the control conditions or heart failure conditions, (3) only in heart failure, iNO signifi-

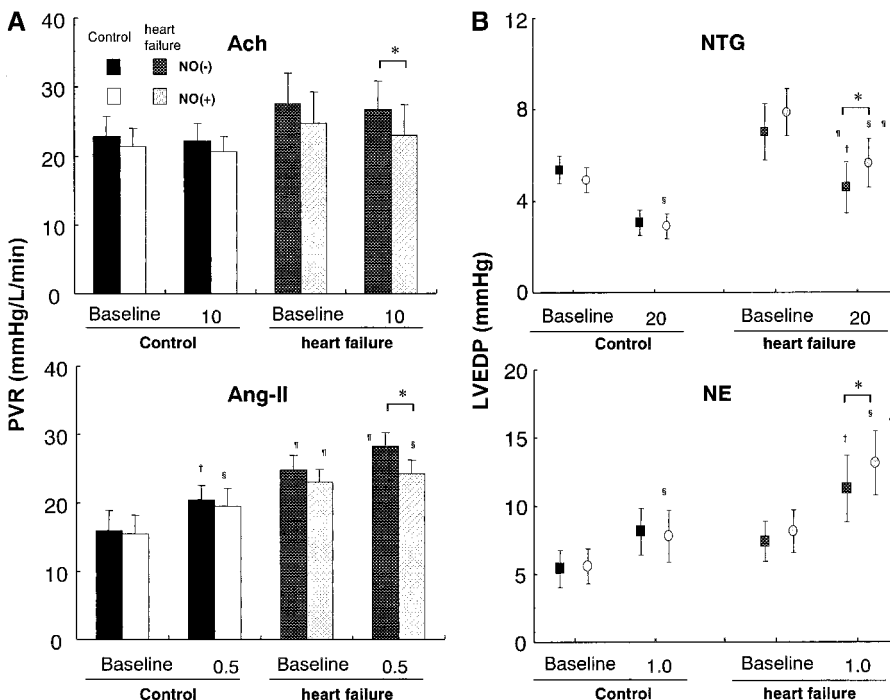


Figure 4. (A) Changes in pulmonary vascular resistance (PVR) with Ach (upper panel) and Ang-II (lower panel). Increased PVR in heart failure was significantly reduced by iNO. (B) Changes in LV end-diastolic pressure (LVEDP) with NTG (upper panel) and NE (lower panel). LVEDP was decreased by NTG and increased by NE, however, in either case it was significantly increased by iNO in heart failure. Data are means \pm SEM. †p Value less than 0.05, ‡p value less than 0.01 versus NO(-) baseline, §p value less than 0.05, §§p value less than 0.01 versus NO(+) baseline, *p value less than 0.05 versus control experiment, *p value less than 0.05 versus without iNO, n = 18.

TABLE 2. EFFECTS OF INHALED NITRIC OXIDE ON THE CHANGES IN LEFT VENTRICULAR DIMENSION WITH VASOACTIVE AGENTS

		iNO(-)	iNO(+)		
NTG, 20 μ g/kg/min	Control condition	LVEDD	28.0 \pm 2.1	29.3 \pm 2.4	
		%FS	19.4 \pm 1.6	18.6 \pm 3.1	
	Heart failure	LVEDD	26.3 \pm 1.1	28.0 \pm 1.2*	
		%FS	9.7 \pm 1.9	10.9 \pm 1.5	
	Ach, 10 μ g/kg/min	Control condition	LVEDD	28.7 \pm 1.4	28.7 \pm 2.0
			%FS	20.3 \pm 2.9	19.4 \pm 2.5
Heart failure		LVEDD	26.0 \pm 1.6	27.4 \pm 1.9*	
		%FS	16.2 \pm 3.9	14.8 \pm 3.2	
NE, 1 μ g/kg/min		Control condition	LVEDD	30.4 \pm 2.8	30.6 \pm 2.6
			%FS	25.7 \pm 4.0	24.1 \pm 3.9
	Heart failure	LVEDD	29.3 \pm 2.1	30.6 \pm 2.1*	
		%FS	26.6 \pm 2.4	26.8 \pm 2.6	
	Ang-II, 0.5 μ g/kg/min	Control condition	LVEDD	30.2 \pm 1.0	30.6 \pm 1.0
			%FS	23.6 \pm 3.5	24.5 \pm 2.6
Heart failure		LVEDD	29.4 \pm 0.9	31.0 \pm 0.6*	
		%FS	17.0 \pm 1.9	21.8 \pm 1.8	

Definition of abbreviations: Ach = acetylcholine; Ang-II = angiotensin II; %FS = fractional shortening; iNO(+) = with inhaled nitric oxide; iNO(-) = without inhaled nitric oxide; LVEDD = left ventricular end-diastolic dimension; NE = norepinephrine; NTG = nitroglycerine.

