

mate of the association of interval myocardial infarction with progressive systolic dysfunction. A fourth limitation is that the EF was used to assess LV systolic performance. The EF is known to overestimate LV systolic function in the setting of concentric hypertrophy,<sup>15</sup> and systolic dysfunction was likely already present at the time of baseline echocardiogram. Nevertheless, a depressed EF does have immediate clinical relevance.

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## Comparison of Effects on Left Ventricular Filling Pressure of Intravenous Nesiritide and High-Dose Nitroglycerin in Patients With Decompensated Heart Failure

Uri Elkayam, MD, Mohammed W. Akhter, MD, Harpreet Singh, MD, Salman Khan, MD, and Ahsan Usman, MD

The results of this study showed an advantage of nesiritide compared with high-dose nitroglycerin in the treatment of patients with decompensated heart failure. Nesiritide resulted in an early decrease in pulmonary capillary wedge pressure ( $\leq 15$  minutes), which was sustained throughout the study period (24 hours) without the need for up-titration. In contrast, the onset of the nitroglycerin-mediated hemodynamic effect was delayed, and despite aggressive up-titration, the decrease in pulmonary capillary wedge pressure was gradually attenuated because of the early development of tolerance. ©2004 by Excerpta Medica, Inc.

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From the Heart Failure Program, Division of Cardiovascular Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California. This study was supported by Scios, Inc., Fremont, California. Dr. Elkayam's address is: Heart Failure Program, Division of Cardiovascular Medicine, Los Angeles County/University of Southern California Medical Center, GH 7621, 1200 North State St, Rm 7440, Los Angeles, California 90033. E-mail: elkayam@usc.edu. Manuscript received July 18, 2003; revised manuscript received and accepted September 22, 2003.

This study represents an analysis of the effect of nesiritide and nitroglycerin on left ventricle filling pressure in 27 consecutive patients who were randomized to the Vasodilation in the Management of Acute Congestive heart failure (VMAC) study at 1 medical center (University of Southern California/Los Angeles County Medical Center) and who required invasive hemodynamic monitoring to manage their congestive heart failure.

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The VMAC study<sup>1</sup> was a prospective, multicenter, randomized double-blind trial that evaluated the hemodynamic and clinical effects of nesiritide, a recombinant human brain natriuretic peptide,<sup>2</sup> compared with intravenous nitroglycerin or placebo, all added to standard care, as determined by the investigators. This study included heart failure therapies, such as diuretics, digoxin, angiotensin-converting enzyme inhibitors, calcium channel blockers, and inotropes. For the first 3 hours of the trial, patients were randomly assigned to receive placebo, intravenous nitroglycerin (Tridil; BMS Pharma, Wilmington, Delaware), or nesiritide (Natrecor; Scios, Fremont, California). After 3 hours, the placebo patients were crossed over to receive double-blind treatment of either intravenous nitroglycerin or nesiritide. Treatment continued for a minimum of 24 hours. The choice of the

Parameter	Nesiritide (n = 15)	Nitroglycerin (n = 12)	p Value
Age (yrs)			
Mean $\pm$ SD	54 $\pm$ 11	56 $\pm$ 12	0.613
Range	40–74	27–76	
Men	12	11	0.605
Left ventricular ejection fraction (%)			
Mean $\pm$ SD	27 $\pm$ 12	26 $\pm$ 10	0.729
Range	12–48	10–41	
Heart rate (beats/min)	84 $\pm$ 14	86 $\pm$ 11	0.644
Systolic blood pressure (mm Hg)	124 $\pm$ 20	124 $\pm$ 26	0.891
Cardiac index (L/min/m <sup>2</sup> )	2.3 $\pm$ 0.47	2.0 $\pm$ 0.65	0.279
Mean PCWP (mm Hg)	29 $\pm$ 6.5	26 $\pm$ 9	0.677
Chronic cardiovascular medications			
ACE inhibitors (%)	7 (47%)	6 (50%)	1.000
All receptor antagonists (%)	1 (7%)	1 (8%)	1.000
Diuretics (%)	8 (53%)	7 (58%)	1.000
Digoxin (%)	5 (33%)	7 (58%)	0.258
$\beta$ blockers (%)	3 (20%)	1 (8%)	0.605
Nitrates (%)	10 (67%)	3 (25%)	0.054
Aldosterone inhibitors (%)	4 (27%)	2 (17%)	0.662

