Journal of the American College of Cardiology Vol. 52, No. 3, 2008

Published by Elsevier Inc.
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.02.083

Sodium Nitroprusside for Advanced Low-Output Heart Failure

Wilfried Mullens, MD, Zuheir Abrahams, MD, PhD, Gary S. Francis, MD, FACC, Hadi N. Skouri, MD, Randall C. Starling, MD, MPH, FACC, James B. Young, MD, FACC, David O. Taylor, MD, FACC, W. H. Wilson Tang, MD, FACC

Cleveland, Ohio

Objectives This study was designed to examine the safety and efficacy of sodium nitroprusside (SNP) for patients with acute decompensated heart failure (ADHF) and low-output states.

Background Inotropic therapy has been predominantly used in the management of patients with ADHF presenting with low cardiac output.

Methods We reviewed all consecutive patients with ADHF admitted between 2000 and 2005 with a cardiac index ≤2 l/min/m² for intensive medical therapy including vasoactive drugs. Administration of SNP was chosen by the attending clinician, nonrandomized, and titrated to a target mean arterial pressure of 65 to 70 mm Hg.

Results Compared with control patients (n = 97), cases treated with SNP (n = 78) had significantly higher mean central venous pressure (15 vs. 13 mm Hg; p = 0.001), pulmonary capillary wedge pressure (29 vs. 24 mm Hg; p = 0.001), but similar demographics, medications, and renal function at baseline. Use of SNP was not associated with higher rates of inotropic support or worsening renal function during hospitalization. Patients treated with SNP achieved greater improvement in hemodynamic measurements during hospitalization, had higher rates of oral vasodilator prescription at discharge, and had lower rates of all-cause mortality (29% vs. 44%; odds ratio: 0.48; p = 0.005; 95% confidence interval: 0.29 to 0.80) without increase in rehospitalization rates (58% vs. 56%; p = NS).

Conclusions In patients with advanced, low-output heart failure, vasodilator therapy used in conjunction with optimal current medical therapy during hospitalization might be associated with favorable long-term clinical outcomes irrespective of inotropic support or renal dysfunction and remains an excellent therapeutic choice in hospitalized ADHF patients. (J Am Coll Cardiol 2008;52:200–7) © 2008 by the American College of Cardiology Foundation

Advances in medical therapies (such as neurohormonal modulation and pacing/defibrillation strategies) have significantly altered the natural history of heart failure and improved long-term outcomes (1–5). However, the pathophysiology and treatment of acute decompensated heart failure (ADHF) remains poorly understood, especially in more advanced stages when cardiac output is significantly reduced. Our treatment goal remains symptomatic relief, primarily by decreasing volume overload and attenuating pulmonary congestion with loop diuretics. In the setting of a low cardiac output, augmentation of contractility with parenteral inotropic therapy is often used. However, vasoactive drugs are often administered at the expense of a potential risk of developing adverse outcomes including worsening renal function or precipitating arrhythmias (6–8). Concern has also arisen from post hoc observations that short-term infusions of newer drugs such as levosimendan, milrinone, and nesiritide in hospitalized ADHF patients might negatively impact long-term outcomes (9–11).

See page 208

There is a resurgence of interest in the use of intravenous vasodilators in the management of ADHF, particularly with the recognition that a large majority of patients present with elevated rather than low blood pressures (12). The latest clinical guidelines from the Heart Failure Society of America (13) advocate the use of intravenous vasodilators as part of the treatment strategy for ADHF (Level of Evidence: C). Despite these guideline recommendations, only about 18% of all patients hospitalized for ADHF received these agents and <1% received sodium nitroprusside (SNP) (14).

From the Department of Cardiovascular Medicine, Kaufman Center for Heart Failure, Cleveland Clinic, Cleveland, Ohio. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the article as written.

Manuscript received November 15, 2007; revised manuscript received February 7, 2008, accepted February 12, 2008.

Sodium nitroprusside is an older intravenous vasodilator, which is often being used to titrate off inotropic therapy in patients with refractory heart failure (15). It is administered almost exclusively in critical care settings with careful invasive hemodynamic monitoring due to the risk of inducing hypotension. Furthermore, prolonged use of SNP has been associated with the risk of thiocyanate toxicity. These concerns have hindered the general enthusiasm in using SNP in the contemporary management of ADHF, even though the favorable hemodynamic effects have been well-documented.

