## High-Dose Intravenous Isosorbide-Dinitrate Is Safer and Better Than Bi-PAP Ventilation Combined With Conventional Treatment for Severe Pulmonary Edema

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**OBJECTIVE** To determine the feasibility, safety and efficacy of bilevel positive airway ventilation (BiPAP) in the treatment of severe pulmonary edema compared to high dose nitrate therapy. BACKGROUND Although noninvasive ventilation is increasingly used in the treatment of pulmonary edema, its efficacy has not been compared prospectively with newer treatment modalities. **METHODS** We enrolled 40 consecutive patients with severe pulmonary edema (oxygen saturation <90% on room air prior to treatment). All patients received oxygen at a rate of 10 liter/min, intravenous (IV) furosemide 80 mg and IV morphine 3 mg. Thereafter patients were randomly allocated to receive 1) repeated boluses of IV isosorbide-dinitrate (ISDN) 4 mg every 4 min (n = 20), and 2) BiPAP ventilation and standard dose nitrate therapy (n = 20). Treatment was administered until oxygen saturation increased above 96% or systolic blood pressure decreased to below 110 mm Hg or by more than 30%. Patients whose conditions deteriorated despite therapy were intubated and mechanically ventilated. All treatment was delivered by mobile intensive care units prior to hospital arrival. RESULTS Patients treated by BiPAP had significantly more adverse events. Two BiPAP treated patients died versus zero in the high dose ISDN group. Sixteen BiPAP treated patients (80%) required intubation and mechanical ventilation compared to four (20%) in the high dose ISDN group (p = 0.0004). Myocardial infarction (MI) occurred in 11 (55%) and 2 (10%) patients, respectively (p = 0.006). The combined primary end point (death, mechanical ventilation or MI) was observed in 17 (85%) versus 5 (25%) patients, respectively (p = 0.0003). After 1 h of treatment, oxygen saturation increased to 96  $\pm$  4% in the high dose ISDN group as compared to  $89 \pm 7\%$  in the BiPAP group (p = 0.017). Due to the significant deterioration observed in patients enrolled in the BiPAP arm, the study was prematurely terminated by the safety committee. CONCLUSIONS High dose ISDN is safer and better than BiPAP ventilation combined with conventional therapy in patients with severe pulmonary edema. (J Am Coll Cardiol 2000;36:832-7) © 2000 by the American College of Cardiology

Continuous positive airway ventilation (CPAP) and bilevel positive airway ventilation (BiPAP) are being increasingly used in the treatment of acute respiratory failure and pulmonary edema (1). However, to date and to our knowledge, no large randomized trials have compared this treatment with other treatment modalities. We have recently demonstrated (2) that the use of intravenous (IV) high dose isosorbide-dinitrate (ISDN) in the treatment of severe pulmonary edema improves control of respiratory failure, and reduces the need for mechanical ventilation and the rate of myocardial infarction (MI). Since the two treatment strategies are commonly used in our institution as well as other emergency departments in Israel, we have undertaken a study in which Bi-PAP ventilation combined with conventional treatment was compared to high dose ISDN in patients with severe pulmonary edema.

Ethical considerations dictated the different ISDN dose in the BiPAP and control group. Patients in the BiPAP arm were treated by BiPAP ventilation and continuous IV ISDN. High dose IV ISDN was not coadministered with BiPAP ventilation due to concerns about a possible hypotensive effect of such treatment combination. The use of standard-dose continuous IV ISDN as a single treatment method was considered unethical by the hospital review board due to the results of our previous study (2). Therefore, we compared in a prospective randomized study the efficacy and safety of BiPAP ventilation versus IV high dose nitrate therapy in patients with severe pulmonary edema.

#### **METHODS**

Between January and June 1999, 40 consecutive patients with severe pulmonary edema were recruited for the present study. The study protocol was approved by the hospital and national ethical review board. Severe pulmonary edema was defined as symptoms and signs of pulmonary edema accompanied by oxygen saturation of <90% measured by pulse

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Abbreviations and Acronyms					
ANOVA	= analysis of variance				
BiPAP	= bilevel positive pressure ventilation				
СК	= creatine phosphokinase				
CPAP	= continuous positive airway pressure				
EPAP	= expiratory positive airway pressure				
IPAP	= inspiratory positive airway pressure				
ISDN	= isosorbide dinitrate				
LVEDP	= left ventricular end diastolic pressure				
MI	= myocardial infarction				

oximetry upon hospital admission, prior to oxygen administration.

Exclusion criteria were as follows:

- previous treatment with nitrates above 40 mg/d, or mono-nitrates or long-acting tri-nitrates administered more than twice daily or short acting tri-nitrates administered more than three times a day;
- 2) previous treatment with furosemide >80 mg/d;
- 3) hypotension (blood pressure <110/70 mm Hg);
- 4) previous adverse effect of nitrates;
- 5) ST elevations consistent with acute MI on baseline ECG; and
- 6) absence of pulmonary edema on chest radiograph obtained on arrival to the emergency department.

On hospital admission, each patient was placed in sitting position and oxygen was administered by facemask with a rebreathing bag at a rate of 10 liter/min. An IV line was inserted and an IV bolus of morphine 3 mg and furosemide 80 mg was administered. Informed consent was obtained. Heart and respiratory rates, blood pressure and oximetric  $O_2$ saturation were obtained at baseline and every 3 min during treatment. Randomization was performed by assigning consecutive patients to one or other of the treatment groups according to their numerical order on a list that had been predetermined by lot.

Patients were randomized to receive one of two treatments:

1) BiPAP and conventional treatment (n = 20): the BiPAP was administered using a BiPAP ventilatory assist system (Respironics), a pressure-limited device that cycles between adjustable (up to 20 cm H<sub>2</sub>O) inspiratory and expiratory pressures using patient flow-triggered (S) mode. The inspiratory positive airway pressure (IPAP) was set at 8 cm  $H_2O$  initially, and the expiratory positive airway pressure (EPAP) was set at 3 cm H<sub>2</sub>O. Supplemental oxygen was blended in via a mask port at a rate of 10 liter/min. Patients were encouraged to coordinate their breathing with the ventilator. During the trial, IPAP was increased by 1 cm H<sub>2</sub>O every 3 to 4 min as tolerated and up to 12 cm H<sub>2</sub>O. Subsequent EPAP was increased by 1 cm H<sub>2</sub>O every 3 to 4 min up to 5 cm H<sub>2</sub>O. Patients were encouraged to use BiPAP for as long as tolerated, aiming for at least 50 min. Masks were tightened just enough to control air leakage. Concomitantly IV ISDN continuous drip was started with 10  $\mu$ mol/min and increased every 5 to 10 min by 10  $\mu$ mol/min.

 High dose IV ISDN (n = 20): IV ISDN, 4 mg-boluses, was administered every 4 min.

The randomization and treatment of pulmonary edema were administered by mobile intensive care unit teams in the patient's home or during delivery to the emergency department. During the study period, no other drug beside protocol study drugs was administered.

IPAP and EPAP as well as ISDN dose up-titration in group 1 and repeated ISDN boluses in group 2 were continued in both groups until the oxygen saturation increased above 96% or systolic blood pressure dropped below 110 mm Hg systolic or 30% below baseline levels. Patients with oxygen saturation below 80% despite therapy or increasing dyspnea accompanied by altered neurologic status were intubated and mechanically ventilated. Additional morphine was administered only prior to intubation.

Primary end points were as follows: adverse events including death, need for mechanical ventilation or MI within 24 h of hospital admission. Myocardial infarction was defined as an increase of CK to more than twice the upper limit of normal of our institution accompanied by an increase in CK-MB to >6%.

Secondary end points were as follows: speed of recovery from pulmonary edema as reflected by a decrease in pulse and respiratory rate and increase in oxygen saturation.

**Statistical analysis.** Comparison between the two treatment groups regarding baseline parameters, treatment and primary end points was performed using the two-tailed Student *t* test to compare continuous variables and the Fisher exact test to compare the distribution of categorical variables. Differences in O<sub>2</sub> saturation, respiratory and pulse rate changes over time were calculated by one-way analysis of variance (ANOVA) with repeated measures. Results are expressed as mean  $\pm$  SD. p values <0.05 were considered statistically significant.

#### RESULTS

Patient recruitment is presented in Figure 1. Baseline characteristics of patients in both groups are presented in Table 1. Treatment with IV ISDN, furosemide and morphine is presented in Table 2. The decrease in mean arterial blood pressure was similar in both groups (Table 3).

**Primary end point (clinical outcome).** Patients treated by BiPAP ventilation had significantly more adverse events. Two patients (10%) died in the BiPAP arm as compared to 0 (0%) in the high dose ISDN group (p = 0.49). These patients succumbed to complications of prolonged mechanical ventilation after 2 and 10 days from treatment. Mechanical ventilation was required during the first hour of treatment in 16 patients (80%) in the BiPAP group compared to 4 patients (20%) in the high dose nitrate group



Figure 1. Recruitment algorithm of the study (six month period).

(p = 0.0004). Myocardial infarction within 24 h of hospital admission was diagnosed in 11 patients (55%) in the BiPAP group compared to 2 patients (10%) in the high dose ISDN group (p = 0.006). Peak CK was 554  $\pm$  236 IU in the BiPAP group versus 104  $\pm$  95 IU in the high dose nitrates group (p = 0.0001). The combined end point (death, need for mechanical ventilation or MI within 24 h of admission) was observed in 17 patients (85%) in the BiPAP group as compared to 5 patients (25%) in the high dose ISDN group (p = 0.0003).

 Table 1. Baseline Characteristics of Patients

	High Dose ISDN	BiPAP	p Value
No. of Patients	20	20	
Age (yr)	$73 \pm 7$	$72 \pm 6$	NS
Gender distribution			NS
Male	10 (50%)	9 (45%)	
Female	10 (50%)	11 (55%)	
Risk factors			NS
Hypertension	12 (60%)	13 (65%)	NS
Diabetes mellitus	11 (55%)	13 (65%)	NS
Hyperlipidemia	8 (40%)	9 (45%)	NS
Positive family history of IHD	8 (40%)	7 (35%)	NS
Current smoker	6 (30%)	4 (20%)	NS
Cardiovascular history			
Prior MI	12 (60%)	14 (70%)	NS
Prior PTCA	2 (10%)	3 (15%)	NS
Prior CABG	5 (25%)	3 (15%)	NS
Echocardiographic findings			
Moderate aortic stenosis	1 (5%)	0 (0%)	NS
Moderate mitral regurgitation	4 (20%)	3 (15%)	NS
EF (%)	43 ± 6	45 ± 7	NS

BiPAP = bilevel positive pressure ventilation; CABG = coronary artery bypass grafting; EF = ejection fraction; IHD = ischemic heart disease; ISDN = isosorbide dinitrate; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

Table 2.	Concomitant	Treatment	During	Study	Period
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	High Dose ISDN	BiPAP	p Value
ISDN dose (mg)	$10.8 \pm 5.7$	$3.5 \pm 2.5$	0.0006*
Furosemide dose (mg)	$85 \pm 28$	$91 \pm 25$	0.47
Morphine dose (mg) BiPAP pressure	$2.5\pm1.6$	$2.2 \pm 2.4$	0.62
IPAP (mm Hg) EPAP (mm Hg)	(-) (-)	$9.3 \pm 2.3$ $4.2 \pm 3.1$	

\*p is significant (p < 0.05).

BiPAP = bilevel positive pressure ventilation; EPAP = expiratory positive airway pressure; IPAP = inspiratory positive airway pressure; ISDN = isosorbide dinitrate.

Secondary end points. The rate of improvement of signs of pulmonary edema was considerably slower in the BiPAP group compared to the high dose ISDN group (Table 3). In the ANOVA analysis, significant time trends were noticed in all three parameters (pulse and respiratory rate and oxygen saturation). In addition, interaction between treatment group and time trend was significant for the three parameters, implying that the change over time in the three treatment groups was significant. Oxygen saturation increased in the BiPAP group from 80  $\pm$  6% at baseline to  $89 \pm 7\%$  at 50 min compared to an increase from  $79 \pm 6\%$ to 96  $\pm$  4% in the high dose ISDN group (p = 0.017, Fig. 2). The respiration rate decreased in the BiPAP group from  $40 \pm 8$  breaths/min at baseline to  $36 \pm 11$  breaths/min at 50 min compared to a decrease from  $40 \pm 5$  breaths/min to  $31 \pm 6$  breaths/min in the high dose ISDN group (p = 0.011). Finally, the pulse rate decreased in the BiPAP group from  $128 \pm 10$  beats/min at baseline to  $121 \pm 18$  beats/min at 50 min compared to a decrease from  $126 \pm 15$  beats/min to  $104 \pm 14$  beats/min in the high dose ISDN group (p = 0.014).

**Study termination.** Due to the significantly high rate of adverse events in the BiPAP-treated group, the study was terminated in the first interim analysis by the safety committee.

#### DISCUSSION

The results of the present study. The results of the present study indicate that BiPAP ventilation combined with conventional treatment is significantly inferior to high-dose nitrates. This is manifested by increased rate of mechanical ventilation and MI and combined primary end point as well as decreased control of pulmonary edema as demonstrated by slower improvement in pulse and respiration rate and oxygen saturation. As mentioned previously, we have recently compared the use of high dose IV nitrates to conventional treatment in patients with severe pulmonary edema (2). Inclusion and exclusion criteria and baseline characteristics were similar in both studies. In both studies, high dose IV ISDN was administered in the same fashion. However, in the control group of the present study, we have added BiPAP ventilation to conventional treatment of pulmonary edema. A treatment arm with only conventional treatment was not incorporated in the present study due to

			Time (min)	Higł IS	n Dose DN	BiPAP
Mean arterial b	blood pressure (m	m Hg)	0	140	± 16	133 ± 26
	1	0.	10	130	$\pm 17$	$127 \pm 19$
			20	123	$\pm 16$	$120 \pm 14$
			30	119	$\pm 16$	$117 \pm 12$
			40	118	$\pm 16$	$116 \pm 12$
			50	118	± 19	$115 \pm 11$
Respiratory rate	e (breaths/min)		0	40	± 5	40 ± 8
			10	37	± 6	38 ± 8
			20	35	± 6	$37 \pm 9$
			30	34	± 6	$36 \pm 11$
			40	33	± 6	$36 \pm 11$
			50	31	± 6	$36 \pm 11$
Pulse rate (beat	ts/min)		0	126	$128\pm10$	
			10	122	$\pm 14$	$127 \pm 13$
			20	117	$\pm 14$	$124 \pm 15$
			30	112	$\pm 13$	$122 \pm 17$
			40	108	$\pm 14$	$121 \pm 18$
			50	104	$104 \pm 14$	
Oxygen saturat	ion (%)		0	79	$79 \pm 6$	
			10	86	$86 \pm 5$	
			20	90	± 5	$88 \pm 7$
			30	93	$\pm 4$	$88 \pm 7$
			40	95	± 4	$88 \pm 7$
			50	96	± 4	$89 \pm 7$
ANOVA Resu	llts					
	Respirato	ory Rate	Pulse	Rate	Oxygen	saturation
	F (5,34)	Р	F (5,34)	Р	F (5,34)	Р
Time	9.92	0.001*	11.67	0.001*	30.3	0.001*
	F (1,38)	Р	F (1,38)	Р	F (1,38)	Р
Treatment	NS	NS	3.93	0.054	5.23	0.028*
	F (5,34)	Р	F (5,34)	Р	F (5,34)	Р
Time X treatment	3.54	0.011*	3.37	0.014*	3.22	0.017*

Table 3. Changes in Secondary End Points During Study

\*p is significant (p < 0.05). BiPAP = bilevel positive pressure ventilation; ISDN = isosorbide dinitrate.

ethical considerations, since the outcome of patients treated by conventional treatment only was worse in our previous study. In both studies, the outcomes of patients treated by high dose IV ISDN were almost identical. The rate of mechanical ventilation and MI were 20% and 10%, respectively, in the present study as compared to 13% and 17% in the previous study. However, the outcome of the patients treated with BiPAP and conventional treatment in the present study is significantly worse than the outcome of patients treated with conventional treatment only in the previous study. The rate of mechanical ventilation and MI in BiPAP-treated patients in the present study was 80% and 55%, respectively, compared to 40% and 37% in the conventional treatment arm in our previous study.