Values are mean \pm SE, n = 8.

* p < 0.05 versus iNO(-).

cantly reduces PVR in the presence of additional stress of vasoactive agents but simultaneously increases LV wall stress at end diastole.

Effects of iNO on Ventricular Function

Negative inotropic effect of NO has been reported in several *in vitro* experiments (22–24), normal (4), and impaired (35) human hearts. However, the direct cardiac effect of iNO has not been confirmed in the previous reports in normal (29) and failed hearts (17–21). We confirmed that iNO did not affect cardiac function in the control conditions or heart failure conditions, i.e., no changes in peak positive and negative dP/dt, ejection indexes

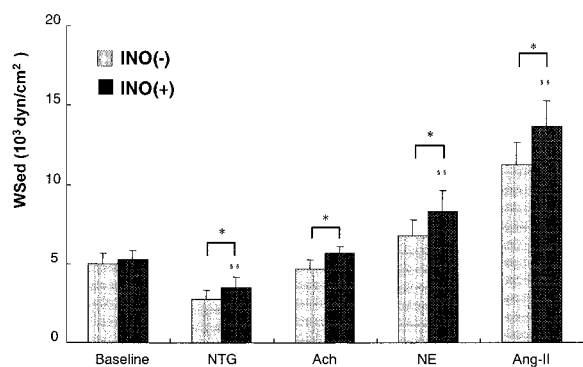


Figure 5. Changes in end-diastolic wall stress (*WSed*) by vasoactive agents with and without iNO in heart failure. *WSed* was decreased by NTG and ACH and increased by NE and ANG-II, and in any case it was significantly increased with iNO. †p Value less than 0.01 versus baseline of NO(-), ‡p Value less than 0.01 versus baseline of NO(+), *p Value less than 0.05 versus without iNO, n = 8.

of transesophageal echocardiography and active relaxation as assessed by logistic time constant of isovolumic relaxation of LV. The direct coronary vasodilating effect of iNO is unlikely because coronary blood flow was not changed. Attenuation of responses to β -adrenergic stimulation by iNO was not observed in the current setting. The half-life of NO *in vivo* is less than 1 second (7–9). We believe the main action of iNO is limited to the pulmonary vascular beds without direct effects on cardiac function.

Reduction of PVR by iNO

iNO did not affect the baseline PVR in the control conditions or heart failure conditions. Even in the presence of additional stress of vasoactive agents, iNO did not affect PVR in the control conditions. These findings indicate that the effect of iNO is not that powerful in the modification of basal pulmonary vascular tone. However, iNO counteracts the additional stress of vasoactive agents, independent of their types in heart failure.

The decreases in PVR with iNO were similarly observed with both endothelium-dependent Ach and endothelium-independent NTG in heart failure. This was unexpected. In our previous study using bolus injection, iNO suppressed the response to Ach but not to NTG (36). At that time, we speculated that iNO might suppress intrinsic NO release and attenuated endothelium-dependent vasodilation (36). These discrepancies probably depend on the way of administration of agents, bolus injection, and continuous infusion. Vasodilating effect of Ach is mediated by M3 receptors and primarily by intrinsic NO and secondarily by inhibition of NE release from adrenergic nerve endings. Ach dilates the whole pulmonary vascular bed, however, NTG predominantly dilates systemic veins resulting in systemic venous pooling (37). Therefore, PBF tended to be increased by Ach but decreased by NTG. In either case, additional pulmonary vasodilating effects of iNO caused further reduction of PVR. iNO may predominantly dilate smaller vasculature adjacent to alveoli.

NE and Ang-II, the major humoral factors characterizing heart failure, act differently in pulmonary circulation. PBF was increased by NE but decreased by Ang-II. NE shows α -adrenergic vasoconstriction and β -adrenergic inotropic action. Ang-II shows vasoconstriction directly by Ang-II Type 1 receptor stimulation and indirectly by enhancement of peripheral NE neurotransmission. Independent of the differences in the changes in PBF by NE and Ang-II, iNO reduces PVR in heart failure conditions.