Based on our extensive experience with SNP over many years in a heart failure intensive care unit, the primary aim of this study was to examine the safety and efficacy of a vasodilator such as SNP as part of the treatment regimen for hospitalized ADHF patients with low-output states. An important objective was to characterize the group selected to receive SNP, compare it with those patients treated with alternative strategies, and determine whether there were any short- and long-term differences in treatment patterns and clinical outcomes between the 2 groups. There are no similar data currently available in the contemporary literature.

Methods

Patient population. We reviewed the electronic medical records of consecutive patients, age ≥18 years, with chronic (>6 months) systolic heart failure (New York Heart Association functional class III to IV), who underwent a right heart catheterization for evaluation of ADHF at the Cleveland Clinic between January 1, 2000, and December 31, 2005. From this large cohort, we narrowed our study population to include only patients actually admitted to the heart failure intensive care unit for intensive medical therapy (15). The inclusion criteria included: 1) impaired cardiac output defined by cardiac index ≤2.0 l/min/m^2; and 2) elevated filling pressures, as defined by pulmonary capillary wedge pressure (PCWP) ≥18 mm Hg and/or right atrial pressure ≥8 mm Hg. Exclusion criteria included: 1) use of inotropic infusion at the time of cardiac catheterization; 2) use of nesiritide during admission; and 3) mean systemic arterial pressure (MAP) ≤60 mm Hg at the time of cardiac catheterization. The Cleveland Clinic Institutional Review Board approved this project.

Protocol for intensive medical therapy. The pharmacologic approach and hemodynamic goals of intravenous therapy for ADHF have been previously described (16). Briefly, optimal hemodynamic response is defined as a decrease in PCWP to ≤18 mm Hg, decrease in mean pulmonary arterial pressure (mPAP) by at least 20%, decrease in right atrial pressure to ≤8 mm Hg, and improvement in cardiac index to ≥2.2 l/min/m^2, all while maintaining MAP >65 mm Hg. The systemic blood pressure was generally measured noninvasively by an automatic cuff sphygmomanometer every 15 min. To achieve the hemodynamic goals, most patients were treated with simultaneous intravenous diuretics in combination with either vasodilators or inotropic agents while continuing previous therapies with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, beta-adrenergic blockers, hydralazine, isosorbide dinitrate, and spironolactone as tolerated. Some patients received both SNP and inotropic drugs, and for purposes of this analysis, they are considered in the SNP group.

Abbreviations and Acronyms

ADHF = acute decompensated heart failure
LV = left ventricle/ventricular
MAP = mean systemic arterial pressure
mPAP = mean pulmonary arterial pressure
PCWP = pulmonary capillary wedge pressure
SNP = sodium nitroprusside

SNP infusion protocol. The decision to use SNP and/or inotropic therapy was at the discretion of the physician caring for the patient and no randomization scheme was employed. In addition, there might have been some selection bias toward greater use of vasodilators in case of higher blood pressure, although we also often use vasodilators to wean people from inotropic or intra-aortic balloon pump support. The SNP was administered intravenously by a continuous infusion at a dose of 10 to 400 μg/min (without bolus) as needed to improve hemodynamics (Table 1). Titration of SNP dose was based on achieving a target MAP of 65 to 70 mm Hg. The titration was mainly done by nursing staff who are well trained and experienced in the use of SNP and are able to titrate drugs without continuous physician input. Once MAP goals were achieved (usually within 24 h), and optimal hemodynamic measures were maintained, SNP infusion was gradually weaned by maintaining the MAP at 65 to 70 mm Hg. Doses of neurohormonal antagonists and/or a combination of hydralazine and isosorbide dinitrate were continued or up-titrated to guideline-recommended therapeutic doses. Titration of oral drugs follows standard protocols (Table 1) in our intensive care unit, but the sequence of drugs was also at the attending cardiologist's discretion. The duration of infusions of intravenous agents in the intensive care unit varied widely, but typically lasted between 24 and 72 h. Standard patient education materials and counseling were given to the patient at the time of admission, and post-discharge follow-up was provided by a heart failure disease management clinic.

Hemodynamic assessment. Central venous pressure, right atrial pressure, systolic and diastolic blood pressure, mPAP, and PCWP were assessed on admission at end expiration with a balloon-tipped catheter at steady state with the patient in a supine position. Cardiac output was determined by calculation using the Fick equation through sampling of a mixed central venous blood gas taken in the pulmonary artery while assuming standard metabolic rates. All initial measurements were performed at the cardiac catheterization laboratory for consistency of results reporting.