Therefore, it seems that the addition of BiPAP ventilation to conventional treatment with standard-dose nitrates, furosemide and morphine is detrimental to patients with severe pulmonary edema.

Previous studies utilizing CPAP or BiPAP ventilation in pulmonary edema. The use of CPAP and BiPAP ventilation in the treatment of pulmonary edema has been reviewed recently (1,3). The results of most previous studies showed a moderate benefit in the use of CPAP regarding improved oxygenation, reduced need for mechanical ventilation and even reduced mortality. Therefore, CPAP was endorsed by many authors for the treatment of pulmonary edema (1,2,4). Ventilation with BiPAP has been examined previously in a few studies (5-7). Most of these studies recruited a small number of patients and the stratification of baseline characteristics was not balanced, making interpretation of the results difficult. However, it seems that BiPAP ventilation, by applying a higher inspiratory pressure and lower expiratory pressure, improves indexes of pulse and respiration rate and oxygen saturation more than CPAP ventilation, without any effect on the rate of mechanical ventilation. Some authors, however, have noticed an increased rate of MI (5,7).

Interpretation of the present study. Although extensively investigated throughout the century, the exact mechanism of pulmonary edema is still largely unknown. In most patients, cardiogenic pulmonary edema is caused by an acute increase of left ventricular end-diastolic pressure (LVEDP)



**Figure 2.** Changes in oxygen saturation during study period comparing the high dose IV ISDN Group and the BiPAP group.

that is transmitted backward to the pulmonary veins inducing fluid exudation to the pulmonary interstitium and alveoli. This increase in LVEDP is usually the result of acute ischemia, which decreases left ventricular diastolic function (thereby increasing LVEDP directly) and systolic function. It has recently been suggested (8) that pulmonary edema is the end result of a vicious cycle in which the decrease in cardiac output is compensated by peripheral vasoconstriction leading to an increase in systemic vascular resistance and afterload. However, if the peripheral vasoconstriction is excessive, the significant increase in afterload results in a further reduction in cardiac output leading to more vasoconstriction and afterload increase. This vicious cycle induces a progressive increase in LVEDP resulting in pulmonary edema. In the present study, high dose IV ISDN administration was more effective than BiPAP ventilation in controlling pulmonary edema. Intravenous nitrates at both standard and high doses induce venodilatation, therefore reducing LVEDP directly. However, when administered at high dose, nitrates induce significant arteriodilatation, therefore, reducing afterload (9) and increasing cardiac output (10). Accordingly, high dose nitrate administration by decreasing afterload may alleviate both the decrease in cardiac output and the increase in LVEDP. Furthermore, this reduction in LVEDP when combined with improved oxygenation (induced by a more rapid improvement of pulmonary congestion) may contribute to faster abortion of ischemia (if present) and prevention of MI.

However, BiPAP and CPAP ventilation improve control of pulmonary edema predominantly by their effect on the lung. These noninvasive ventilation methods improve pulmonary compliance (11,12), reduce atelectasis and intrapulmonary shunting and increase the functional residual capacity. The BiPAP ventilation, particularly, increases tidal volume even more than CPAP and reduces the work of breathing (13). The effects of CPAP and BiPAP on the cardiovascular system are controversial. Both increase intrathoracic pressure, which induces a decrease in preload and afterload. However, the increased intrathoracic pressure per se may reduce stroke volume directly. It is possible that this would lead to an increase in LVEDP, reduce control of pulmonary edema and increase the need for mechanical ventilation. The reduced control of pulmonary edema and elevated LVEDP may increase ischemia and rate of MI.

The results of the present study are in conflict with previous studies. This might be explained by the more severe pulmonary edema in the present cohort.

Baseline oxygen saturation of patients included in the present study was 80% corresponding to Po2 of <50 mm Hg while in most studies demonstrating the efficacy of CPAP and BiPAP ventilation, patients included had much higher baseline Po<sub>2</sub>. Furthermore, in both the present study and our previous one (2), the treatment of pulmonary edema was administered by mobile intensive care unit teams at the patient's home or in the ambulance. Accordingly, it is possible that the conditions of some of the patients treated in previous studies would have deteriorated significantly during the initial treatment and transportation, and they would have required intubation and mechanical ventilation prior to arrival to the emergency department. This would introduce a further bias, causing a recruitment drift toward milder cases in the previous studies, explaining the lower baseline oxygen saturation in the present study. Therefore, it is possible that noninvasive ventilation is effective only in patients with mild-to-moderate pulmonary edema. In such patients, the improved oxygenation achieved is probably sufficient to initiate a gradual improvement in the patient's clinical condition that is later enhanced throughout the gradual build-up of medical therapy.

However, in patients with severe pulmonary edema, the decrease in cardiac output and increase in LVEDP are probably more pronounced at baseline. In such patients, further decrease in stroke volume induced by increased intrathoracic pressure might be detrimental, resulting in patient condition deterioration toward respiratory failure, mechanical ventilation, ischemia and MI.

Therefore, the results of both the present study and our previous one (2) substantiate the notion that the target of treatment in severe pulmonary edema should be decreasing the excessive vasoconstriction and afterload, thereby improving cardiac output. This vasodilatation could be achieved by high dose nitrates and perhaps in the future with enthotelin antagonists. These treatment modalities should be preferred over the nonspecific and possibly harmful attempts to improve oxygenation by noninvasive positive pressure ventilation.

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#### Articles

### Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema

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#### Summary

**Background** Nitrates and furosemide, commonly administered in the treatment of pulmonary oedema, have not been compared in a prospective clinical trial. We compared the efficacy and safety of these drugs in a randomised trial of patients with severe pulmonary oedema and oxygen saturation below 90%.

Methods Patients presenting to mobile emergency units with signs of congestive heart failure were treated with oxygen 10 L/min, intravenous furosemide 40 mg, and morphine 3 mg bolus. 110 patients were randomly assigned either to group A, who received isosorbide dinitrate (3 mg bolus administered intravenously every 5 min; n=56) or to group B, who received furosemide (80 mg bolus administered intravenously every 15 min, as well as isosorbide dinitrate 1 mg/h, increased every 10 min by 1 mg/h; n=54). Six patients were withdrawn on the basis of chest radiography results. Treatment was continued until oxygen saturation was above 96% or mean arterial blood pressure had decreased by 30% or to below 90 mm Hg. The main endpoints were death, need for mechanical ventilation, and myocardial infarction. The analyses were by intention to treat.

**Findings** Mechanical ventilation was required in seven (13%) of 52 group-A patients and 21 (40%) of 52 group-B patients (p=0.0041). Myocardial infarction occurred in nine (17%) and 19 (37%) patients, respectively (p=0.047). One patient in group A and three in group B died (p=0.61). One or more of these endpoints occurred in 13 (25%) and 24 (46%) patients, respectively (p=0.041).

**Interpretation** High-dose isosorbide dinitrate, given as repeated intravenous boluses after low-dose intravenous furosemide, is safe and effective in controlling severe pulmonary oedema. This treatment regimen is more effective than high-dose furosemide with low-dose isosorbide nitrate in terms of need for mechanical ventilation and frequency of myocardial infarction.

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#### Introduction

Pulmonary oedema is a consequence of acute heart failure. This type of heart failure results from a sudden decrease in stroke volume, causing an increase in systemic vascular resistance, which in turn further reduces stroke volume, finally leading to pulmonary oedema.<sup>1</sup> A combination of furosemide and nitrates is the standard treatment for pulmonary congestion. However, the effects of these two drugs have not been compared in a controlled clinical trial.<sup>2</sup>

Furosemide, when administered intravenously, causes venodilatation after 15 min, thus decreasing the preload of both right and left ventricles.<sup>3</sup> Furosemide also induces diuresis, which starts 30 min after administration and peaks at 1-2 h.<sup>3-6</sup> However, furosemide also activates both the sympathetic and the renin angiotensin systems,<sup>7</sup> increasing peripheral resistance. This effect might increase afterload and have a negative effect on cardiac output<sup>6</sup> and stroke volume.

Nitrates are vasodilators. At low doses they induce only venodilatation, but as the dose is gradually increased they cause the arteries, including the coronary arteries, to dilate,<sup>8</sup> thereby decreasing both preload and afterload.

In theory, patients with pulmonary oedema may benefit from higher doses of nitrates. Patients with heart failure have nitrate resistance, and many require high doses of nitrates for everyday treatment.9 Furthermore, since at high doses nitrates induce both general and coronary arteriodilatation, they reduce both preload and afterload and potentially increase cardiac output.6 In our study of the effects of high-dose nitrates administered as repeated intravenous boluses in the treatment of unstable angina, 33% of patients had significant pulmonary congestion that rapidly resolved on treatment with high-dose nitrates.<sup>10,11</sup> In a preliminary study, Bosc and colleagues<sup>12</sup> administered isosorbide dinitrate as an intravenous 3 mg bolus to patients with cardiogenic pulmonary oedema, with good clinical response. We therefore used this regimen in our study.

The effect of intravenous isosorbide dinitrate peaks 5 min after administration.<sup>13</sup> Administration of intravenous furosemide causes dilatation after 15 min and diuresis that starts within 30 min and peaks at 1-2 h.<sup>3</sup> We therefore compared the effect of isosorbide dinitrate administered intravenously as a 3 mg bolus every 5 min (combined with low-dose furosemide) with that of furosemide, administered intravenously as an 80 mg bolus every 15 min (combined with low-dose nitrates), in the treatment of severe pulmonary oedema. The use of both drugs in both treatment groups, albeit in different ratios, was dictated by restrictions imposed by the hospital and national ethics committees who approved the study design.



Figure 1: Trial profile

#### Methods

#### Patients

Patients were recruited from the Emergency Medical Services of the cities of Rishon-le-Tzion, Ramla, and Lod (total population about 250 000). All were screened by a physician and a paramedic for signs and symptoms of congestive heart failure, and all underwent electrocardiography (ECG) and chest radiography. Inclusion criteria were the presence of clinical pulmonary oedema that was confirmed by chest radiographic findings in the emergency room, and oxygen saturation of less than 90%, measured by pulse oximetry before oxygen administration, with the patient sitting. Exclusion criteria were current treatment with oral nitrates in excess of 40 mg daily, isosorbide mononitrate more than twice daily, isosorbide trinitrate more than three times daily; current furosemide treatment in excess of 80 mg daily; blood pressure below 110/70 mm Hg; and previous adverse reaction to the study drugs.

#### Treatment protocol

Since both nitrates and furosemide are deemed essential in the treatment of acute heart failure, we were obliged, for ethical reasons, to include both of them in both treatment groups, though in different ratios. The study was designed to compare the effects of therapy with two different combinations of nitrates and furosemide administered intravenously in patients with acute heart failure, one group of patients being treated mainly with nitrates and the other mainly with furosemide.

On admission, each patient was placed in the sitting position and oxygen was administered by face mask with a rebreathing bag at a rate of 10 L/min. An intravenous line was inserted and a bolus of morphine 3 mg and furosemide 40 mg was given. Informed consent was obtained. Heart and respiratory rates, blood pressure, and oximetric oxygen saturation were obtained at baseline and every 3 min during treatment. Randomisation was done by assigning consecutive patients to one or other of the treatment groups according to their numerical order on a list that had been predetermined by lot.

In addition to this initial treatment, patients in group A (n=52) received a 3 mg bolus of isosorbide dinitrate every 5 min. Patients in group B (n=52) received an 80 mg bolus of furosemide every 15 min and isosorbide dinitrate 1 mg/h

	Group A (n=52)	Group B (n=52)
Mean (SD) age in years	74 (9)	74 (9)
Sex		
Male	26 (50%)	28 (54%)
Female	26 (50%)	24 (46%)
Risk factors		
Hypertension	28 (54%)	23 (44%)
Diabetes mellitus	20 (38%)	22 (42%)
Ischaemic heart disease	31 (60%)	36 (69%)
Current smoker	16 (31%)	15 (29%)
Mean (SD) clinical features		
Mean arterial blood pressure (mm Hg)	132 (19)	124 (24)
Heart rate (beats/min)	117 (18)	113 (22)
Respiratory rate (breaths/min)	42 (17)	35 (8)
Oxygen saturation (%)	78 (8)	79 (7)
Current treatment		
Nitrates	40 (77%)	43 (83%)
Mean dose (mg/16 h)	25.8 (17.7)	26·9 (15·1)
Furosemide	45 (87%)	44 (85%)
Mean dose (mg)	52·7 (27·0)	53·0 (24·0)
β-blockers	28 (54%)	24 (46%)
ACE inhibitors	44 (85%)	46 (88%)
Calcium blockers	10 (19%)	13 (25%)
Digoxin	12 (23%)	11 (21%)
ECG		
Q waves	12 (23%)	10 (19%)
ST depressions	19 (37%)	18 (35%)
T-wave inversions	19 (37%)	14 (27%)
Echocardiography*		
Aortic stenosis	5 (10%)	6 (12%)
Mitral stenosis	2 (4%)	2 (4%)
Mitral regurgitation	14 (27%)	9 (17%)
Mean (SD) ejection fraction (%)	42.3 (11.0)	42.7 (13.0)

ACE=angiotensin-converting enzyme.

\*Valvular lesions reported if moderate or worse

# Table 1: Baseline characteristics of participants in group A(predominant isosorbide dinitrate) and group B (predominantfurosemide)

(16  $\mu$ g/min) increased by 1 mg/h every 10 min. Treatment was continued in both groups until oxygen saturation increased to at least 96% or mean arterial blood pressure decreased by at least 30% or to lower than 90 mm Hg.

Intubation and mechanical ventilation were used for patients whose oxygen saturation remained below 80% for more than 20 min; those who had progressive deterioration of oxygen saturation to below 80%; and those with progressive dyspnoea, apnoea, or severe arrhythmias despite treatment. Additional morphine was administered only before intubation.

ECG examination was repeated 24 h after admission and as required during the stay in hospital. Creatine phosphokinase values were measured on admission to the emergency room and 24 h later. Echocardiography was undertaken for all patients during the hospital stay.

#### Outcome measures

The main outcome measures were death in hospital, need for mechanical ventilation within 12 h of admission, and development of myocardial infarction within 24 h of admission. Myocardial infarction was defined as the appearance of new Q waves on ECG or an increase in value of creatine phosphokinase above our upper normal value (150 IU/L) with an MB fraction greater than 6%. Patients were also monitored for adverse events, such as severe bradyarrhythmia or tachyarrhythmia or excessive reduction of mean blood pressure

Primary outcome	Group A (n=52)	Group B (n=52)	р
Died	1 (2%)	3 (6%)	0.61
Required mechanical ventilation	7 (13%)	21 (40%)	0.0041
Myocardial infarction	9 (17%)	19 (37%)	0.047
Any adverse event	13 (25%)	24 (46%)	0.041

Table 2: Results for primary outcome measures in group A (predominant isosorbide dinitrate) and group B (predominant furosemide)



Figure 2: Change in oxygen saturation during treatment in group A (predominant isosorbide dinitrate) and group B (predominant furosemide)

beyond the defined goal of 30% below baseline or below 90 mm Hg.

Secondary outcome measures were changes in heart rate, respiratory rate, and oxygen saturation during the first hour of treatment.

#### Statistical methods

100

90

65

Analyses were by intention to treat. Student's two-tailed t test was used to compare continuous variables, the paired t test to compare paired variables, and the  $\chi^2$  test to compare the distribution of categorical variables. Differences in heart and respiratory rates and changes in oxygen saturation over time were calculated by one-way ANOVA with repeated measures. p values lower than 0.05 were considered significant. The sample size (about 50 patients in each treatment group) was chosen to detect a 30-50% decrease in the rate of mechanical ventilation and myocardial infarction.

#### Results

Between July 1, 1996, and June 30, 1997, 446 patients with symptoms and signs that suggested acute heart failure were screened by the Emergency Medical Services team (figure 1). We excluded 64 who had severe pulmonary oedema with respiratory failure that required immediate tracheal intubation and mechanical ventilation; 153 who had mild pulmonary congestion with oxygen saturation above 90% on admission; and 119 who met one or more of the exclusion criteria. Of the 110 patients who were randomly assigned to the two treatment groups, six were later excluded because the findings on chest radiography were not compatible with pulmonary congestion. Thus, 104 patients were finally enrolled in the study. Their baseline characteristics and current drug therapy are shown in table 1. The only significant difference between the randomised groups was in respiratory rate.