ACE = angiotensin-converting enzyme; All = angiotensin<sub>2</sub>.

initial dose of intravenous nitroglycerin as well as its titration throughout the study was at the discretion of the investigators. Nesiritide was given as a 2  $\mu\text{g}/\text{kg}$  bolus followed by a fixed dose infusion of 0.01  $\mu\text{g}/\text{kg}/\text{min}$  for the first 3 hours, after which, in a small group of patients, the dose was incrementally increased every 3 hours to a maximum of 0.03  $\mu\text{g}/\text{kg}/\text{min}$  in accordance with pre-specified criteria (pulmonary capillary wedge pressure [PCWP]  $\geq 20$  mm Hg and systolic blood pressure  $\geq 100$  mm Hg).<sup>1</sup> Down-titration of both study drugs was also permitted according to the investigators' discretion.

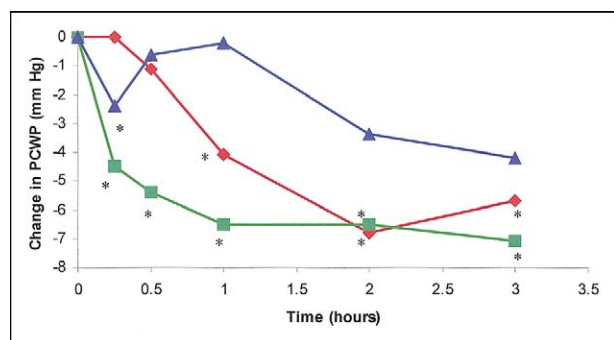
The study enrolled adults with acutely decompensated congestive heart failure that was severe enough to require hospitalization and intravenous therapy, including dyspnea at rest and a mean PCWP of  $\geq 20$  mm Hg. Patients with the following conditions were excluded from the study: systolic blood pressure  $< 90$  mm Hg; cardiogenic shock or volume depletion; an acutely unstable clinical status that would not permit a 3-hour placebo period; use of intravenous nitroglycerin that could not be withheld; mechanical ventilation; and anticipated survival of  $< 30$  days.

Right-sided heart catheterization was performed with a balloon-tipped, triple-lumen Swan-Ganz catheter. The reference point for the procedure was at the mid-chest level with the patient in a supine position. Mean PCWP was measured at baseline and again at 15 minutes, 30 minutes, and at 1, 2, 3, 6, 9, 12, and 24 hours after initiation of therapy.

Descriptive statistics (mean  $\pm$  SD) were provided for catheterized patients in the site by treatment group (nesiritide and nitroglycerin). Nesiritide-treated patients who were randomized to either the fixed or adjustable dose groups were analyzed as 1 group. Placebo patients were included in the dose group to which they were randomized after the 3-hour placebo

Time Point (hr)	Nesiritide ( $\mu\text{g}/\text{kg}/\text{min}$ )	Nitroglycerin ( $\mu\text{g}/\text{min}$ )
	(n = 13)	(n = 9)
0.25	0.01 $\pm$ 0	41.1 $\pm$ 20.3
0.50	0.01 $\pm$ 0	77.8 $\pm$ 54.3
1	0.01 $\pm$ 0	120 $\pm$ 74
2	0.01 $\pm$ 0	146 $\pm$ 77
3	0.01 $\pm$ 0	155 $\pm$ 73
	(n = 15)*	(n = 12)*
6	0.010 $\pm$ 0.002	161 $\pm$ 68
9	0.011 $\pm$ 0.004	161 $\pm$ 68
12	0.012 $\pm$ 0.005	161 $\pm$ 68
24	0.011 $\pm$ 0.004	150 $\pm$ 86

\*Includes additional patients randomized from the placebo group after the 3-hour time point.