Table 1 Standard Medication Protocols for the Cleveland Clinic Heart Failure Intensive Care Unit

Sodium nitroprusside
Begin at 10 to 40 μg/min (without bolus)
↑ as tolerated to achieve desired hemodynamic goals, targeting MAP 65 to 70 mm Hg
Do not ↑ dose beyond 400 μg/min
To wean off: ↓ infusion gradually as tolerated while maintaining MAP goals and initiating/increasing oral vasodilators
Captopril
Incremental ↑ 6.25→12.5→25→50 mg
Begin at 6.25 to 12.5 mg orally
After 2 h, if initial dose tolerated, ↑ incrementally to next dose
After 2 h, if previous dose tolerated, ↑ incrementally to next dose
After 6 h, if previous dose tolerated, then 50 mg orally TID*
Isosorbide dinitrate
Begin 10 mg orally
After 2 h, if initial dose tolerated, ↑ to 20 mg
After 8 h, if 20 mg tolerated, ↑ to 40 mg
After 8 h, if 40 mg tolerated, ↑ to 60 mg
After 8 h, if 60 mg tolerated, then 60 mg orally TID*
Hydralazine
Begin 25 mg orally (or 10 mg if MAP is low or patient is in labile condition)
After 2 h, if initial dose tolerated, ↑ to 50 mg
After 6 h, if 50 mg tolerated, ↑ to 75 mg
After 6 h, if 75 mg tolerated, ↑ to 100 mg
After 6 h, if 100 mg tolerated, then 100 mg QID*

*If previous dose is not tolerated, administer highest dose tolerated TID or QID.
MAP = mean arterial pressure; QID = 4 times daily; TID = 3 times daily.

End points. Three pre-specified end points were analyzed and compared between cases and control patients during follow-up: all-cause mortality, cardiac transplant, and first readmission for heart failure following discharge. A combined end point of all-cause mortality and cardiac transplant was also analyzed. The duration of total follow-up was defined as the interval from the index right heart catheterization on the day of admission to all-cause mortality or cardiac transplant. Death was determined using data documented in the medical record and confirmed by surveying the Social Security Death Index.

Statistical analysis. All data are expressed as mean ± standard deviation for continuous variables and as a ratio for categorical data. Univariate and multivariate comparisons of these variables were performed between both treatment groups for the different end points using SPSS for Windows, Release 11.5 (SPSS Inc., Chicago, Illinois). A paired and unpaired *t* test for continuous data and chi-square or Fisher exact test for categorical data was used for appropriate comparisons. All continuous variables were assessed for normal distribution and otherwise nonparametric tests were employed. The Cox proportional hazards regression model was used to determine which variables were related significantly to the different end points during the follow-up period. Variable selection in multivariable modeling was based on statistical significance of the univariate analysis. Statistical significance was set at a 2-tailed probability level of <0.05.

Results

Baseline characteristics. A total of 175 patients fulfilled all inclusion and exclusion criteria. Of these, 78 received SNP during their hospitalization (cases) and 97 did not receive SNP (control patients). Baseline clinical characteristics were similar among patients in the 2 study groups (Table 2). Mean intensive care and hospital duration was 3.5 ± 1 and 8 ± 7 days, respectively, and was also similar between groups. Brain natriuretic peptide measurements within 3 days of admission were available in 32% of eligible subjects and were comparable between SNP-treated and non–SNP-treated patients (median [25%, 75%]: 823 [577, 1,445] vs. 987 [571, 1,200] pg/ml).

Hemodynamic assessment. As shown in Table 3, the patients treated with SNP presented with higher baseline filling pressures and systemic and pulmonic vascular resistance, while demonstrating a lower cardiac output and cardiac index. Furthermore, the average mean arterial blood pressure and systolic blood pressure at baseline was slightly higher in the SNP cases than in control patients. Mean left ventricular (LV) ejection fraction, LV end-diastolic diameter, and severity of mitral regurgitation (assessed within 3