The mean dose of isosorbide dinitrate administered during treatment was 11.4 (SD 6.8) mg in group A and 1.4 (0.6) mg in group B. The mean furosemide doses were 56 (28) mg and 200 (65) mg, respectively.

Apart from sinus tachycardia and mild, transient episodes of sinus bradycardia, no severe arrhythmias were recorded during drug treatment. The mean arterial blood pressure decreased from 132 (14) mm Hg to 107 (15) mm Hg (mean reduction 19% [SD 9]; p<0.0001) in group A and from 124 (24) mm Hg to 103 (19) mm Hg in group B (15% [5]; p<0.0001). The difference between the groups was not significant (p=0.26). Mean arterial blood pressure decreased excessively (>30%) in five (10%) patients in group A and in seven (13%) in group B (p=1.0), but no patient had a decrease to below 85 mm Hg or required specific treatment for hypotension. The rates of mechanical ventilation, myocardial infarction, and increase in oxygen saturation in these patients were similar to those in the rest of the respective group.

Tracheal intubation and mechanical ventilation were required in significantly fewer patients in group A than in group B (p=0.0041; table 2). Myocardial infarction also occurred in significantly fewer patients in group A than in group B (p=0.047). There was one death in group A and three in group B (p=0.61). The composite endpoint (ie, one or more of the three main outcome measures-death, mechanical ventilation, or myocardial infarction) was recorded in 13 (25%) patients in group A and in 24 (46%) in group B (p=0.041).

The improvements in all three secondary outcomespulse rate, respiratory rate, and oxygen saturation (figure 2)—were significantly better in group A than in group B (table 3).

#### Discussion

We undertook this study of patients who, before hospital admission, were treated in a mobile intensivecare unit for pulmonary oedema, to compare the safety and clinical efficacy of nitates and furosemide in the treatment of severe pulmonary oedema in a prospective randomised investigation.

The treatment protocol was designed not only to achieve rapid resolution of pulmonary oedema, but also to avoid significant hypotension. Treatment was administered in a stepwise way under stringent bloodpressure control. This precaution was needed because, in this cohort of patients with acute heart failure, 64% had ischaemic heart disease. In such patients, significant hypotension might result in coronary hypoperfusion, which could increase the degree of ischaemia and thus lead to a further reduction of cardiac output. The mean reductions in arterial blood pressure were within the prespecified range, which is probably the preferred range for providing relief of pulmonary oedema without jeopardising coronary perfusion. Only five patients in group A and seven in group B had excessive reductions in arterial blood pressure (>30%), and even in those patients the efficacy of the treatment regimens in controlling pulmonary oedema was not reduced. Furthermore, no arrhythmic or other severe adverse

Variable Group A			Group B (n=52)			p*	
	Before treatment	After treatment	Change	Before treatment	After treatment	Change	
Pulse (beats/min)	117 (18)	102 (15)	-15 (12)†	113 (22)	104 (19)	-9 (14)†	0.024
Respiratory rate (breaths/min)	42 (17)	31 (14)	-11(7)†	35 (8)	30 (8)	-5 (6)†	<0.0001
Oxygen saturation (%)	78 (8)	96 (7)	18 (9)†	79 (7)	92 (10)	13 (9)†	0.0063

\*For difference in mean change between group A and group B. + p<0.0001 for change.

Table 3: Results for secondary outcome measures in group A (predominant isosorbide dinitrate) and group B (predominant furosemide)

events were recorded during treatment in either group. We therefore conclude that both treatment regimens were safe.

Ethical considerations dictated the use of both furosemide and isosorbide dinitrate, albeit in different ratios, in both groups of patients. However, we believe that in the final protocol we succeeded in producing two treatment groups in which one of the drugs was predominant. Patients in group A received eight times more isosorbide dinitrate than those in group B, whereas patients in group B received four times more furosemide than those in group A.

We do not believe that the administration of low-dose furosemide in the isosorbide dinitrate group (group A) and of low-dose isosorbide dinitrate in the furosemide group significantly affected the study results, for three main reasons. First, the two study groups were well matched for all relevant variables, the only difference between them being in the amount of the study drugs administered, yet the two groups differed in terms of all major and minor outcome measures. Second, most of the patients in both groups had been on background treatment with furosemide and long-acting nitrates before the study (table 1). On admission to the study, group-A patients (predominant isosorbide dinitrate) received, on average, 56 (28) mg furosemide, a dose almost identical to the background daily dose. During first hour of treatment, group-B patients the (predominant furosemide) received 1.4 (0.6) mg isosorbide dinitrate, almost identical to their background dosage (26.9 [15.1] mg nitrates over 16 h, equivalent to 1.6 mg/h). Third, nitrates have different effects at high and low doses.8 At low doses nitrates induce only venodilatation, reducing mainly the preload. At higher doses, such as those administered in group A, they induce arteriodilatation,<sup>10,11</sup> reducing afterload and potentially increasing cardiac output. Therefore, the effect of the high doses of nitrates administered in the isosorbide dinitrate group is likely to be very different from that of the lower doses administered in the furosemide group.

We therefore believe that the two treatment regimens used in this study adequately reflect the differential effects of isosorbide dinitrate and furosemide in the treatment of severe pulmonary oedema.

Substantial relief of congestive symptoms was achieved in both treatment groups. However, the effect of treatment in group A was greatly superior to that in group B (tables 2 and 3).

The regimen applied in group B (furosemide, morphine, and low-dose nitrates) is the classic approach to the treatment of pulmonary oedema. This treatment combination causes mainly venodilatation and therefore reduction of preload. Exactly how relief of pulmonary oedema is achieved by this treatment regimen is not known. Atherton and colleagues14 have suggested that the reduction of right-ventricular preload as a result of the decrease in right-ventricular volume may lead to an increase in left-ventricular volume, thereby inducing an increase in left-ventricular stroke volume. We did not measure the diuretic response to treatment, since it is not our usual practice to insert urinary catheters in patients with pulmonary oedema. However, data from previous studies<sup>3-6</sup> suggest that the diuretic effect of furosemide starts only 30 min after administration and peaks at 1-2 h. Since we assessed the effects of

treatments mainly during the first 60 min, we believe that the contribution of diuresis was not significant.

Higher doses of nitrates cause arteriodilatation, reducing systemic peripheral resistance and thus also afterload.<sup>8</sup> The decrease in afterload, by increasing cardiac output, might further relieve the acute heart failure and improve pulmonary congestion.<sup>6</sup> Accordingly, we suggest that high-dose nitrates, by causing reductions in both preload and afterload, may confer better relief of severe pulmonary oedema than furosemide.<sup>2</sup> Our findings support this hypothesis.

Our results indicate that the administration of intravenous boluses of high-dose nitrates is safe and effective in the treatment of severe pulmonary oedema. However, the ideal dose of furosemide remains to be determined. Control of pulmonary oedema in the group that received an average furosemide dose of 200 mg (group B) was less effective than that in group A (average furosemide dose 56 mg), which implies that higher doses of furosemide are not beneficial in the treatment of severe pulmonary oedema. We should emphasise that the mean dose of furosemide used for group-A patients was higher than that specified by the treatment protocol, owing to protocol violations by physicians who felt that the patient "needed more furosemide" for the control of pulmonary oedema. Whether further reduction in furosemide dose in the treatment of severe pulmonary oedema is feasible therefore remains to be investigated.

Nitrates are traditionally used in the treatment of acute heart failure and unstable angina. They are known to be effective in reducing angina and improving left-ventricular function.<sup>15</sup> However, their effectiveness in reducing ischaemia and in aborting myocardial infarction is controversial. We have shown previously that the intravenous administration of boluses of high-dose nitrates to patients with unstable angina reduces ischaemia clinically and on ECG.<sup>11</sup> In that study, the rate of myocardial infarction was reduced by 35% after treatment with high-dose nitrates, but this effect was not statistically significant.

In this study, the rate of myocardial infarction showed a significant difference of 53% in favour of the group receiving high-dose nitrates. Although we did not monitor ECG changes during treatment, the results of our previous study suggest that the administration of high-dose nitrates, by causing a more rapid resolution of ischaemia, may contribute to the rapid resolution of the heart failure and the reduction in myocardial-infarction rate. We therefore believe that the intravenous administration of boluses of high-dose nitrates to patients in acute heart failure induces rapid resolution of ischaemia, thereby reducing the rate of myocardial infarction and contributing to a more rapid resolution of congestion.

The intravenous administration of high-dose isosorbide dinitrate as repeated 3 mg boluses is more effective than furosemide treatment in controlling severe pulmonary oedema and reduces the need for mechanical ventilation. High-dose nitrate treatment may be more effective than furosemide in reducing the incidence of myocardial infarction.

#### Contributors

All the investigators were involved in the design of the study. In addition, Gad Cotter, Einat Metzkor, Rami Miller, Avi Simovitz, Ori Shahan, Doron Marghitay, Maya Koren, and Alex Blatt carried out the investigations and, with Yaron Moshkovitz, collected the data; Gad Cotter, Einat Betzkor, Edo Kaluski, Zwi Faigenberg, Maya Koren, Alex Blatt, Yaron Moshkovitz, Ronit Zaidenstein, and Ahuva Golik interpreted the findings; and Edo Kaluski, Zwi Faigenberg, Ronit Zaidenstein, and Ahuva Golik were responsible for safety monitoring. Gad Cotter, Einat Metzkor, Edo Kaluski, Maya Koren, Alex Blatt, Yaron Moshkovitz, Ronit Zaidenstein, and Ahuva Golik wrote the paper.

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## Nitrate Therapy Is an Alternative to Furosemide/Morphine Therapy in the Management of Acute Cardiogenic Pulmonary Edema

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#### ABSTRACT

**Background:** Nitrates are superior to furosemide in the management of acute pulmonary edema associated with myocardial infarction; however, their role in the absence of infarction is unclear. **Methods and Results:** A randomized comparison was undertaken of the relative effectiveness of primary therapy with either intravenous morphine/furosemide (men/women; n = 32) or nitroglycerin/*N*-acetylcysteine (NTG/NAC; n = 37) in consecutive patients with acute pulmonary edema. The primary end point was change in Pao<sub>2</sub>/Fto<sub>2</sub> over the first 60 minutes of therapy. Secondary end points were needed for mechanical respiratory assistance (ie, continuous positive airway pressure via mask or intubation and ventilation) and changes in other gas exchange parameters. Both treatment groups showed improvement in oxygenation after 60 minutes of therapy; however, this reached statistical significance only with NTG/NAC therapy. There was no significant difference between groups in the assessed parameters (95% Cl for differences in Pao<sub>2</sub>/Fto<sub>2</sub>: furosemide/morphine -12 to 23 and NTG/NAC 4 to 44), a finding also confirmed in 32 patients presenting with respiratory failure. Only 11% of the study group required mechanical ventilatory assistance (continuous positive airway pressure in 4 patients and intubation and ventilation in 3 patients).

**Conclusions:** NTG/NAC therapy is as effective as furosemide/morphine in the initial management of acute pulmonary edema, regardless of the presence or absence of respiratory failure. The necessity for mechanical ventilatory assistance is infrequent in these patients, regardless of the initial medical treatment regimen.

Key words: acute pulmonary edema, acute heart failure, diuretics, nitrate tolerance.

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The management of acute cardiogenic pulmonary edema is familiar to most practicing physicians. Morphine, diuretics, and oxygen are the fundamentals of current treatment prescribed by standard texts, such as the *Oxford Textbook of Medicine* (1). However, it is surprising that there are few available controlled trial data to establish the optimal management of acute pulmonary edema, a condition that represents almost 3% of hospital admissions to a general regional hospital (2).

Thus, in an era when evidence-based medicine is the major goal and the randomized trial the major assessment tool of therapeutics, the management of acute pulmonary edema seems to have been neglected. Therapies such as furosemide or nitrates have been assessed by small, open-labeled observational studies, whereas some treatments (such as morphine) have not been assessed in formal clinical trials. Furthermore, the available randomized studies have focused on treatment of patients with pulmonary edema associated with acute myocardial infarction, yet this subgroup represent fewer than 15% of all acute pulmonary edema patients (2–4).

Nitrates have been shown to be hemodynamically superior to furosemide in the management of pulmonary edema complicating acute myocardial infarction (5,6). The theoretical advantages of nitrates over furosemide in the management of acute pulmonary edema are: (1) they have better hemodynamic properties, thereby producing a balanced reduction in preload and afterload) (7), whereas furosemide may increase afterload (8), probably via activation of the sympathetic and renin-angiotensin systems and (2) they have antiischemic properties that may be beneficial in acute pulmonary edema (7). The implications of these hemodynamic effects in the management of pulmonary edema occurring in the absence of acute myocardial infarction are unknown.

The objective of this study was to compare intravenous furosemide/morphine (F/M) with intravenous nitroglycerin/*N*-acetylcysteine (NTG/NAC) in patients with acute cardiogenic pulmonary edema but without electrocardiographic evidence of acute myocardial infarction (ie, ST elevation), using their effects on oxygenation as a primary end point. Other clinical markers of acute cardiac failure were examined as secondary end points.

NAC is a sulfhydryl donor that potentiates the antiischemic (9,10) and preload-reducing (11,12) effects of NTG. We performed pilot evaluations of NTG/NAC in patients with acute pulmonary edema, which suggested beneficial effects. NAC is also potentially useful if prolonged nitrate therapy is required, because it may reduce the risk of the subsequent development of nitrate tolerance (11,13,14).

Because acute pulmonary edema has a spectrum of severity, we also elected to prospectively compare the efficacy of the therapeutic regimens in patients with admission blood gas criteria for respiratory failure, because these patients would potentially receive the greatest benefit from the treatment.

#### **Materials and Methods**

In a prospective open-label randomized design study, we examined consecutive patients admitted to hospital with acute cardiogenic pulmonary edema, comparing F/M with NTG/NAC, with respect to clinical status, gas exchange, failure of therapy, and the need for supplementary respiratory assistance (ie, intubation and mechanical ventilation or continuous positive airway pressure [CPCP] by face mask). Informed consent was not sought when the patients first presented because of the nature of the disease but was obtained as soon as possible after study entry (ie, within the first hour of therapy). The study was approved by the Institutional Ethics Committee of Human Research and the difficulty with delayed informed consent accepted, because both therapies were in common clinical use in the hospital.

#### **Patient Selection**

Selection criteria for patients presenting to the emergency department were:

1. Acute onset of dyspnea within the preceding 6 hours

2. Clinical findings consistent with pulmonary edema including tachypnea; signs of increased respiratory work, as indicated by use of accessory muscles; gallop rhythm; widespread crepitations in the absence of any history of chest infection; or aspiration

3. Radiological evidence of pulmonary edema, as defined by Kostuk et al. (15)

Patients with the following features were excluded from the study:

1. History suggestive of noncardiogenic pulmonary edema

2. Cardiogenic shock, defined on the basis of a systolic blood pressure of  $\leq 90 \text{ mmHg}$ 

3. Overt acute myocardial infarction as evidenced by ST segment elevation or severe anginal pain necessitating treatment with intravenous nitrates and/or morphine 4. Severe valvular heart disease

5. Past history of obstructive airways disease with known  $CO_2$  retention

6. Clinical status requiring immediate intubation

7. Cardiac arrhythmias requiring immediate cardio-version

8. Known chronic renal failure (creatinine >250  $\mu$ mol/L)

#### **Study Protocol**

On arrival at the emergency department, patients were immediately given 50% oxygen via a Multi-Vent mask (Hudson Inc, Temecula, CA), intravenous access established, arterial and venous samples taken for blood gas, electrolyte and cardiac enzyme estimations taken, electrocardiogram performed, baseline clinical parameters assessed, and if suitable, randomized to F/M or NTG/ NAC therapy. Trial therapy was then instituted and a chest radiograph performed. reassessment of patients' status was performed after 30 minutes, 60 minutes, 3 hours, and 24 hours.