**FIGURE 1.** Change in PCWP from baseline during the first 3 hours of drug infusion. *Triangles*, placebo; *squares*, nesiritide; and *diamonds*, nitroglycerin. \* $p < 0.05$  versus baseline.

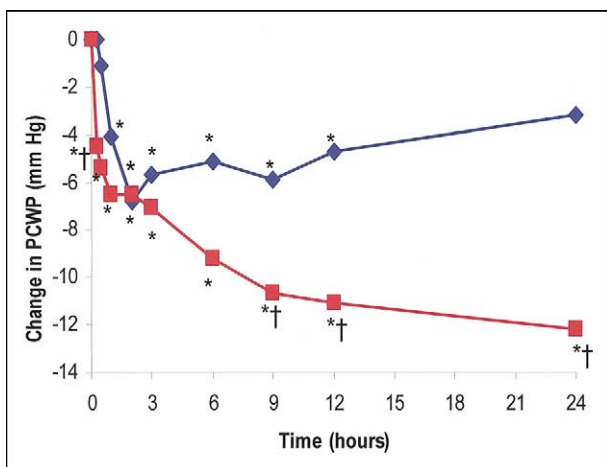
period. Baseline characteristics between the catheterized patients in the 2 treatment groups were compared using a 2-sample Student's *t* test for continuous variables and a Fisher's exact test for categorical variables. Mean PCWP changes were analyzed for each treatment group using a 1-sample Student's *t* test.

The 27 patients evaluated in this study included 23 men and 4 women, aged 27 to 76 years (mean 55  $\pm$  11). Left ventricular ejection fraction ranged from 10% to 48% (mean 27  $\pm$  10%). Baseline heart rate, systolic blood pressure, PCWP, and cardiac index were similar between the treatment groups (Table 1). Nine patients were initially randomized to receive intravenous nitroglycerin, 13 to receive nesiritide, and 5 to receive placebo. After 3 hours of treatment, the 5 placebo patients were rerandomized: 3 to receive intravenous nitroglycerin and 2 to receive nesiritide. For the remainder of the study, a total of 15 patients received nesiritide (9 were assigned to the fixed-dose group and 6 were assigned to the adjustable-dose group), and 12 patients received nitroglycerin.

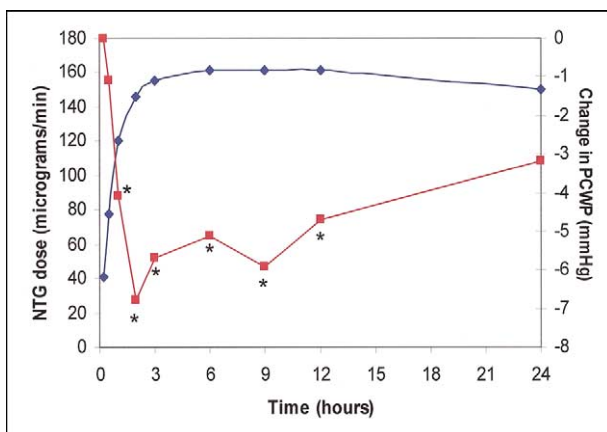
At study entry, all patients had dyspnea at rest and were categorized in New York Heart Association functional class IV. There were no significant differences among the treatment groups with regard to demographics, hemodynamic parameters, or long-term use of cardiovascular medications (Table 1). All patients exhibited a negative fluid balance during the 24-hour study period;