Table 2 Baseline Patient Characteristics

	No Nitroprusside (n = 97)	Nitroprusside (n = 78)	p Value
Demographics			
Age (yrs)	55 ± 11	55 ± 11	NS
Men (%)	80	84	NS
Caucasian (%)	80	76	NS
African American (%)	19	22	NS
NYHA functional classification (%)			
III	44	42	NS
IV	56	58	NS
Medical history (%)			
Hypertension	77	70	NS
Hyperlipidemia	51	61	NS
Diabetes	28	27	NS
Smoking	47	55	NS
Previous CABG	28	36	NS
ICD	42	46	NS
CRT-D	16	13	NS
Etiology heart failure (%)			
Ischemic	48	52	NS
Idiopathic dilated	39	39	NS
Valvular	8	5	NS
Other	5	3	NS
Serology			
Hemoglobin (g/dl)	13.3 ± 1.8	13.2 ± 1.9	NS
BUN (mg/dl)	31 ± 17	31 ± 21	NS
Sodium (mmol/l)	136 ± 4	137 ± 4	NS
Serum creatine baseline (mg/dl)	1.4 ± 0.5	1.3 ± 0.5	NS
Serum creatine peak (mg/dl)	1.5 ± 0.6	1.4 ± 0.6	NS
Serum creatine discharge (mg/dl)	1.3 ± 0.5	1.3 ± 0.5	NS

Values are mean ± SD or percentage.
BUN = blood urea nitrogen; CABG = coronary artery bypass graft; CRT-D = cardiac resynchronization therapy with defibrillator; ICD = implantable cardioverter-defibrillator; NS = not significant; NYHA = New York Heart Association.

Table 3 Baseline Hemodynamic and Echocardiograph Variables

	No Nitroprusside (n = 97)	Nitroprusside (n = 78)	p Value
Hemodynamics			
Sinus rhythm (%)	82	90	NS
Heart rate (beats/min)	86 ± 20	81 ± 18	NS
MAP (mm Hg)	82 ± 11	86 ± 11	0.01
Systolic BP (mm Hg)	106 ± 14	110 ± 15	0.05
CVP (mm Hg)	13 ± 7	15 ± 5	0.002
Systolic PAP (mm Hg)	51 ± 15	63 ± 14	<0.001
Diastolic PAP (mm Hg)	26 ± 9	32 ± 7	<0.001
PCWP (mm Hg)	24 ± 8	29 ± 7	<0.001
CO (l/min)	3.6 ± 0.8	3.2 ± 0.7	0.002
CI (l/min/m^2)	1.7 ± 0.2	1.6 ± 0.2	0.005
SVR (dynes/cm^5)	1,601 ± 419	1,846 ± 567	0.002
PVR (Woods unit)	2.9 ± 1.4	4.3 ± 2.6	<0.001
Echocardiography			
EF (%)	15 ± 7	15 ± 5	NS
LVEDD (cm)	7 ± 1	7 ± 1	NS
MR (grade)	2 ± 1	2 ± 1	NS

Values are mean ± SD or percentage.

BP = blood pressure; CI = cardiac index; CO = cardiac output; CVP = central venous pressure; EF = ejection fraction; LVEDD = left ventricular end-diastolic diameter; MAP = mean arterial pressure; MR = mitral regurgitation; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance.

days of admission) were similar between the 2 groups. Of note, none of the patients had complications during insertion of the pulmonary artery catheter, and none of the early deaths could be directly attributed to catheter-related complications.

Hemodynamic assessments at the time of removal of the pulmonary artery catheter were retrievable in 63% of the study patients (Table 4). Missing data were due to incomplete recording of hemodynamic data in the charts and not attributable to futility in achieving hemodynamic targets. When compared with the initial hemodynamic assessment, statistically significant reduction of mPAP and increase in cardiac index were achieved in both groups. However, reduction in intracardiac pressures and the increase in cardiac index were higher in the SNP-treated patients, though the overall mean hemodynamic measurements at the time of pulmonary artery catheter removal were similar between the 2 groups. Only cardiac index at this time was higher in the SNP-treated patients (p = 0.0156). In the same cohort of patients, we also retrieved the last MAP measured before discharge from the hospital after optimization with oral medications. A significant reduction in MAP was noticed in both cohorts, but overall MAP on discharge was similar between the 2 groups.

Use of concomitant medications. As shown in Table 5, adherence to optimal pharmacological therapy was high on admission and discharge and comparable between the 2 groups. Patients treated with SNP had higher use of beta-adrenergic blockers on admission but not on discharge. The percentage of patients treated with other agents during hospitalization was similar in both groups. There was a trend toward more use of inotropic agents at discharge in patients not treated with SNP. The use of isosorbide dinitrate and hydralazine separately and/or in combination at the time of discharge was significantly higher in patients treated with SNP. Use of oral vasodilators did not differ between Caucasian or African-American patients.