#### Medical Therapy

Patients randomized to F/M therapy were given a 40 mg intravenous furosemide bolus as de novo therapy or twice the individual patient's previous daily maintenance dose. An equivalent second dose was administered at 60 minutes if there was an inadequate response from the initial bolus. Further increments could be administered in the subsequent 3- to 24-hour period if required. Morphine was given by slow intravenous injection (1-2 mg/5 min) to a maximum dose of 10 mg.

Patients randomized to NTG/NAC therapy received intravenous NTG at 2.5  $\mu$ g/min simultaneously infused with NAC at 6.6  $\mu$ g/min over a 24-hour period via volumetric infusion pumps (I-med 960, San Diego, CA; Milton). Provided that systolic blood pressure was stable, the NTG infusion rate could be increased to 5  $\mu$ g/min after 15 minutes and/or 10  $\mu$ g/min at 60 minutes if there was an inadequate clinical response.

No additional therapy was used unless it was considered that there had been failure of the initial treatment regimen (see below). Preadmission medical therapy was adjusted as follows:

1. Calcium antagonists and  $\beta$ -adrenoceptor antagonists were ceased

2. Oral diuretics and angiotensin-converting enzyme inhibitors were continued

3. Long-acting nitrates were continued in patients randomized to F/M but ceased in the NTG/NAC patients

4. Other usual maintenance therapy including theophylline and aspirin was continued.

Maintenance of oral diuretics and long-acting nitrates were not administered in the first hour of therapy.

#### **Parameters Assessed**

Response to therapy was assessed on the basis of: (1) clinical status (2) gas exchange, and (3) necessity for supplementary respiratory assistance. Clinical status assessment involved measurement of the respiratory rate, pulse rate, and blood pressure, as well as quantifying clinical observations by using a scoring system (16) for dyspnea, sweating, and pulmonary crepitations (see Appendix for details). Acute myocardial infarction was defined on the basis of elevation of plasma creatine kinase concentration to at least twice the upper limit of the reference range. Other clinical variables, such as the duration of hospital admission, were also recorded.

Gas exchange was assessed by arterial blood measurement of pH,  $Pao_2$ , and  $Paco_2$  at the above time intervals. The inspiratory oxygen concentration was noted for each sample to permit calculation of a normalized  $Pao_2/Fio_2$  ratio (17). The primary end point of the study was change in  $Pao_2/Fio_2$  ratio over the first hour of therapy.

Patients who continued to deteriorate clinically with blood gas criteria for respiratory failure, despite 50% oxygen therapy and the randomized medical therapy, were considered to have failed medical therapy and could also receive clinically appropriate adjunctive therapy, such as mechanical ventilatory assistance.

#### **Data Analysis**

The major purpose of this study was to compare the randomized treatment regimens on an intention to treat basis with respect to gas exchange parameters. Hence, the primary end point was the relative change in Pao<sub>2</sub>/ Fio<sub>2</sub> over the first 60 minutes after study entry. These changes were also examined in a prospectively defined subgroup, (ie, those with respiratory failure defined on admission blood gas criteria as Pao<sub>2</sub> <60 mmHg or Paco<sub>2</sub> >55 mmHg).

Sizing of the study population was based on the probability of detecting a 10 mmHg difference in Pao<sub>2</sub> (approximately equivalent to a difference of 20 units in Pao<sub>2</sub>/Fio<sub>2</sub> ratio) between treatment groups 1 hour post onset of therapy. Previous studies (18–22) have shown a standard deviation of 8 to 12 mmHg in the Pao<sub>2</sub> for patients with acute pulmonary edema. On the basis of a standard deviation of 12 mmHg, a target sample size number of 62 patients would provide a 90% power at the  $\alpha = 0.05$  level for detection of the above-mentioned Pao<sub>2</sub> difference between groups.

To determine whether differences in baseline characteristics existed between treatment groups, comparison of nonparametric data was performed by using a Mann-Whitney U Test and an unpaired *t*-test for parametric data. The nonparametric clinical scores data were compared by using the Friedman test. Parametric data were compared by using a repeated measures analysis of variance (23). Statistical significance was defined at the  $\alpha <$ 0.05 level. Results for normally distributed data are expressed as means  $\pm$  SD.

#### Results

Over a 16-month period, 87 consecutive patients presented to the emergency department with acute pulmonary edema. Eighteen patients were not enrolled because of exclusion criteria (ie, coexistent acute transmural [ST elevation] myocardial infarction in 10 patients, chronic renal failure in 3 patients, requirement for immediate intubation in 4 patients, and 1 patient unable to provide informed consent because of profound deafness.

Of the 69 patients enrolled, 4 were subsequently shown not to have acute pulmonary edema, with the final diagnoses being obstructive airways disease in 2 patients, septicemia in 1 patient, and lung carcinoma in 1 patient. However, all were included in the intention to treat analysis. Patients were generally elderly (77  $\pm$  8 years); 54% had a past history of congestive heart failure and 57% were receiving diuretics before study entry. Mean left ventricular ejection fraction was 40  $\pm$  14%. Although more than one-third of patients with previously diagnosed cardiac failure were receiving angiotensinconverting enzyme inhibitors on admission, all patients with documented left ventricular dysfunction were discharged on these medications.

Thirty-two patients were randomized to F/M therapy and 37 to NTG/NAC. These study groups were similar in their baseline clinical characteristics, with the exception that prior digoxin therapy had been used in a higher proportion (P = .01) of patients treated with F/M (Table 1). Baseline clinical (Table 2) and gas exchange (Table 3) parameters also did not vary significantly between treatment groups. Patients randomized to F/M therapy received a median dose of 80 mg intravenous furosemide and 3 mg intravenous morphine over the first hour. Those randomized to NTG/NAC received a median infusion rate of 2.5 µg/min of NTG over the first hour.

Sixty minutes after the initiation of therapy, clinical (dyspnea and crepitations score, respiratory rate, pulse rate, and systolic blood pressure; Table 2) and gas exchange (pH, Pao<sub>2</sub>/Fio<sub>2</sub> ratio, and Paco<sub>2</sub>; Table 3) parameters had significantly improved (ANOVA, P < .01), regardless of the randomized therapy. Comparison between therapies showed no significant differences in clinical or gas exchange parameters. However, only the NTG/NAC group showed a significant improvement (P < .05) in Pao<sub>2</sub>/Fio<sub>2</sub> ratio over the first hour of treatment (mean and 95% confidence intervals on improvement in Pao<sub>2</sub>/Fio<sub>2</sub> ratio: F/M 5, -12 to +23, NTG/NAC 24, 4-+44; ANOVA, P = .169) (Fig. 1).<sup>5</sup>

Over the following 23-hour period, clinical and gas exchange parameters continued to improve with no significant difference between therapies (Tables 2 and 3). Only seven patients required respiratory assistance (CPAP in four patients and intubation + ventilation in three patients), with no difference between the study

Table 1. Baseline Characteristics of Study Population

Characteristic	F/M	NTG/NAC
n	32	37
Age (yrs)	$77\pm 6.6$	$76 \pm 9$
Ratio of men to women	14:18	17:20
Past History		
Ischemic heart disease	11 (34%)	15 (41%)
Chronic heart failure	17 (53%)	20 (54%)
Acute pulmonary edema	11 (34%)	15 (41%)
Diabetes	12 (38%)	14 (38%)
Hypertension	18 (56%)	13 (35%)
Admission drug therapy		
Nitrates	11 (34%)	12 (32%)
Diuretics	18 (56%)	21 (57%)
Calcium antagonists	9 (28%)	8 (22%)
β-Adrenoceptor		
antagonists	4 (13%)	3 (8%)
Aspirin	9 (28%)	7 (19%)
Digoxin*	10 (31%)	3 (8%)
ACE inhibitors	10 (31%)	11 (30%)

\* Delineates significant differences between treatment groups. (P < .05).

n = 69. Values refer to number of patients (except where otherwise stated) with the particular characteristic for each randomized treatment. ACE, angiotensin-converting enzyme; F/M, furosemide/morphine;

NTG/NAC, nitroglycerin/N-acetylcysteine.

groups. Acute myocardial infarction occurred in 10 (14%) patients, of whom 4 (12%) were treated with F/M and 6 (16%) were treated with NTG/NAC. Duration of hospitalization (overall mean 5.6  $\pm$  3.0 days) did not vary between treatment groups. There were three inhospital deaths during the study, none attributed to acute cardiogenic pulmonary edema.

Thirty-two of the patients had blood gas criteria for respiratory failure at enrolIment; 17 were randomized to F/M and 19 to NTG/NAC. Again, treatment groups were well matched on baseline characteristics. Clinical parameters improved significantly after 60 minutes of medical therapy, although the Pao<sub>2</sub>/Fio<sub>2</sub> ratio did not improve significantly until 3 hours. Comparison between therapies revealed no difference in the first 60 minutes of treatment in clinical parameters, gas exchange parameters (Fig. 2), the number of patients requiring respiratory assistance, or in the duration of hospital stay. All patients eventually requiring respiratory assistance had initial blood gas criteria for respiratory failure.

#### Discussion

This randomized investigation is the first comparison of nitrate-based therapy with diuretic based acute therapy in patients presenting with acute cardiogenic pulmonary edema in the absence of clinical evidence of acute infarction. The patient cohorts were similar to those described in other recent studies (2,24). Interestingly, preadmission therapy in approximately 50% of patients

Parameter	0 min	30 min	60 min	3 hr	24 hr
Dyspnea Score (0–3)*		<u></u>			
F/m	$3.0 \pm 0.2$	$2.6 \pm 0.7$	$2.2 \pm 0.9$	$1.2 \pm 1.0$	$0.3 \pm 0.7$
NTG/NAC	$2.8\pm0.5$	$2.3 \pm 0.8$	$2.0 \pm 1$	$1.4 \pm 1.0$	$0.3\pm0.6$
Respiratory rate (breaths/min)					
F/m	$35 \pm 7$	$30 \pm 6$	$27 \pm 5$	$23 \pm 6$	$20 \pm 6$
NTG/NAC	$32 \pm 6$	29 ± 7	$27 \pm 6$	$23 \pm 5$	$20 \pm 4$
Pulse rate (bpm)					
F/m	$111 \pm 21$	$107 \pm 19$	$102 \pm 18$	$94 \pm 18$	$88 \pm 15$
NTG/NAC	$115 \pm 21$	$106 \pm 20$	$101 \pm 18$	$96 \pm 21$	$92 \pm 19$
Systolic blood pressure (mmHg)					
F/m	$164 \pm 34$	$149 \pm 25$	$145 \pm 25$	$139 \pm 22$	$139 \pm 23$
NTG/NAC	$161 \pm 32$	$144 \pm 24$	$138 \pm 26$	$134 \pm 26$	$133 \pm 22$
Crepitation score (0-4)*					
F/m	$3.2 \pm 0.9$	$2.9 \pm 0.9$	$2.5\pm0.9$	$2.2\pm1.0$	$1.3 \pm 0.6$
NTG/NAC	$3.2 \pm 1.0$	$2.8 \pm 1.1$	$2.4 \pm 1.0$	$1.9 \pm 1.0$	$1.1 \pm 0.9$

 Table 2. Intention to Treat Analysis: Clinical Parameters

\* Dyspnea and Crepitations were assessed using a clinical score (see Appendix).

Clinical parameters for all patients randomized to furosemide/morphine (F/M) or nitroglycerin/N-acetylcysteine (NTG/NAC) over the 24 hour study period. There were no significant differences between treatments for each of the clinical parameters assessed.

with acute-on-chronic heart failure may have been suboptimal in some cases, because many of these were receiving neither angiotensin-converting enzyme inhibitors nor digoxin; again this is consistent with previous patient cohorts (24).

The preliminary results of this study have previously been published (25 and the major findings include:

1. Medical therapy in the group of patients with NTG/ NAC is approximately equieffective with F/M in increasing oxygenation over the first hour of therapy. Furthermore, these two treatment regimens produce similar results in clinical status and the need for ventilatory assistance. These findings apply regardless of the presence or absence of respiratory failure on presentation.

2. Few study patients require mechanically assisted ventilation, even in patients with respiratory failure on admission.

Both of these findings have important implications in the clinical management and future research of acute pulmonary edema and merit further discussion.

#### **Clinical Implications**

Diuretics have been regarded as the cornerstone of therapy for acute pulmonary edema, yet there are few trials showing their efficacy (26,27) and some suggesting that they produce deleterious activation of the sympathetic and renin-angiotensin system (28). Evidence supporting the acute efficacy of morphine is even more scant (29) and its use may be particularly detrimental if respiratory failure is incorrectly attributed to acute pulmonary edema (30).

Nitrates have been shown to be beneficial in the management of acute pulmonary edema (31–36), and as Northbridge (7) has recently summarized, should theo-

Parameter	0 min	30 min	60 min	3 hr	24 hr			
pH								
F/m	$7.28 \pm 0.12$	$7.30 \pm 0.11$	$7.32 \pm 0.10$	$7.36 \pm 0.07$	$7.42 \pm 0.04$			
NTG/NAC	$7.26 \pm 0.12$	$7.30 \pm 0.12$	$7.33\pm0.09$	$7.36 \pm 0.09$	$7.42 \pm 0.04$			
PaO <sub>2</sub> (mmHg)								
F/m	$79\pm29$	$85 \pm 32$	$84 \pm 26$	$102 \pm 35$	$87 \pm 25$			
NTG/NAC	$74 \pm 25$	$87 \pm 40$	$86 \pm 29$	$95 \pm 26$	$88 \pm 19$			
Pao <sub>2</sub> /Fio <sub>2</sub> ratio								
F/m	$163 \pm 65$	$161 \pm 64$	$168 \pm 72$	$212 \pm 88$	$319 \pm 75$			
NTG/NAC	$152 \pm 69$	$173 \pm 77$	$176 \pm 74$	$216 \pm 82$	$316 \pm 90$			
Paco <sub>2</sub> (mmHg)								
F/m	$53 \pm 20$	$50 \pm 14$	$49 \pm 16$	$47 \pm 10$	$41 \pm 8$			
NTG/NAC	$52 \pm 18$	$48 \pm 15$	$45 \pm 11$	$42 \pm 8$	39 ± 5			

Table 3. Intention to Treat Analysis: Gas Exchange Parameters

Gas exchange parameters for all patients randomized to furosemide/morphine (F/M) or nitroglycerin/N-acetylcysteine (NTG/NAC) over the 24 hour study period. There were no significant differences between treatments for each of the parameters assessed.



**Fig. 1.** Normalized oxygen ratio after 60 minutes of therapy. Pao<sub>2</sub>/Fio<sub>2</sub> ratio on admission and 60 minutes after commencing either furosemide/morphine (F/M) (A) or nitroglycerin/*N*-acetylcysteine (NTG/NAC) (B) in patients presenting with acute pulmonary edema.

retically be more effective than diuretics. Although this has been shown in the setting of acute myocardial infarction (5,6), there have been few studies in the broader noninfarct pulmonary edema group. Two previous randomized studies have examined the efficacy of nitrates in this broader group of patients. The first involved out-ofhospital diagnosis of pulmonary edema by paramedic staff; 23% of patients studied did not have pulmonary edema on subsequent assessment by the emergency room medical staff (30). An analogous problem occurred in 5% of patients in this study.

A recent multicenter study (37) involving patients with acute pulmonary edema, compared a predominantly nitrate-based regimen (high dose nitrate, and low dose furosemide) with a predominantly diuretic-based regimen (low dose nitrate and high dose furosemide) and found that the former is associated with a more rapid improvement in oxygenation. Although these results are consistent with the trend in favor of NTG/NAC treatment in this study, there are major differences between the two studies regarding patient characteristics. In this study, most patients had acute-on-chronic heart failure and only 14% showed enzymatic evidence of acute myocardial infarction. By contrast, 27% of patients in the investigation by Cotter et al. (37) had acute myocardial infarction. Furthermore, these patients, who were treated with high dose nitrates, had a significantly lower rate of infarction, suggesting that the superior efficacy of this regimen may relate to an antiischemic effect.