The responses of PVR to NTG and NE were opposite to what we expected. PVR was determined by the balance of changes in PBF and Ppa, therefore the degree of relative changes in both the indices could make the discrepancy. The changes in PBF were slightly greater compared with those of Ppa with NTG, consequently PVR was calculated to be increased by intravenous infusion of NTG. Similarly, PBF was significantly increased but Ppa was not significantly affected with NE, consequently PVR was calculated to be decreased by intravenous infusion of NE in the present study using anesthetized dogs.

Elevation of LVEDP and End-diastolic Wall Stress by iNO

We observed unfavorable increase of LVEDP by iNO in heart failure. The increases in left atrial or LV filling pressure by iNO have been reported in several studies on heart failure (17, 18, 20, 21), however, the mechanism remains unknown. One explanation is a negative inotropic action of NO (4, 22–24). However, the increases in LVEDP were observed not only with NTG and Ach, which decreases LV dP/dt, but also with NE and Ang-II, which increases LV dP/dt. The β -adrenergic inotropic response was not altered by iNO. These findings suggest that the increase

in LVEDP by iNO is independent of further depression of LV function in heart failure.

An alternative and plausible explanation is volume shifts from the selectively dilated pulmonary vasculature to the failing LV. iNO reduces right ventricular afterload, which increases right ventricular \dot{Q} , subsequently increasing LV preload. It increases LV \dot{Q} by Frank–Starling mechanism. However, with an impaired LV function, failure to increase forward \dot{Q} leads to elevation of LVEDP. We confirmed the specific increases in the indices of diastolic LV loading, i.e., LVEDP, LVEDD, and W_{Sed} with iNO in heart failure. We believe that an increase in LV preload secondary to pulmonary vasodilation is the major mechanism of increased LVEDP. Of note, iNO showed beneficial hemodynamic effects in patients implanted with an LV assist device, who needed additional support only of right ventricle (38, 39).

Procainamide-induced Heart Failure

To investigate the effects of iNO on cardiovascular hemodynamics in heart failure, we tried to minimize the prominent pulmonary vasodilating effects of iNO, which would potentially buffer the effects of iNO on cardiac function. Thus, we chose procainamide-induced heart failure as a model without pulmonary hypertension but with serious cardiac dysfunction. A continuous infusion of procainamide causes marked cardiac suppression, moderate vasodilation, and heart rate reduction due to its potent sodium channel blocking and weak autonomic ganglia blocking actions. Consequently, this model dose-dependently shows a marked cardiac dysfunction, moderate hypotension, bradycardia, and most importantly, no pulmonary hypertension. The pulmonary vasodilating effect of iNO could be buffered in this heart failure model lacking pulmonary hypertension. We could study the effects of iNO on LV preload under the condition of stepwisely modified cardiac function and hemodynamics with the additional vasoactive agents in this model.

Study Limitations

In the assessment of the effects of the various vasoactive agents, we used the time constant of isovolumic relaxation calculated by a logistic regression, which was relatively load independent (32, 33). In contrast, indices of contractility we used were relatively load dependent. Therefore, we could not simply conclude that the increase in LVEDP by iNO was independent of further depression of LV function in heart failure. However, iNO itself did not significantly affect LVEDP, LV dP/dt, LV ejection fraction, or LVSV in heart failure. Only in the presence of vasoactive agents, iNO increased LVEDP either with preload reducing agent of NTG or with afterload increasing agent of NE. In the presence of these agents, the relationship between LVEDP and LVSV seemed to shift right upward on the almost identical curve with iNO (data not shown). We believe iNO increases LV preload without significantly affecting LV contractility in heart failure.

We used an experimental heart failure model without pulmonary hypertension to minimize the prominent pulmonary vasodilating effects of iNO, which would potentially buffer the effects of iNO on cardiac function. Pulmonary hypertension is one of the hallmarks of heart failure. Therefore, our results are not applicable to every condition of clinical heart failure.

In summary, the effects of iNO on cardiac function and hemodynamics are minor in normal subjects. The cardiac actions of β -adrenergic stimulation are not affected by iNO. Despite the reduction of PVR in heart failure, iNO could significantly increase LV end-diastolic stress. Its major mechanism appears to be volume shifts from the pulmonary vascular beds to the failing LV, which cannot sufficiently increase forward \dot{Q} rather than direct effects on the myocardium. Therefore, we may not be

able to expect the full beneficial effects of iNO in heart failure with serious LV dysfunction without significant pulmonary hypertension.

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