Clinical outcomes. Patients were followed for a median duration of 25.7 months (379 patient-years) after the index right heart catheterization. No patient was lost during follow-up. There were 66 (38%) deaths and 60 (34%) cardiac transplants. Primary outcome differences between 2 cohorts are shown in Table 6. Treatment with SNP during hospitalization was associated with lower all-cause mortality (OR: 0.48; p = 0.005; 95% confidence interval: 0.29 to 0.80) and all-cause mortality/cardiac transplant (OR: 0.64; p = 0.016; 95% confidence interval: 0.45 to 0.92) when compared with those not treated with SNP (Fig. 1). Both early and late all-cause mortality (defined as within or after 30 days after admission, respectively) were significantly lower in the SNP-treated patients (both p values < 0.01). The 2 treatment groups did not differ in cardiac transplant or heart failure rehospitalization rates. Median time to first heart failure rehospitalization, cardiac transplant, and death were 8, 8.6, and 17.3 months, respectively, and did not differ significantly between the 2 cohorts. Use of SNP was not associated with an increased use of inotropic therapy, nor did it contribute to worsening renal dysfunction during hospitalization. Blood sampling for thiocyanate toxicity was not routinely performed. However, no clinical signs of thiocyanate toxicity were noted in any patient receiving SNP.

To further validate our findings, we performed a subanalysis to include only the patients with a MAP of ≤85 mm Hg. In this cohort, use of SNP was still associated with reduced all-cause mortality (p = 0.0001)

Table 4 Hemodynamics at Admission and Time of Pulmonary-Artery Catheter Removal (CI and PAP) and Discharge From Hospital (MAP) Between Patients Who Did and Did Not Receive SNP During Hospitalization

	No Nitroprusside (n = 49)			Nitroprusside (n = 60)		
	Admission	Discharge	p Value	Admission	Discharge	p Value
MAP (mm Hg)	82 ± 12	74 ± 8	<0.001	87 ± 12	74 ± 11	<0.001
Systolic PAP (mm Hg)	55 ± 14	41 ± 13	<0.001	65 ± 13	42 ± 12	<0.001
Diastolic PAP (mm Hg)	28 ± 8	20 ± 7	<0.001	33 ± 7	19 ± 6	<0.001
CI (l/min/m^2)	1.6 ± 0.2	2.4 ± 0.5	<0.001	1.6 ± 0.2	2.6 ± 0.5	<0.001

Abbreviations as in Table 3.

JACC Vol. 52, No. 3, 2008
July 15, 2008:200–7

Table 5 Use of Medication on Admission, During Admission, and on Discharge

	No Nitroprusside (n = 97)	Nitroprusside (n = 78)	p Value
At admission (%)			
Aspirin/clopidogrel	37	47	NS
Coumadin	55	44	NS
ACE-I/ARB	88	83	NS
Digoxin	70	68	NS
Beta-blockers	62	77	0.038
Spironolactone	37	35	NS
Loop diuretic	94	96	NS
Hydralazine	11	16	NS
Isosorbide dinitrate	28	26	NS
Statin	35	44	NS
Amiodarone	28	17	NS
Insulin	16	12	NS
During admission (%)			
Nitroglycerine	1	5	NS
Dopamine	4	3	NS
Dobutamine	36	38	NS
Milrinone	37	25	NS
Dobutamine or milrinone	64	60	NS
Norepinephrine	1	0	NS
IABP	5	2	NS
Dobutamine or milrinone or IABP	67	61	NS
UF/dialysis	1	2	NS
At discharge (%)			
Aspirin/clopidogrel	44	50	NS
Warfarin	50	37	NS
ACE-I/ARB	93	94	NS
Digoxin	72	73	NS
Beta-blockers	50	56	NS
Spironolactone	55	56	NS
Loop diuretic	92	96	NS
Hydralazine	28	54	0.001
ISDN	50	69	0.017
Hydralazine or ISDN	52	75	0.004
Hydralazine and ISDN	26	48	0.006
Statin	33	45	NS
Amiodarone	36	27	NS
Insulin	13	10	NS
Dobutamine	5	2	NS
Milrinone	7	3	NS
Dobutamine or milrinone	12	6	0.08

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; IABP = intra-aortic balloon pump; ISDN = isosorbide dinitrate; NS = not significant; UF = ultrafiltration.

and the combined end point of all-cause mortality plus cardiac transplant ($p = 0.02$). Also, if patients who received an inotropic agent at discharge were excluded from the analysis, use of SNP was still associated with reduced all-cause mortality ($p = 0.003$) and all-cause mortality/cardiac transplant ($p = 0.03$). Finally, although the use of oral vasodilators was not associated with improved outcomes on univariate analysis, a successful transition from SNP to oral vasodilators at the time of discharge was associated with reduced all-cause mortality independent from race ($p = 0.03$).