The parameter Pao<sub>2</sub>/Fio<sub>2</sub> was chosen as the major end point because of its critical importance in defining the need for assisted ventilation. With both treatment regimens, Pao<sub>2</sub>/Fio<sub>2</sub> improved during the first 60 minutes of therapy (Table 3; Fig. 1), and this improvement provided the basis for the infrequent requirement of both CPAP and intubation/ventilation in this study. Not only were the treatment regimens equieffective but also both were well tolerated; in particular there were no cases of severe hypotension induced by NTG/NAC nor respiratory depression with morphine. Use of a relatively low infusion rate of NTG in this study may have been critical in minimizing the risk of negative inotropic (38) and hypotensive effects.

This study has also provided some insight into the frequency with which respiratory assistance is required for acute pulmonary edema. Only 11% (7/65) patients with documentary pulmonary edema) of patients required such support. All of these were in the subgroup with respiratory failure on admission. Only 3 (5%) patients required intubation and mechanical ventilation. This rate is similar to those in previous studies that used medical and oxygen therapy alone (18,22,30). However, other studies have reported 20% to 60% of patients requiring intubation (16,21,32). Even when the four excluded patients who required immediate intubation are considered, there is considerable disparity between studies in intubation rates, possibly reflecting differences in patient selection and clinical decision-making thresholds. Nevertheless, the results establish that medical therapy alone is effective in stabilizing most patients who are admitted with acute cardiogenic pulmonary edema not requiring immediate intubation, including most patients with initial respiratory failure.

#### Study Limitations

Although this is the largest randomized study of acute pulmonary edema therapy, its failure to show differences between the efficacy of F/M and NTG/NAC may reflect a type 2 error. Post hoc analysis suggests that this study had an 80% power to detect a 18.5 mmHg Pao<sub>2</sub> difference between therapies. Thus, approximately double the number of the patients enrolled would be required to show a 10 mmHg Pao<sub>2</sub> difference between therapies.

As with some previous trials (30) in acute pulmonary edema, emergency diagnosis may be difficult. Four patients were enrolled who did not have pulmonary edema in retrospect. As the data were analyzed primarily on an intention to treat basis, these patients might have distorted the results. However, exclusion of these four patients did not significantly alter the primary findings of this study.

The precise treatment regimen used is also worthy of



**Fig. 2.** Analysis of patients with respiratory failure (n = 32). Clinical and gas exchange data over the 24 hour study period for patients admitted with acute pulmonary edema and blood gas criteria for respiratory failure who were randomized to furosemide/morphine (F/M) (open squares) or nitroglycerin/*N*-acetylcysteine (NTG/NAC) (closed diamonds) therapy. The Po<sub>2</sub> ratio (ie, Pao<sub>2</sub>/Fio<sub>2</sub> ratio) is the primary end point of the study. There were no significant differences between treatments for each of the parameters assessed.

discussion. Morphine was administered in low incremental dosages to avoid the adverse effects of respiratory depression, particularly in patients with respiratory failure. This resulted in small (3 mg) total cumulative dosages of morphine being administered which may potentially represent suboptimal dosing. However, this approach is a common clinical practice. Alternatively, the nitrate regimen may have been suboptimal, particularly over the first hour, because NTG infusion rates were slowly increased to avoid NTG/NAC-induced hypotension (39). Recent investigations (37) suggest that the risk of nitrate-induced hypotension is relatively low in patients with acute pulmonary edema, perhaps reflecting a reduction in vascular responsiveness to incremental concentrations of nitric oxide. The design of this study also precludes evaluation of the individual components of the two treatment regimens, or anticipation of incremental effects from a combination of these regimens.

#### **Future Studies**

In general, previous studies of acute pulmonary edema management have used changes in hemodynamics with various medical therapies as major end points. Because this requires invasive monitoring, the patients usually reflect a selected group and often the sample size is small. Furthermore, some patients with acute pulmonary edema may not have elevated left ventricular filling pressures (40,41) at times when gas exchange is still impaired (40). Other acute pulmonary edema studies have used clinical criteria (16) or duration of hospital stay (24); whereas studies evaluating the efficacy of CPCP have measured gas exchange as an end point. No prospective randomized treatment trial has shown variation in in-hospital mortality because of its low incidence.

In this study, we used clinical and gas exchange criteria for the assessment of response to treatment of acute pulmonary edema. This has allowed the investigation of a large number of "typical" acute pulmonary edema patients and should be used in future pulmonary edema trials. Such studies are required to determine whether combined diuretic/nitrate therapy may have incremental effects over those seen with either of the currently compared treatment regimens.

#### Conclusion

This study represents the largest randomized trial of medical therapy for acute cardiogenic pulmonary edema in patients without acute transmural myocardial infarction. It shows that nitrate therapy is as effective a conventional F/M therapy in these patients. The study also suggests that most patients admitted with acute cardiogenic pulmonary edema can be managed medically, even if they have admission blood gas criteria for respiratory failure. The therapeutics of acute pulmonary edema remain incompletely explored. Additional studies should be conducted by using simple clinical/gas exchange parameters, thus enabling optimal patient recruitment of those patients routinely seen in clinical practice.

#### Appendix: Clinical Assessment Scores

The following scores use data from Flammang et al. (16):

Dyspnea score:

- 0 = no dyspnea on lying
- 1 =orthopnea (dyspnea on lying only)
- 2 = dyspnea if semirecumbent/lying, but not sitting
- 3 = dyspnea on sitting

Pulmonary crepitation score:

- 0 = no creptitations
- 1 =crepitations at bases
- 2 = crepitations up to basal one-half
- 3 = crepitations up to basal two-thirds
- 4 = crepitations over entire lung fields

#### Sweating:

- 0 = no visible perspiration
- 1 = visible forehead perspiration
- 2 = profuse for head perspiration
- 3 = profound diaphoresis

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## **Diuretic Efficacy of High Dose Furosemide in Severe Heart Failure: Bolus Injection Versus Continuous Infusion**

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*Objectives.* The efficacy of high dose furosemide as a continuous infusion was compared with a bolus injection of equal dose in patients with severe heart failure.

*Background*. The delivery rate of furosemide into the nephron has been proved to be a determinant of diuretic efficacy in healthy volunteers.

*Methods.* In a randomized crossover study we compared the efficacy of a continuous infusion of high dose furosemide (mean daily dosage 690 mg, range 250 to 2,000) versus a single bolus injection of an equal dose in 20 patients with severe heart failure. The patients received an equal dosage, either as a single intravenous bolus injection or as an 8-h continuous infusion preceded by a loading dose (20% of total dosage).

*Results.* Mean ( $\pm$ SEM) daily urinary volume (infusion 2,860  $\pm$  240 ml, bolus 2,260  $\pm$  150 ml, p = 0.0005) and sodium excretion

Loop diuretic drugs are commonly required in the management of heart failure. In most patients, orally administered conventional dosages of furosemide mobilize edema and maintain adequate hydration. However, with progression of the disease state, diuretic resistance—a potentially life-threatening phenomenon—frequently occurs, resulting in fluid and sodium retention. To overcome this complication the oral dosage of the loop diuretic drug is often increased. There are two reasons for this strategy: 1) In the course of heart failure, impairment of renal function often occurs (1). In renal insufficiency, higher dosages of furosemide are necessary to create effective concentrations in the intraluminal site of the ascending limb of Henle's loop, the site of action of loop diuretic drugs. 2) In patients with heart failure, higher concentrations of furosemide in the renal tubule are required to induce an adequate (infusion  $210 \pm 40$  mmol, bolus  $150 \pm 20$  mmol, p = 0.0045) were significantly higher after treatment with continuous infusion than with bolus injection, despite significantly lower urinary furosemide excretion (infusion  $310 \pm 60$  mg every 24 h, bolus  $330 \pm 60$  mg every 24 h, p = 0.0195). The maximal plasma furosemide concentration was significantly higher after bolus injection than during continuous infusion (infusion  $24 \pm 5 \mu$ g/ml, bolus  $95 \pm 20 \mu$ g/ml, p < 0.0001). Short-term, completely reversible hearing loss was reported only after bolus injection in 5 patients.

*Conclusions.* We conclude that in patients with severe heart failure, high dose furosemide administered as a continuous infusion is more efficacious than bolus injection and causes less ototoxic side effects.

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natriuretic response; in other words, in these patients the dose-response curve is shifted to the right and downward (2).

In addition to the absolute amount of drug carried to the site of action, the time course of delivery to the site of action appears to be an important determinant of overall diuretic response (3,4). This means that, theoretically, diuretic treatment can be optimized by the administration of furosemide as a continuous intravenous infusion. This mode of administration provides a constant delivery rate of furosemide to the renal tubule. Furthermore, sodium retention during the drug-free intervals may be avoided and the risk of ototoxic side effects reduced (5,6).

Only two controlled studies have compared the efficacy of a continuous intravenous infusion of a loop diuretic drug with intravenous bolus administration in patients with heart failure (7,8), with conflicting results with respect to the supposed superior efficacy of continuous infusion. However, on the basis of the previous arguments and the results of studies in healthy volunteers and patients with renal insufficiency, optimizing furosemide delivery to the renal tubule may have a beneficial effect. Consequently, we hypothesized that high dose furosemide administered as a continuous intravenous infusion would be more efficacious and less toxic than an intravenous bolus of an equal dosage of furosemide in patients with severe chronic heart failure.

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#### Table 1. Clinical Characteristics of 20 Study Patients

Pt No.	Age (yr)/Gender	Weight (kg)	Weight Change (kg)	Creatinine Clearance (ml/min)	Hydration Status	Diagnosis	Dose (mg)	Additional Medication
1	74/M	70.1	0.0	46	Comp	CAD	500	A, C
2	74/M	106.9	-1.6	92	Comp	CP	1,000	Al, P, T, Th
3	73/F	78.5	-0.3	70	Comp	CAD	250	A, T, N, P
4	83/F	83.9	-1.2	59	Comp	CAD	250	A, C, D, I, T
5	56/M	90.4	+1.2	87	Comp	СМ	500	A, Am, C, P
6	76/M	57.2	-1.3	27	Comp	CAD	500	Al, I, Ib, Th
7	73/F	83.0	-1.6	16	Comp	CAD	500	A, Am, I, P, T
8	72/M	48.3	-0.5	15	Comp	CAD	1,500	A, Am, I
9	51/F	36.6	-0.5	15	Comp	CAD	2,000	A, I, Ib, Ac
10	82/M	61.2	-2.7	43	Decomp	CAD	500	D, T, Tr
11	71/M	81.9	-6.6	50	Decomp	CM	250	Ac, Am, C, D, I, Pr, T, Th
12	85/M	72.4	-12.8	32	Decomp	CAD	250	C, D, Ac
13	86/F	56.3	-3.8	34	Decomp	CAD	500	Al, C
14	89/F	63.9	-0.9	32	Decomp	CAD	1,000	D, Ib
15	69/F	76.5	-1.0	52	Decomp	СР	250	A, C, H, Th
16	66/M	78.0	-0.5	50	Decomp	CAD	500	Am, C, P, T
17	66/M	71.0	-1.3	57	Decomp	CM	2,000	A, All, C, D, Th
18	57/M	79.7	-2.7	46	Decomp	VD	250	C, D, P
19	69/M	63.6	-1.8	24	Decomp	CAD	1,000	С, Т
20	51/M	98.2	-4.4	45	Decomp	CAD	250	Al, D
Mean	71	72.9	-2.3	45			690	
±SEM	2.5	3.7	-0.7	4.8			120	

A = amiloride; Ac = acenocoumarol; Al = Aldactone; All = allopurinol; Am = amiodarone; C = captopril; CAD = coronary artery disease; CM = cardiomyopathy; Comp = compensated heart failure; CP = cor pumonale; D = digoxin; Decomp = decompensated heart failure; F = female; H = hydrochlorothiazide; I = isosorbide dinitrate; Ib = ibopamine; M = male; N = nifedipine; P = potassium; Pr = prednisone; Pt = patient; T = tolbutamide; Th = theophylline; Tr = triamterene; VD = valvular disease.

#### Methods

**Subjects.** After approval by the local ethics committee, we included 20 patients (7 women, 13 men) with severe heart failure of differing etiologies (New York Heart Association functional class III or IV) and long-term use of orally administered high dose furosemide (at least 250 mg). Each patient provided written informed consent before the start of the study. No patient was taking nonsteroidal anti-inflammatory drugs or probenecid. Patients with a cardiomyopathy due to alcoholism were excluded.

At the time of the study, 9 patients were in a clinically compensated state without edema, and 11 patients had decompensated heart failure with an estimated edematous mass of at least 5 kg. Mean ( $\pm$ SEM) body weight at the start of the study was 72.9  $\pm$  3.7 kg. Mean pretreatment endogenous creatinine clearance rate was 45  $\pm$  4 ml/min. The clinical characteristics of the study patients are shown in Table 1.

**Study design.** The study was a randomized crossover study. All patients were placed on a standard diet of 80 mmol of sodium and 100 mmol of potassium and a fluid intake of 1,500 ml. Extra potassium was administered for hypokalemia (<3.5 mmol/liter). During the study, patients did not drink coffee, tea or alcohol. The daily furosemide dosage was left unchanged throughout the study. All other medication was continued as previously prescribed. Patients underwent physical examination with emphasis on hydration status. Standing and supine blood pressures and weight were determined daily. An indwelling urinary catheter was inserted when patients could not void on request. The patients remained in the hospital for the duration of the study.

During days 1 and 2 of the study, the patients received a single dose of orally administered furosemide (Lasix, Hoechst). At that time, blood samples were obtained for baseline measurement of serum electrolytes, blood cell counts, serum albumin, plasma epinephrine and norepinephrine, plasma renin and plasma aldosterone. Urine samples were collected over 24 h for measurement of volume and concentrations of creatinine, sodium, potassium, chloride and furosemide.

On day 3, patients were randomized to receive furosemide either as an intravenous bolus injection (injected within 5 min) or as a continuous intravenous infusion. The continuous intravenous infusion started with a loading dose consisting of 20% of the total dose and administered within 5 min as a bolus injection, followed by an 8-h continuous intravenous infusion at an infusion rate of 10% of the total dose per hour (model STC-521 infusion pump, Terumo Corp., Tokyo, Japan). Either of the administration modes was started at 8 AM, after initial bladder emptying. Blood samples were taken from the antecubital vein in the arm contralateral to the drug infusion at 0, 15, 30, 45, 60, 90, 120, 150, 180, 240, 360, 480 and 1,440 min after the start of the intravenous furosemide administration for determination of plasma furosemide concentrations. Urine

<b>Table 2.</b> Mean Values $(\pm SEM)$ of Biochemical Variables in 20 Patients with Severe Heart	
Failure Before and After Intravenous Treatment with High Dose Furosemide (daily dosage	
$690 \pm 560 \text{ mg}$ )	

	Days 3-5					
	Day 2	Before Infusion (t = 0 h)	After Infusion (t = 24 h)	Before Bolus (t = 0 h)	After Bolus (t = 24 h)	Day 6
Serum sodium (mmol/liter)		137 ± 1	$137 \pm 1$	138 ± 1	138 ± 1	
Serum potassium (mmol/liter)		$4.2 \pm 0.1$	$4.3 \pm 0.2$	$4.1 \pm 0.1$	$4.3 \pm 0.1$	
Serum chloride (mmol/liter)		95 ± 1	$94 \pm 2$	$95 \pm 1$	$94 \pm 2$	
Serum creatinine (µmol/liter)		$132 \pm 8$	$139 \pm 9^{*}$	$134 \pm 8$	$139 \pm 8^{+}_{-}$	
Serum urea (mmol/liter)		$18 \pm 2$	$19 \pm 2$	$19 \pm 2$	19 ± 2	
Serum albumin (g/liter)		$36 \pm 1$	$37 \pm 1$	$36 \pm 1$	$36 \pm 1$	
Aldosterone (nmol/liter)	$1.5\pm0.2$					$1.8\pm0.5$
Renin (ng/liter)	$222\pm62$					$336\pm109$
Epinephrine (nmol/liter)	$0.4 \pm 0.1$					$0.3 \pm 0.1$
Norepinephrine (nmol/liter)	$3.5\pm0.5$					$2.8\pm0.4$

\*p < 0.01,  $\dagger p < 0.05$  versus before treatment (Student *t* test for paired data). t = time.

was collected at 30, 60, 120, 180, 240, 360, 420, 480 and 1,440 min after the start of furosemide administration for measurements of volume, sodium, potassium, chloride, creatinine and furosemide. Intravenous furosemide preparations as well as all urine samples were protected against light to prevent photochemical degradation of furosemide.