Time Point (hr)	Nesiritide Group (n = 13)*	p Value Compared With		Nitroglycerin Group (n = 9)	p Value (comparison with Baseline)
		Baseline	NTG		
0.25	-4.5 ± 3.9	0.001	0.013	0.0 ± 4.4	1.000
0.50	-5.4 ± 5.2	0.003	0.075	-1.1 ± 5.7	0.573
1	-6.5 ± 6.0	0.002	0.303	-4.1 ± 4.4	0.023
2	-6.5 ± 8.12	0.014	0.917	-6.8 ± 5.6	0.007
3	-7.1 ± 7.1 (n = 15)*	0.004	0.637	-5.7 ± 6.1 (n = 12)*	0.023
6	-9.2 ± 6.2	<0.001	0.091	-5.1 ± 4.6	0.003
9	-10.7 ± 5.4	<0.001	0.019	-5.9 ± 4.0	0.000
12	-11.1 ± 5.7	<0.001	0.004	-4.7 ± 4.4	0.003
24	-12.2 ± 7.5	<0.001	0.005	-3.2 ± 7.0	0.148

\*Includes patients randomized from the placebo group after the 3-hour time point.



**FIGURE 2.** Change in PCWP from baseline during 24 hours of intravenous infusion of nitroglycerin and nesiritide. *Squares*, nesiritide; *diamonds*, nitroglycerin. \*p <0.05 versus baseline; †p <0.02 versus nitroglycerin.



**FIGURE 3.** Nitroglycerin (NTG) dose and change in PCWP during treatment with NTG. *Squares*, change in PCWP; *diamonds*, nitroglycerin dose. \*p <0.05 versus baseline.

the volume loss was similar between treatment groups (nesiritide: 1,806 ± 2,408 ml vs nitroglycerin: 1,864 ± 2,259 ml). During the 24-hour study period, the 12 patients at this study center who were randomized to

intravenous nitroglycerin received on average a threefold higher dose of nitroglycerin compared with all catheterized patients in the VMAC study. These patients also received higher nitroglycerin doses compared with their noncatheterized cohorts at the same study center (mean range over 24 hours 41 to 59 μg/min). The mean dose at 15 minutes was 41 ± 20 μg/min and was up-titrated to a maximum of 161 ± 68 μg/min by 6 hours. This dose was maintained until 24 hours, at which time the mean dose was 150 ± 86 μg/min (Table 2). All 12 patients randomized to receive nitroglycerin had their dose increased at some point

during the study. Eight patients had their doses decreased; 6 of them because the clinical effect had been achieved and 2 due to adverse events. The mean nesiritide dose ranged from 0.010 to 0.012 μg/kg/min (Table 2) and remained fairly constant throughout the study. Only 3 patients had their nesiritide dose increased (1 patient's dose was increased to 0.015 μg/kg/min at 12 hours; another patient reached 0.025 μg/kg/min by 20 hours; and the third patient reached 0.03 μg/kg/min by 17 hours). Two patients had their nesiritide dose decreased, 1 because the clinical end point was achieved and 1 because of an adverse event.

The administration of nesiritide, at a dose of 2 μg/kg bolus followed by an infusion of 0.01 μg/kg/min, resulted in an early and significant (p ≤0.01) decrease in PCWP compared with baseline; this trend persisted through the 3-hour time period (Figure 1 and Table 3). In contrast, intravenous nitroglycerin was not associated with an early decrease in PCWP, and a significant decrease was not observed until 1 hour after initiation of the nitroglycerin infusion. Gradual up-titration of nitroglycerin resulted in a further decrease of PCWP and reached a maximum effect at 2 hours. Despite diuresis and continuous infusion of nitroglycerin, no further decrease in PCWP was seen by 3 hours. Administration of placebo resulted in no significant decrease in PCWP during the first 3 hours (Figure 1). Continuous infusion of nesiritide resulted in a sustained decrease in PCWP (12.2 ± 7.5 mm Hg at 24 hours; p = 0.02) (Figure 2). In contrast, the effect of nitroglycerin diminished over time despite the increased dose, resulting in a decrease in PCWP of 3.2 ± 7.0 mm Hg at 24 hours (p = 0.15) (Figure 3).