Urine losses were not replaced isovolumetrically. Day 4 was used as a washout period: Patients received oral furosemide medication, and blood and urine sampling was identical to the first 2 days.

On day 5 the crossover mode of intravenous administration was performed as described previously. On the final day (day 6), urine was collected, and blood samples (including renin, aldosterone and catecholamines) were taken for comparison with baseline measurements.

Analytic methods. Sodium and potassium concentrations were measured by flame photometry, chloride concentrations by a semiautomatic colometric titration method and creatinine concentrations according to the Jaffe reaction in an autoanalyzer. Plasma and urine concentrations of furosemide were measured by a rapid and sensitive high performance liquid chromatographic assay, as described previously (9). Plasma aldosterone was determined by radioimmunoassay (10). Plasma renin was measured by means of an immunoradiometric sandwich technique with the use of two monoclonal antibodies and without enzymatic step (ERIA Diagnostics Pasteur, Marnes La Coquette, France) (11). Blood samples for measurement of plasma catecholamines were collected in prechilled tubes on melting ice containing glutathione (0.2 mol/ liter) and ethylenediaminetetraacetic acid (0.25 mol/liter). The tubes were centrifuged at 4°C, and plasma was stored at -80°C; analyses of plasma samples occurred within 2 months of collection. Plasma samples were analyzed for concentrations of catecholamines by high performance liquid chromatography with fluorometric detection after precolumn derivatization with the selective detection agent 1,2-diphenylethylenediamine.

The laboratory procedure is a modification of a previously described method (12).

Data analysis. The plasma concentration data obtained after bolus injection were fitted to an open two-compartment model by use of the PCNonlin computer program (13). The area under the curve (AUC) was calculated by direct integration, and the half-life of furosemide was obtained from the terminal elimination rate constant. The AUC below the plasma concentration-time curve during continuous infusion was calculated by means of the trapezoid rule and extrapolation to infinity using the terminal elimination rate constant of the curve after bolus injection. Systemic clearance was determined by dividing the furosemide dose by the AUC. Renal clearance was calculated as the amount of excreted drug during 24 h divided by the AUC. Nonrenal clearance was defined as the systemic clearance minus the renal clearance. Overall efficiency was calculated by dividing the excreted amount of sodium (mmol/24 h) by the excreted amount of furosemide (mg/24 h).

Statistical analysis. Statistical analyses of unpaired and paired data were made using the Student *t* test and the Student *t* test for paired data, respectively. A p value <0.05 was considered significant. Data are expressed as mean value  $\pm$  SEM.

#### Results

**Biochemical measurements.** Mean values of the biochemical measurements, including catecholamines, renin and aldosterone, did not change significantly during the study, with the exception of serum creatinine, which showed a significant increase after both treatment modes (Table 2). As shown in Table 1, the endogenous creatinine clearance was reduced in the majority of the patients. According to the natriuresis, 13 patients were not resistant to oral therapy (Table 3). However, six of these patients had a clearly negative sodium balance

		B	olus	Infu	ision	Bolus Vers (p va	us Infusion alue)
	Oral, 0–26 h	0-8 h	0–24 h	0-8 h	0–24 h	0-8 h	0-24 h
U, (ml)	$2,200 \pm 160$	$1,350 \pm 90$	$2,260 \pm 150$	$1,700 \pm 120$	$2,860 \pm 240$	0.0002	0.0005
U <sub>Na</sub> (mmol)	$130 \pm 30$	$110 \pm 10$	$150 \pm 20$	$140 \pm 20$	$210 \pm 40$	0.0010	0.0045
U <sub>K</sub> (mmol)	$70 \pm 6$	$30 \pm 5$	$70 \pm 5$	$40 \pm 4$	$80 \pm 5$	0.0006	< 0.0001
U <sub>Cl</sub> (mmol)	$130 \pm 20$	$120 \pm 10$	$150 \pm 20$	$150 \pm 20$	$220 \pm 35$	0.0006	0.0018
U <sub>furosemide</sub> (mg)	$140 \pm 30$	$290 \pm 50$	$330 \pm 60$	$220 \pm 40$	$310 \pm 60$	< 0.0001	0.0195
Recovery (%)	$21 \pm 2$	44 ± 2	$50 \pm 2$	$33 \pm 2$	$44 \pm 2$	< 0.0001	0.0195
Efficiency (mmol/mg)	$2.9 \pm 1.5$	$0.7 \pm 0.2$	$0.9 \pm 0.3$	$1.1 \pm 0.3$	$1.3\pm0.4$	0.0005	0.0019

**Table 3.** Urinary Volume, Electrolyte and Furosemide Excretion (mean  $\pm$  SEM) 8 and 24 h After Administration of Furosemide as Oral Dosage (day 2), Intravenous Bolus Injection or Continuous Infusion in Patients With Heart Failure

Statistical analyses were made using the Student *t* test for paired data.  $U_{Cl}$  = urinary chloride excretion;  $U_{furosemide}$  = urinary furosemide excretion;  $U_{K}$  = urinary potassium excretion;  $U_{Na}$  = urinary sodium excretion;  $U_{v}$  = urinary volume.

(>20 mmol/24 h) and did not lose weight during this phase of the study, suggesting poor compliance with the dietary restrictions.

An influence of cotreatment with angiotensin-converting enzyme on the diuretic response could not be observed. The renin levels between captopril-treated and non-captopriltreated patients did not differ significantly.

Pharmacokinetic measurements. Apart from the maximal plasma furosemide concentration, which was significantly higher after intravenous bolus injection, the pharmacokinetic measurements were similar in the two treatment modes (Table 4). The plasma furosemide concentration-time profiles of the two dose regimens of one representative patient are shown in Figure 1. The furosemide plasma concentrations were in the supposed ototoxic range (>100  $\mu$ g/ml) in seven patients immediately after bolus injection and in one patient during continuous infusion. During continuous infusion, the plasma furosemide concentration remained at steady state throughout the infusion period, with a significantly lower maximal plasma concentration (bolus 95  $\pm$  20  $\mu$ g/ml, infusion 24  $\pm$  5  $\mu$ g/ml, p < 0.0001). However, the plasma furosemide concentration was determined first at 15 min, after the start of the administration. This implies that immediately after injection of the bolus, the plasma furosemide concentration was even higher. The urinary furosemide excretion rate followed a similar pattern for both methods of administration (Fig. 1). After bolus injection, most of the furosemide was excreted within

**Table 4.** Pharmacokinetic Variables (mean  $\pm$  SEM) of FurosemideAfter Administration as Bolus or Continuous Infusion in 20 PatientsWith Heart Failure

	Bolus	Infusion
AUC (g/ml per min)	$14.2 \pm 4.0$	$13.1 \pm 4.1$
Systemic clearance (ml/min)	$64 \pm 8$	$67 \pm 6$
Renal clearance (ml/min)	$30 \pm 3$	$31 \pm 3$
Nonrenal clearance (ml/min)	$34 \pm 4$	$36 \pm 4$
Half-life (min)	$139 \pm 7$	
Furosemide excretion (mg/24 h)	330 ± 60*	$310\pm60$

\*p < 0.05, Student *t* test for paired data. AUC = area under the curve.

2 h, whereas during continuous infusion, the urinary excretion rate was constant.

**Pharmacodynamic measurements.** Although a smaller amount of furosemide was excreted in the urine during both 8 and 24 h with the use of continuous infusion, the urinary volume and natriuresis during both 8 and 24 h were significantly larger (Table 3). The differences in natriuretic response between the two intravenous modes of administration and the

Figure 1. Furosemide plasma concentration (top) and urinary furosemide excretion rate (bottom) for a representative study patient (Patient 1) after 500 mg of furosemide as a bolus injection or continuous infusion (50 mg/h during 8 h preceded by a loading dose of 100 mg).



Time (min)



Figure 2. Cumulative urinary sodium excretion (mean  $\pm$  SEM) 24 h after bolus injection (open squares) and continuous infusion (solid squares) of high dose furosemide.

interindividual variability of these responses are shown in Figures 2 and 3.

Separate analysis of data of patients with compensated (n = 9) and decompensated (n = 11) heart failure revealed similar results for these subgroups, except for the urinary furosemide excretion. In the two dose regimens there appeared to be a significantly lower excretion only in patients with compensated heart failure after continuous infusion. The sequence of drug administration did not influence the natriuretic response in either of the two intravenous administration methods.

Compared with oral therapy (day 2), bolus injection did not differ significantly with respect to volume and electrolyte excretion. However, urinary recovery of furosemide was significantly lower (oral  $21 \pm 2\%$ , bolus  $50 \pm 2\%$ , p < 0.0001), and thus efficiency was higher. When continuous infusion was compared with oral therapy, volume and electrolyte excretion were significantly higher after continuous infusion, whereas urinary furosemide recovery was significantly lower after oral administration (oral  $21 \pm 2\%$ , infusion  $44 \pm 2\%$ , p < 0.0001).

**Figure 3.** Individual values for urinary sodium excretion 24 h after continuous infusion and bolus injection of high dose furosemide in 20 patients with severe heart failure.



A dose–response curve was created for each patient. However, sigmoid-shaped curves, as seen in healthy subjects, were not observed (data not shown). Moreover, a high interindividual variability was observed.

To gain insight into the potential development of acute diuretic tolerance during continuous infusion of furosemide, we compared the efficiency (mmol excreted sodium/mg excreted furosemide) during two time intervals—30 to 60 min and 420 to 480 min. The amount of drug excreted per hour during each interval did not differ significantly, nor did the amount of sodium. Hence, the efficiency was equal in both periods, indicating that acute diuretic tolerance did not occur during continuous infusion. Because of the design of the study (a single bolus instead of multiple), we could not determine whether acute drug tolerance was present after bolus injection.

**Side effects.** Although five patients reported hearing loss or tinnitus, or both, shortly after bolus injection, these effects appeared to be transient in all five and disappeared within 15 min. No other side effects were observed or reported during this study.

#### Discussion

General conclusions. Our results clearly show that in patients with severe heart failure, continuous infusion of high dose furosemide causes excretion of a higher volume of urine and electrolytes than an equal dose administered as an intravenous bolus, and the maximal plasma furosemide concentration is significantly lower. A crossover design in combination with a washout period was used to balance out any possible time or sequence trends. Moreover, the pharmacokinetic data obtained supported the outcome of the study.

Comparison with previous studies. Few data are available on the usefulness of continuous infusion of furosemide in disease, particularly heart failure. In an animal study, Lee et al. (14) compared different durations of infusion of an equal dosage of furosemide. The diuretic response increased with increasing infusion times. In healthy volunteers a controlled comparison of bolus injection with continuous infusion of a conventional dosage of furosemide showed a larger diuretic effect of the latter mode of administration (5). In chronic renal insufficiency, continuous infusion of bumetanide was more effective and less toxic than intermittent bolus therapy (15). Several uncontrolled reports describing small series of patients with congestive heart failure demonstrate successful application of continuous infusion of loop diuretic drugs (5,16-20). To our knowledge only two controlled studies on this subject have been performed in adult patients with heart failure (7,8). Copeland et al. (8) did not find any significant pharmacodynamic differences in a comparison of continuous intravenous infusion and an equal dose given as two separate bolus injections in patients after cardiac surgery. However, that study lacked a crossover design, use of a loading dose before the start of continuous infusion and adequate study period. Lahav et al. (7) compared intermittent administration of furosemide with a continuous infusion of an equal dose in patients with congestive heart failure. In their study, which lacked pharmacokinetic data, continuous infusion was shown to be the preferred method of administration. In both studies, conventional dosages of furosemide were used.

In our study the dosage of furosemide was >250 mg/day in all patients. The results of the present study cannot be generalized to patients receiving furosemide in the conventional dose range. However, in the conventional dose range, a continuous infusion is usually not necessary because diuretic resistance can be overcome by simply increasing the dosage.

Interpretation of pharmacokinetic and pharmacodynamic data. In the present study, we included those patients who would benefit most from the presumed advantages of continuous infusion of furosemide, that is, patients with heart failure and, often, impaired renal function. High dose furosemide is used in these patients because of diuretic resistance to conventional dosages. Thus, they are in need of an optimal diuretic regimen without toxic side effects. The higher efficiency of continuous infusion is demonstrated by the observation that a smaller amount of drug excreted into the urine produced a larger natriuretic effect (Table 3). Several mechanisms may elicit this superior response: 1) the time course of delivery of furosemide into urine. Because the amount of drug excreted into the urine is even smaller after continuous infusion, the time course of delivery is consequently an important factor influencing the diuretic response. The maximally efficient excretion rate of furosemide can be calculated, and the slope factor of the dose-response curve appears to be an important determinant in this calculation (3,4). In healthy volunteers the maximally efficient excretion rate appeared to be 115  $\mu$ mol/min (4). As in patients with heart failure studied by Brater et al. (2), the dose-response curves of the patients in the present study were shifted to the right. Moreover, the sigmoid shape could not be recognized, making calculation of the maximally efficient excretion rate impossible. For this reason and because of the larger interindividual variability, an optimal infusion rate of furosemide cannot be predicted in these patients. However, it is obvious that during continuous infusion, the urinary furosemide excretion rate will be closer to the maximally efficient excretion rate over a longer period.

2) Another reason for the observed difference in response between the two modes of administration could be the development of a more pronounced acute drug tolerance after bolus injection (21). Because of a greater diuresis during the period immediately after the injection, the intravascular volume might decrease even in a volume-overloaded patient, causing activation of sodium- and volume-retaining mechanisms. The net result may be lower diuretic efficacy despite adequate urinary furosemide concentrations. Because we used only one bolus injection instead of multiple intermittent injections, the presence of acute tolerance could not be verified. Acute diuretic tolerance during continuous infusion appeared to be absent.

3) After bolus injection, the drug-free interval, during which counteracting sodium-retaining mechanisms are active, is longer. Although catecholamine levels were increased at the start of the study, they were not further increased at the end of the study. Activation of the renin-angiotensin-aldosterone axis was not observed (Table 2). However, variables were measured at the start and end of the study, so a transient activation could have been missed.

In chronic heart failure, long-term coadministration of angiotensin-converting enzyme inhibitors may enhance furosemide-induced natriuresis, possibly owing to a change in the set point for renal sodium handling (22). In 9 of 20 patients in this study, angiotensin-converting enzyme inhibitors were withdrawn in an earlier phase because of further deterioration of renal function or symptomatic hypotension. Comparison of the patients treated with and without angiotensin-converting enzyme inhibitors did not reveal any differences in furosemideinduced natriuresis for any of the modes of administration, and the mean daily dosage of furosemide did not differ significantly between the two groups.

Side effects. An important advantage of the use of continuous infusion is a smaller risk of ototoxicity because high peak plasma levels of furosemide are avoided (6). In the present study the measured maximal plasma concentration during continuous infusion was lower than that after bolus injection in all patients. However, even a continuous infusion of high dose furosemide may lead to concentrations in the supposed ototoxic range in patients with severe renal insufficiency, as illustrated by one of the study patients (Patient 9, endogenous creatinine clearance 15 ml/min per 1.73 m<sup>2</sup>, furosemide dosage 2,000 mg, maximal plasma concentration in the course of continuous infusion 119  $\mu$ g/ml). According to our clinical experience, an infusion rate of 160 mg/h seems safe when the endogenous creatinine clearance rate is >20 ml/min per 1.73 m<sup>2</sup> (5).

Intravenous versus oral treatment. We observed a higher urinary recovery of furosemide after bolus injection than with continuous infusion. This difference reached significance only in the compensated group of patients. The exact mechanism of this discrepancy is not clear and needs further exploration. Although the urinary recovery of furosemide after oral therapy is much lower (Table 3), owing to lower bioavailability than after bolus injection, its efficacy is equal. This means that the efficacy is greater after oral therapy than after bolus injection, which is probably the result of a better time course of delivery. Although efficacy was equal for both oral therapy and continuous infusion, continuous infusion of an equal dose is more efficacious than oral administration because of a higher urinary excretion rate of furosemide with continuous infusion (Table 3). In patients with congestive heart failure, absorption of furosemide after oral therapy is delayed, which results in a lower drug concentration at the site of action. An increase in oral dosage is less attractive because the exact duration of delay is unknown, making the response unpredictable. For this reason, patients with manifest decompensated heart failure should preferably be treated with intravenous therapy until the hydration state is corrected.

**Summary.** The value of continuous infusion of furosemide in patients with severe congestive heart failure can be summarized as follows: A higher efficiency (than with bolus injection) and a higher, more predictable urinary excretion rate of drug (than after oral therapy) results in an improved diuretic response combined with a reduced risk for ototoxicity. Continuous infusion of furosemide should be considered in patients with decompensated heart failure whenever the diuretic response after oral therapy with high dose furosemide is insufficient, especially in those patients at risk for furosemideinduced toxicity because of impaired renal function.

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# Effect of diuresis on the performance of the failing left ventricle in man.

#### Wilson JR, Reichek N, Dunkman WB, Goldberg S.

To determine the effect of diuresis on the performance of the failing left ventricle, we measured cardiac output, pulmonary wedge pressure and M-mode echo left ventricular diastolic dimension before and after diuresis in 13 patients with heart failure. Diuresis increased stroke volume (43 +/- 23 ml to 50 +/- 18 ml (p less than 0.05)) and decreased pulmonary wedge pressure ( $28 \pm 3$  mm Hg to  $19 \pm 5$  mm Hg (p less than 0.01)), mean blood pressure (100  $\pm 14$  mm Hg to 88 +/- 10 mm Hg (p less than 0.01)) and systemic vascular resistance (2,059 +/- 622 dynes-sec-cm-5 to 1,783 +/- 556 dynes-sec-cm-5 (p less than 0.05)). Echo left ventricular diastolic dimension was not changed by diuresis  $(6.0 \pm 0.8 \text{ cm to } 6.0 \pm 0.8 \text{ cm})$ . Percent change in stroke volume correlated with systemic vascular resistance (r = 0.60, p less than 0.05) and with left ventricular diastolic dimension (r = 0.62, p less than 0.05) but not with pulmonary wedge pressure (r = 0.12) or right atrial pressure (r = 0.04). Thus, diuresis improved the performance of the failing ventricle and reduced afterload, but it did not alter left ventricular diastolic dimension, an index of preload. These data suggest that diuresis improves ventricular function by decreasing afterload.

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## Determining the Optimum Dose for the Intravenous Administration of Nicardipine in the Treatment of Acute Heart Failure — A Multicenter Study —

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Nicardipine is a potent arteriolar vasodilator with a negligible negative inotropic effect. Although intravenous administration of this drug has been reported to be effective in the treatment of heart failure, the optimal dose by this route is not clear. This study was designed to determine the optimum dose for the intravenous infusion of nicardipine in the treatment of heart failure. In Trial 1, nicardipine was administered intravenously at a dose of 0.5  $\mu$ g/kg per min to 14 patients with acute heart failure. The dose was increased to 1.0  $\mu$ g/kg per min in 13 cases with marked improvement at 2 h. In Trial 2, nicardipine was administered in a double-blind manner to 53 patients at 3 different rates of infusion for 2 h: 1.0 (Group 1, n=19), 2.0 (Group 2, n=15), and 3.0 (Group 3, n=19)  $\mu$ g/kg per min. Neither heart rate nor mean right atrial pressure changed in any of the 3 groups. Favorable hemodynamic effects were evident in all groups beginning 30 min after the start of infusion, with an increase in cardiac index (control vs 2 h after infusion, L/min per m<sup>2</sup>)(Group 1:  $2.2\pm0.4$  vs  $3.1\pm0.8$ , Group 2:  $2.2\pm0.4$  vs  $2.9\pm0.5$ , Group 3:  $2.3\pm0.3$  vs  $3.1\pm0.7$ , all p<0.01 compared to the control) and a decrease in diastolic pulmonary artery pressure (Group 1:  $26 \pm 10$  vs  $19 \pm 7$ , Group 2:  $27 \pm 10$  vs  $20 \pm 8$ , Group 3:  $26\pm7$  vs  $18\pm5$  mmHg, all p<0.01). The decrease in systolic pressure was greatest in Group 3 (Group 1: 141±31 vs 119±18, Group 2: 149±25 vs 118±17, Group 3; 147±27 vs 107±14 mmHg, all p<0.01 compared to control, and p < 0.05 between Groups 1 and 3). The intravenous drip infusion of nicardipine is effective in the treatment of heart failure by inducing an increase in cardiac output and a decrease in pulmonary artery wedge pressure. The optimal dose in this study was  $1.0 \,\mu$ g/kg per min.

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Key Words: Heart failure; Vasodilator therapy; Calcium channel blockade; Intravenous nicardipine

Treatment of acute heart failure is a potentially lifesaving procedure the aim of which is to reduce pulmonary congestion to restore normal breathing and to maintain adequate cardiac output to ensure appropriate perfusion of the vital organs. Various intravenous agents have been used, including catecholamines to increase cardiac output via an increase in the inotropic state<sup>1,2</sup> phosphodiesterase inhibitors to reduce afterload as well as to increase the inotropic state<sup>3,-5</sup> loop diuretics to decrease pulmonary congestion via rapid diuresis<sup>6,7</sup> and various nitrate compounds to decrease pulmonary congestion via vasodilatation of capacitance vessels<sup>8-10</sup>

Nicardipine, a dihydropyridine derivative calcium

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Table	1	Exclusion	Criteria

Patients with the following diseases or conditions were excluded:

- 1. within 1 week after the onset of acute myocardial infarction
- 2. obstructive diseases of the ventricle
- 3. predominantly right heart failure
- 4. infective endocarditis
- 5. hypotension and cardiogenic shock
- 6. cerebrovascular accidents with active bleeding or increased intracranial pressure
- 7. thyroid dysfunction
- 8. malignant arrhythmias
- 9. severe liver or kidney dysfunction
- 10. severe infection elsewhere in the body
- 12. known to be allergic to nicardipine
- 13. pregnant or possibility of being pregnant

#### Table 2 Study Population in Trial 1

Gender (Male/Female)	11/3
Age (years)	$68.2 \pm 10.4$
Underlying Heart Disease	
ischemic heart disease	6
valvular heart disease	4
dilated cardiomyopathy	3
hypertensive heart disease	1
NYHA Functional Class (III/IV)	4/10

channel blocker, is widely used for the treatment of hypertension. This agent is a potent arteriolar vasodilator with a negligible negative inotropic effect.<sup>11</sup> Although nicardipine has been used intravenously for the treatment of heart failure,<sup>12–14</sup> the results to date have not been impressive. In contrast to these previous studies, however, recent preliminary data in a small study population suggested a marked improvement of symptoms and hemodynamic parameters by the administration of minimal doses of this drug.<sup>15</sup> Therefore, we postulated that the reason for the poor results obtained with this agent to date might be related to an excessive decrease in afterload, and that favorable results might be obtained with doses smaller than those usually employed.

This multicenter study was designed to 1) investigate the efficacy of the intravenous infusion of nicardipine in the treatment of heart failure, and 2) establish the most effective dose for such treatment.

#### Methods

#### Study Populations

Patients who had been admitted to the hospital with the a diagnosis of acute heart failure and who were under hemodynamic monitoring with a Swan-Ganz catheter in the pulmonary artery were eligible for enrollment. Patients were observed for at least 30 min. Treatment with nicardipine was started when stability was obtained in 2 consecutive hemodynamic measurements 15 min apart. Entry criteria were as follows: 1. cardiac index less than 2.5 L/min per m<sup>2</sup>; 2. pulmonary diastolic or wedge pressure greater than 15 mmHg; 3. age greater than 20 and younger than 80; and 4. systolic blood pressure higher than 100 mmHg. Patients with the underlying diseases or conditions listed in Table 1 were excluded. The investigations were started at least 6 h after the oral administration of inotropic agents, nitrates,  $\alpha$  or  $\beta$  blockers, angiotensin-converting enzyme inhibitors, calcium antagonists, or diuretics. Oxygen inhalation was continued without changing the dose in patients who required it.

Trials 1 and 2 were both approved by the ethics committees of the participating hospitals. Written informed consent was obtained from each patient or his/her family before starting the study.

#### Study Protocols

#### Trial 1

Patient backgrounds are shown in Table 2. A 10-ml ampule containing 10 mg of nicardipine HCl was dissolved in 40 ml of normal saline, and intravenous infusion was started at a rate of  $0.5 \,\mu$ g/kg per min. Hemodynamic measurements were repeated every 30 min. The infusion rate was increased to  $1.0 \,\mu$ g/kg per min when the clinical or hemodynamic response was judged to be inadequate by the investigator. The total observation period with adequate dosing was limited to 2 h.

#### Trial 2

Patient backgrounds are shown in Table 3. Each infusion set consisted of 3 ampules which contained either 10 mg of nicardipine HCl or an indistinguishable placebo and an ampule of dissolving solution for the

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Group infusion speed	1 1.0 μg/kg per min	2 2.0 µg/kg per min	3 3.0 μg/kg per min
No. (Male/Female)	20 (17/3)	16 (8/8)	21 (14/7)
Age (years)	$62.0 \pm 14.9$	$64.5 \pm 9.4$	$64.0 \pm 11.9$
Underlying Heart Disease			
ischemic heart disease	7	8	11
valvular heart disease	3	3	4
dilated cardiomyopathy	7	3	3
hypertensive heart disease	3	2	3

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	Before infusion	At the end of 0.5 μg/kg per min	At the end of 1.0 μg/kg per min
HR (beats/min)	<i>89</i> ± <i>12</i>	87±12	<i>86</i> ± <i>12</i>
BP (S/D, mmHg)	$153 \pm 29/85 \pm 15$	146±34/77±13	$129 \pm 20/69 \pm 13$
DP	$13692 \pm 3406$	$12675 \pm 3310$	$11024 \pm 2028$
PAP (S/D, mmHg)	$58 \pm 21/25 \pm 8$	$52 \pm 21/22 \pm 9$	$46 \pm 17/18 \pm 6$
RAP (mmHg)	$8\pm7$	$6\pm5$	$5\pm4$
$CI$ (l/min per $m^2$ )	$2.2 \pm 0.5$	$2.6 \pm 0.7$	$2.9 \pm 0.6$
SWI (g·m/beat per $m^2$ )	$28 \pm 7$	$32 \pm 10$	$34 \pm 12$
SVR (dyne·sec·cm <sup>-5</sup> ) (n=11)	$2509 \pm 813$	$2053 \pm 734$	$1559 \pm 357$
PAR (dyne·sec·cm <sup>-5</sup> ) (n=11)	$255\pm151$	$213 \pm 144$	$162\pm78$

n=13

 $Mean \pm SD$ , Abbreviations: HR, heart rate; BP, blood pressure; S/D, systolic/diastolic; DP, double product; PAP, pulmonary artery pressure; RAP, right atrial pressure; CI, cardiac index; SWI, stroke work index; SVR, systemic vascular resistance; PAR, pulmonary arteriolar resistance.

infusion of 1.0, 2.0 or  $3.0 \,\mu$ g/kg per min per patient. Subjects were randomly assigned to the groups by the controllers (RH and KO), and 6 infusion sets were distributed to each participating institution. Each patient received either 1.0 (Group 1), 2.0 (Group 2) or 3.0 (Group 3)  $\mu$ g/kg per min of nicardipine by intravenous infusion for 2 h. The case cards were reviewed by the primary investigators; patients who did not satisfy the inclusion criteria were eliminated from the analysis before the keys were opened.

#### Measurements

Hemodynamic variables were measured in triplicate every 30 min. Arterial and pulmonary arterial blood samples for gas analysis were obtained before, at 30 min after the start of dosing, and at the end of the observation. Venous blood was examined at baseline and at 24 h after infusion for determination of complete blood counts and blood chemistry.

Using the pressures and cardiac output (CO), left ventricular (LV) stroke work index (SWI), systemic vascular resistance (SVR) and pulmonary arteriolar resistance (PAR) were obtained as follows: SWI  $(g \cdot m/beat \text{ per } m^2) = \text{SVI} \times (\text{MAP} - \text{RAP}) \times 0.0136$ , SVR (dyne·sec·cm<sup>-5</sup>)=79.92×(MAP-RAP)/CO and PAR (dyne·sec·cm<sup>-5</sup>)=79.92×(MPAP-DPAP)/CO, where MAP is mean arterial pressure, RAP is right atrial pressure, DPAP is diastolic pulmonary artery pressure and MPAP is mean pulmonary artery pressure. Although these parameters are ideally calculated using pulmonary wedge pressure, pulmonary diastolic pressure was used here since most of the patients had cardiac dilatation, which made it difficult to measure a constant wedge pressure.

Oxygen delivery (O<sub>2</sub>D), and oxygen consumption ( $\dot{V}O_2$ ) were calculated from arterial and pulmonary arterial gas: O<sub>2</sub>D (ml/min per m<sup>2</sup>)=CI×(1.34×Hb× AO<sub>2</sub>sat+0.031×PaO<sub>2</sub>), and  $\dot{V}O_2$  (ml/min per m<sup>2</sup>)=CI×1.34×Hb (AO<sub>2</sub>sat-mvO<sub>2</sub>sat), where CI is cardiac index, Hb is the blood hemoglobin concentration, AO<sub>2</sub>sat is arterial oxygen saturation, PaO<sub>2</sub> is arterial partial oxygen pressure and mvO<sub>2</sub>sat is mixed venous oxygen saturation.

#### Statistical Analysis

The data are expressed as the mean  $\pm$  SD. Since a cumulative dose effect at 0.5  $\mu$ g/kg per min could not be avoided, it was impossible to compare the effects of



Fig 1. Changes in the cardiac index and diastolic pulmonary artery pressure with infusion of nicardipine.

Infusion of nicardipine induced an increase in cardiac index (CI) and a decrease in diastolic pulmonary artery pressure (DPAP). These beneficial effects were greater with the infusion at  $1.0 \,\mu$ g/kg per min, and all 7 patients in Forrester's Subset IV moved to better classifications.

 Table 5 Undesirable Effects Observed in Trial 2

Group 1:	Case 1 Case 2	sinus tachycardia hypoxemia
Group 2:	Case 1 Case 2 Case 3 Case 4	hypotension hypotension and hypoxemia hypoxemia nausea, back pain and dyspnea
Group 3:	Case 1 Case 2 Case 3 Case 4 Case 5 Case 6	chill, cyanosis and hypotension hypoxemia hypotension and ventricular tachycardia nausea hypotension ventricular premature beats

doses of 0.5 and  $1.0 \,\mu g/kg$  per min, and a statistical analysis was not performed in Trial 1. In Trial 2, the paired Student's t test was used to compare intragroup data before and after treatment. The Kruskal-Wallis method was used to compare the data of the 3 groups; when significant differences were observed, Scheffe's multiple comparison was used to compare data between 2 groups.

#### Results

#### Trial 1

Among the 14 patients treated with intravenous nicardipine, an adequate response was obtained with a dose of  $0.5 \,\mu$ g/kg per min in only 1: pulmonary arterial diastolic and right atrial pressures fell from 29 and 10 to 18 and 5 mmHg, respectively, and the cardiac index increased from 2.36 to 2.95 L/min perm<sup>2</sup>.

Therefore, the dose was increased to  $1.0 \,\mu g/kg$  per

min in the remaining 13 patients; at 30 min after the start of infusion in 11 and at 1 h in 2. Hemodynamic changes in these 13 patients are summarized in Table 4. The decrease in systemic vascular resistance, and hence in systemic pressure, induced by the drug was associated with a decrease in pulmonary artery diastolic pressure and an increase in cardiac output (Fig 1). At this dose, all 7 patients classified as Forrester's subset  $IV^{16}$  improved to a better classification (to subset III in 1 patient, II in 2 and I in 4).