This study compared the effect of high-dose intravenous nitroglycerin and standard-dose nesiritide on left ventricular filling pressure in patients hospitalized for decompensated heart failure and demonstrated an advantage of nesiritide compared with nitroglycerin that is reflected in both the early and the late effects of the 2 drugs. Results of the present study confirm previous reports that showed that resistance to nitroglycerin-mediated vasodilation observed in patients with heart failure<sup>3-5</sup> can be overcome by dose escalation.<sup>6,7</sup> At the same time, the overall findings of the VMAC trial, as

well as our own experience, demonstrate the reluctance of physicians to up-titrate nitroglycerin doses, especially in patients being treated without hemodynamic monitoring.<sup>1</sup> Our findings also reflect the temporary nature of the nitrate-induced hemodynamic effect because of the early development of tolerance.<sup>8,9</sup> Attenuation of effect with continuous vascular exposure to nitrates has recently been suggested to be caused by increased production of oxygen-free radicals, which leads to decreased bioavailability of nitrate-derived nitric oxide<sup>10,11</sup> and a negative effect on the function of nitric oxide synthase, the enzyme responsible for endothelial control of vascular tone.<sup>12,13</sup>

This study represents a subgroup analysis of data from 1 individual center participating in the VMAC study. As such, the results are limited by a relatively small sample size and the derivative experience. In addition, although the maximum mean dose of nitroglycerin used at this site was high relative to that for all sites participating in the VMAC study, even higher doses may be used in clinical practice. Higher doses of nitroglycerin may have similar or different clinical outcomes.

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## Meta-Analysis of Effectiveness or Lack Thereof of Angiotensin-Converting Enzyme Inhibitors for Prevention of Heart Failure in Patients With Systemic Hypertension

Fabio Angeli, MD, Paolo Verdecchia, MD, Gian Paolo Reboldi, MD, PhD, MSc, Roberto Gattobigio, MD, Maurizio Bentivoglio, MD, Jan A. Staessen, MD, PhD, and Carlo Porcellati, MD

We undertook a meta-analysis of large, randomized controlled trials in hypertensive subjects that compared angiotensin-converting enzyme (ACE) inhibitors with different classes of antihypertensive drugs. Compared with subjects randomized to drugs different from ACE inhibitors, those treated with ACE inhibitors did not show a different risk of congestive heart failure (CHF) (odds ratio 1.03, 95% confidence interval 0.96 to 1.12,  $p = 0.407$ ). The degree of protection from CHF associated with the use of ACE inhibi-

tors showed a nonsignificant trend to increase with age and the degree of blood pressure control. Thus, the hypothesis that ACE inhibitors are superior to other antihypertensive drugs for prevention of CHF in hypertension remains unproven. ©2004 by Excerpta Medica, Inc.

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**A**ngiotensin-converting enzyme (ACE) inhibitors improve symptoms and prolong survival in patients with congestive heart failure (CHF). In a meta-analysis of 7 large studies in patients with CHF or left ventricular dysfunction, ACE inhibitors were associated with a significant decrease in a composite of death, myocardial infarction, and hospital admission for patients with CHF (odds ratio [OR] 0.72, 95% confidence interval [CI] 67 to 78).<sup>1</sup> However, although the benefits of ACE inhibitors in patients with CHF are well established, their potential value for

From the Department of Cardiovascular Disease, Hospital R. Silvestrini, Perugia, Italy; Dipartimento di Medicina Interna, Università degli Studi di Perugia, Perugia, Italy; and Laboratory of Hypertension, Department of Molecular and Cardiovascular Research, Campus Gasthuisberg, Leuven, Belgium. Dr. Verdecchia's address is: Dipartimento Malattie Cardiovascolari, Ospedale R. Silvestrini, Località S. Andrea delle Fratte, 06156, Perugia, Italy. E-mail: erdec@tin.it. Manuscript received July 22, 2003; revised manuscript received and accepted September 18, 2003.