The partial pressure of arterial oxygen (before infusion:  $102\pm33$  mmHg; after infusion:  $74\pm19$ mmHg) and oxygen saturation ( $97\pm2\%$  to  $94\%\pm3\%$ ) decreased without any change in the partial pressure of arterial carbon dioxide ( $34\pm8$  mmHg to  $35\pm8$ mmHg). However, oxygen delivery increased ( $387\pm$ 102 to  $483\pm125$  ml/min per m<sup>2</sup>) and oxygen consumption decreased ( $169\pm27$  to  $151\pm27$  ml/min per m<sup>2</sup>). No serious adverse effects were seen during infusion.

#### Trial 2

A total of 68 patients were enrolled in this doubleblind study. However, 11 patients were excluded from the analysis before the keys were opened; some did not satisfy the inclusion criteria while others had an underlying heart disease as listed in the exclusion criteria (Table 1). Among the remaining 57 cases, treatment was terminated prematurely because of an inadequate response or adverse effects in 4 cases. All of the adverse effects that occurred among the 68 patients during the investigation are listed in Table 5.

Hemodynamic data were analyzed in the 19 patients in Group 1, 15 in Group 2 and 19 in Group 3 who completed 2 h of infusion (Table 6). Beneficial effects

Table 6Hemodynamic Changes in Trial 2

	Group	No.	Before	30 min	60 min	120 min
HR (beat/min)	1	19	$95 \pm 19$	97±20	$96 \pm 20$	$95\pm19$
	2	15	$93 \pm 17$	$91 \pm 13$	$90 \pm 13$	$88 \pm 11$
	3	19	$91 \pm 20$	$90 \pm 20$	$88 \pm 20$	$88 \pm 21$
differences			ns	ns	ns	ns
SBP (mmHg)	1	19	141 + 31	127+25**	120+17**	$119 \pm 18^{**}$
(8)	2	15	149 + 25	$128 + 29^{*}$	$121 + 20^{**}$	$118 \pm 17^{**}$
	3	19	147 + 27	$118 + 14^{**}$	$109 + 14^{**}$	$107 + 14^{**}$
differences	·		ns	$1 vs 3^*$	1 vs 3*	1 vs 3*
DBP (mmHg)	1	19	79 + 24	$68 + 16^{**}$	66+15**	65+15**
DDI (mmilg)	2	15	$87 \pm 17$	$72 + 18^*$	$67 \pm 15^{**}$	$66 + 15^{**}$
	3	19	$83 \pm 15$	$65 \pm 11^{**}$	$59 \pm 10^{**}$	$58 \pm 13^{**}$
differences	5	17	ns	ns	ns	ns
מת	1	10	13478 ± 4312	12313 + 3355	11383 + 2502**	11326+2775*
DI	2	15	$13775 \pm 2050$	$12313 \pm 3533$ $11724 \pm 3612$	$11303 \pm 2372$ $10037 \pm 2701*$	$11320 \pm 2773$ $10437 \pm 2230**$
	2	15	$13723 \pm 2930$ $12415 \pm 2722$	$11724 \pm 3012$ $10537 \pm 3406**$	$10937 \pm 2701$ 0616 $\pm$ 2668**	$0.436 \pm 2718^{**}$
liffananaaa	3	19	13413 <u>+</u> 3732	10557 ±2490	9010 <u>+</u> 2000	9450 <u>1</u> 2/10
aijjerences			ns	ns	115	113
SPAP (mmHg)	1	19	$54 \pm 17$	47±15**	44±13**	<i>43</i> ± <i>13</i> **
	2	15	57±13	$49 \pm 12^{*}$	$45 \pm 13^{**}$	<i>46</i> ± <i>12</i> **
	3	. 19	$52 \pm 14$	$45 \pm 9^{*}$	$43 \pm 9^{**}$	$41 \pm 10^{**}$
differences			ns	ns	ns	ns
DPAP (mmHg)	1	19	$26 \pm 10$	$21 \pm 8^{**}$	$19 \pm 7^{**}$	$19 \pm 7^{**}$
	2	15	$27 \pm 10$	$23 \pm 10^{**}$	$20 \pm 8^{**}$	$20 \pm 8^{**}$
	3	19	$26 \pm 7$	$20\pm6^{**}$	$18 \pm 6^{**}$	$18 \pm 5^{**}$
differences			ns	ns	ns	ns
RAP (mmHg)	1	19	10 + 6	9 + 6	9+6	. 8+6
(//////////////////////////////////////	2	14	12+6	$\frac{-}{11+5}$	10+5	10+6
	3	19	11 + 4	$10 + 4^*$	$9+5^{*}$	9+4
differences	,		ns	ns	ns	ns
CI (llmin ner m²)	1	19	22+04	3 1+0 9**	$3.0+0.8^{**}$	$3.1 \pm 0.8^{**}$
er (innur per m)	2	15	$2.2 \pm 0.1$ 2 2 + 0 4	$2.7 \pm 0.6^{**}$	$3.0+0.6^{**}$	$2.9 \pm 0.5^{**}$
	3	19	$2.2 \pm 0.1$ 2 3+0 3	$32+08^{**}$	$3.1 \pm 0.8^{**}$	$3.1 \pm 0.7^{**}$
differences	5	17	2.0 ± 0.0 ns	ns	ns	ns
SWI $(a,m/heat ner m^2)$	1	19	24 + 11	$30 + 16^*$	30 + 15	31 + 14
SWI (g moeur per m)	2	14	$27 \pm 11$ $28 \pm 14$	$28 \pm 10$	$30 \pm 10$ $30 \pm 11$	29+9
	2	19	$20 \pm 17$ $28 \pm 9$	$\frac{20 \pm 12}{32 \pm 9}$	$29 \pm 7$	$\frac{29}{29+8}$
differences	5	17	$20 \pm 20$ ms	$\frac{52}{ns}$	ns	ns
SVD (duna and our 5)	1	10	2012 + 590	1211 + 240**	1275 ± 345**	1221 ± 316**
SVR (uyne-sec-cm <sup>-5</sup> )	1	19 17	$2043 \pm 309$	1511 <u>T</u> 549 1552   576**	1210 <u>-</u> 343 1310 - 456**	$1221 \pm 510$ $1207 \pm 321 **$
	2	14	$2204 \pm 301$	$1333 \pm 370$ $1324 \pm 462**$	$1319 \pm 430$ $1129 \pm 402**$	$1297 \pm 301$ $1110 \pm 292**$
1:00	3	19	$2130 \pm 0.004$	$1224 \pm 402$	$1130 \pm 402$	1110±302
aijjerences			ns	ns 100 x 60	122 + 00	115
PAR (dyne·sec·cm <sup>-5</sup> )	1	17	$172 \pm 129$	$122 \pm 92$	$132 \pm 88$	$144 \pm 70$
	2	13	$207 \pm 126$	$140 \pm 65$	$128 \pm 65^{*}$	$144 \pm 60$
	3	12	$126 \pm 109$	$104 \pm 38$	$103 \pm 26$	$96\pm64$
differences			ns	ns	ns	ns

Mean  $\pm$  SD, \*: p < 0.05, \*\*: p < 0.01 compared to control values. Differences indicate statistical significance among 3 groups. See Table 4 for other abbreviations.

on congestive heart failure, as evidenced by a decrease in LV filling pressure with an increase in cardiac output, were seen in all 3 groups beginning at 30 min of infusion. Cardiac work (stroke work index) did not decrease with the a decrease in filling pressure. Heart rate did not increase in any of the 3 groups, while

	Group	No.	Before	30 min	120 min
$PaO_2$ (mmHg)	1	16	86.7±20.4	67.2±18.7**	73.6±17.9**
	2	14	88.1±39.8	72.3±31.3**	66.2±20.2**
	3	16	85.9±27.3	$73.4 \pm 21.6^*$	$72.8 \pm 22.7^*$
differences			ns	ns	ns
aO <sub>2</sub> sat (%)	1	16	$96.5 \pm 1.9$	$92.2 \pm 5.9^*$	94.4±3.2*
	2	12	$95.6 \pm 3.0$	92.6±3.7**	$92.2 \pm 3.8^{**}$
	3	14	$95.2 \pm 3.1$	$93.5 \pm 3.1^{**}$	$93.7 \pm 3.6$
differences			ns	ns	ns
$O_2$ delivery (ml/min per m <sup>2</sup> )	1	15	<i>364.5</i> ± <i>87.3</i>	<i>471.3</i> ± <i>144.2</i> **	504.4±162.5**
	2	12	<i>347.9</i> ± <i>87.3</i>	<i>441.0±130.9</i> **	<i>482.0</i> ± <i>137.5</i> **
	3	13	$365.6 \pm 78.8$	509.0±143.4**	<i>485.3</i> ± <i>121.3</i> **
differences			ns	ns	ns
PaCO <sub>2</sub> (mmHg)	1	16	<i>33.0</i> ±5.4	<i>34.2</i> ±6.7	<i>33.0</i> ± <i>6.1</i>
	2	14	$33.2 \pm 6.5$	$34.3 \pm 5.2$	$34.8 \pm 5.9$
	3	16	$35.5 \pm 5.3$	$35.9 \pm 4.6$	$35.2 \pm 5.0$
differences			ns	ns	ns
$mvO_2sat$ (%)	1	8	<i>61.2</i> ± <i>8.7</i>	$68.5 \pm 11.3^*$	$70.5 \pm 7.8^{**}$
	2	7	$59.5 \pm 11.6$	62.6±13.8	$63.2 \pm 11.7$
	3	6	63.7±11.3	$69.9 \pm 8.2$	$70.5 \pm 9.9^{*}$
differences			ns	ns	ns
<sup>.</sup> VO <sub>2</sub> (ml/min per m <sup>2</sup> )	1	7	<i>136.0±37.4</i>	143.6±78.4	138.8±65.6
	2	6	$123.6 \pm 9.6$	$126.9 \pm 37.5$	<i>132.9</i> ± <i>35.1</i>
	3	5	$106.9 \pm 30.7$	113.6±33.9	$108.9 \pm 36.0$
differences			ns	ns	ns

Table 7Blood Gas Changes in Trial 2

Mean  $\pm$  SD, \*: p < 0.05, \*\*: p < 0.01 compared to control values. Differences indicate statistical significance among 3 groups. PaO<sub>2</sub>, partial arterial oxygen pressure; aO<sub>2</sub>sat, arterial oxygen saturation rate; O<sub>2</sub> delivery, blood oxygen delivery; PaCO<sub>2</sub>, partial arterial carbon dioxide pressure; mvO<sub>2</sub>sat, mixed venous oxygen saturation;  $\dot{VO}_2$ , oxygen consumption

myocardial oxygen consumption decreased significantly as evidenced by a decrease in the double product. Systemic vascular resistance and systolic pressure decreased significantly, but no change was seen in pulmonary arteriolar resistance or right atrial pressure. The decrease in systolic pressure was greater in Group 3 than in Group 1; however, no other differences were seen among these 3 doses.

Partial arterial oxygen pressure and arterial oxygen saturation decreased to the same extent with the 3 doses. Although oxygen delivery increased significantly with infusion, oxygen consumption did not change (Table 7).

#### Discussion

Nicardipine, a dihydropyridine derivative, has a potent arteriolar vasodilatory effect and negligible negative inotropic and veno-dilating effects<sup>11</sup> This drug has been administered intravenously in patients with acute myocardial infarction and heart failure.

Silke and his coworkers<sup>12</sup> showed that nicardipine induces a dose-dependent decrease in systemic vascular resistance and arterial pressure, and an increase in heart rate and cardiac output without any significant change in LV filling pressure. Furthermore, Greenbaum et al<sup>13</sup> and Burlew et al<sup>14</sup> reported that nicardipine induces a significant decrease in filling pressure. The doses used in these previous investigations ranged from 1.25 to 10 mg injected over 5 to 20 min. Since nicardipine induces a marked decrease in systemic pressure, a nonsignificant decrease in LV filling pressure, and tachycardia, this agent is not well-regarded for the treatment of heart failure<sup>17,18</sup> In a preliminary study, we evaluated the dose response to nicardipine at 10, 20 and 40  $\mu$ g/kg given over 5 min in patients with heart failure; except for a greater decrease in systemic vascular resistance and systolic blood pressure at the higher doses, the response was almost identical among these 3 doses<sup>15</sup> Therefore, the present investigation was performed on the assumption that the optimal dose of this agent for the treatment of heart failure might be much smaller than has been used to date.

In Trial 1, a  $0.5 \,\mu$ g/kg per min infusion of nicardipine produced an approximately 18% decrease in systemic vascular resistance associated with an 18% increase in cardiac output and a 13% decrease in LV filling pressure. These respective changes each improved to 30% when the dose was increased to  $1.0 \,\mu$ g/kg per min, and dyspnea improved. The increases in cardiac output and decreases in LV filling pressure obtained at 1.0, 2.0 and  $3.0 \,\mu$ g/kg per min in Trial 2 were similar to each other and also similar to the changes at  $1.0 \,\mu$ g/kg per min in Trial 1. The only difference among these 3 doses was the greater decrease in systolic blood pressure with  $3.0 \,\mu$ g/kg per min.

The main goals of treatment in acute heart failure are to reduce LV filling pressure to relieve dyspnea, and to improve the peripheral metabolic state through increased cardiac output. Nicardipine infusion achieved these important goals without increasing myocardial oxygen consumption, as manifested by a significant (15% to 30%) decrease in the double product. Although nicardipine has been reported to cause reflex tachycardia without a significant decrease in filling pressure<sup>12</sup> these adverse effects in heart failure seem to be dose-dependent. An excessive decrease in systemic vascular resistance might cause reflex tachycardia and augmentation of venous return via an increase in cardiac output, since as nicardipine has essentially no effect on the venous system. Although filling pressure decreased by about 30%, we did not observe tachycardia in this investigation. The difference between our data and those reported previously appears to be related to the dosage used, which indicates that smaller doses are preferable in the treatment of heart failure.

The major adverse effect noted in the present infusion regimen was hypoxemia, which caused the interruption of treatment in some patients (Table 5). Although the cause of hypoxemia with nicardipine infusion is not clear, this phenomenon is not specific to nicardipine and has been seen with other vasodilators used to treat acute heart failure<sup>19-21</sup> This phenomenon may be the result of pulmonary vasodilation and poorly ventilated alveoli, which would explain the aggravation of the imbalances in ventilation and perfusion in acute heart failure. A second problem observed with this nicardipine regimen was hypotension. This phenomenon may be more frequent in patients with relatively low systolic pressure, since nicardipine is a potent arteriolar vasodilator and the effect seems to be dose-dependent.

#### Conclusion

Intravenous nicardipine infusion therapy is effective for the treatment of acute heart failure, especially in patients with elevated LV filling pressure, low cardiac output, and elevated systemic blood pressure. The optimal dosage in the patients studied here was  $1.0 \mu g/kg$  per min: half of this dose had inadequate effects, while, 2 or 3 times this dose had similar effects.

#### Appendix

#### Participating Institutions

Asahikawa City Hospital, Akita University School of Medicine, Iwate Medical University School of Medicine, Yamagata University School of Medicine, Utsunomiya Saiseikai Hospital, Ashikaga Red Cross Hospital, National Defense Medical College, Yokohama City University School of Medicine, Shizuoka General Hospital, Hamamatsu Rosai Hospital, Okazaki Municipal Hospital, Toyota Memorial Hospital, Nagova University School of Medicine, Nagova Daini Red Cross Hospital, Nagoya Ekisaikai Hospital, Nagahama Red Cross Hospital, Shiga Medical Center For Adult Disease, Shiga University of Medical Science, Otsu Red Cross Hospital, Faculty of Medicine Kyoto University, Rakuwakai Otowa Hospital, Takeda Hospital, Daini Okamoto Hospital, Nara Medical University, Nara Prefectural Hospital, Osaka Medical College, National Cardiovascular Center, Kitano Hospital, Sakurabashi Watanabe Hospital, Osaka Red Cross Hospital, Kawachi General Hospital, Osaka Police Hospital, Osaka Prefectural Hospital, Kinki University School of Medicine, Wakayama Red Cross Hospital, Hyogo Prefectural Amagasaki Hospital, Hvogo College of Medicine, Kobe University School of Medicine, Kurashiki Central Hospital, Tokuyama Central Hospital, Yamaguchi University School of Medicine, Kokura Memorial Hospital, Nagasaki University School of Medicine

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