Table 6 Primary Outcomes

Primary Outcome, % (n)	No Nitroprusside (n = 97)	Nitroprusside (n = 78)	p Value
All-cause mortality	44 (43)	29 (23)	0.005
Cardiac transplant	35 (34)	33 (26)	NS
All cause mortality + cardiac transplant	79 (77)	63 (49)	0.016
Heart failure rehospitalization	56 (54)	60 (47)	NS

On univariate analysis, the absence of diabetes mellitus, presence of beta-adrenergic blocker on admission, absence of inotropic therapy during admission, lower creatinine during hospitalization and at discharge, and SNP use during hospitalization were all associated with lower all-cause mortality and all-cause mortality/cardiac transplant (all $p < 0.01$). When these parameters were entered in a multivariate model for all-cause mortality, SNP use remained an independent predictor of survival (Table 7).

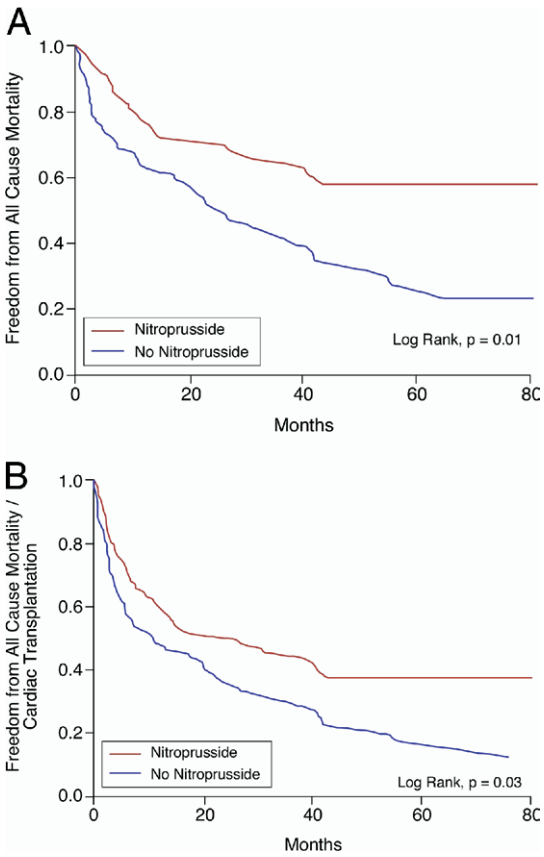

Figure 1 Clinical Outcomes According to Use of Sodium Nitroprusside

Kaplan-Meier curves of all cause mortality **(A)** and the combined end point of all-cause mortality and cardiac transplant **(B)** between patients who did and did not receive intravenous sodium nitroprusside during hospitalization.

Table 7 Predictors of All-Cause Mortality on Multivariate Analysis

	Hazard Ratio	95% Confidence Interval	p Value
Sodium nitroprusside	0.54	0.33–0.88	0.015
Beta-blocker	0.48	0.29–0.78	0.03
Diabetes mellitus	1.13	0.62–2.07	0.7
Inotropic agent	2	1.36–3.6	0.01
Creatinine	2.16	1.56–3.24	0.001

Discussion

The key finding of our retrospective, nonrandomized case-control series is that vasodilator therapy with SNP, in an in-patient setting of guideline recommended care, can be safely administered to achieve hemodynamic improvement in patients presenting with advanced low-output heart failure. Importantly, our observations suggest that the use of SNP according to a clinical protocol based on achieving a target MAP is associated with more hemodynamic improvement that may facilitate the institution of a more aggressive oral vasodilator regimen over standard neurohormonal antagonists at the time of discharge. Taken together, the use of SNP was associated with significantly lower all-cause mortality and fewer clinical adverse events at long-term follow-up, irrespective of the use of inotropic therapy or underlying renal function. These data underscore the importance of assessing the potential for adding vasodilator therapy in patients with advanced low-output heart failure yet seemingly reasonable mean arterial blood pressure.

Despite clinical evidence suggesting hemodynamic and concordant clinical improvement, there have been limited data on the impact of continuous infusion of SNP on long-term outcomes in ADHF. Furthermore, SNP is infrequently used today for ADHF exacerbations especially when the cardiac output is significantly depressed and blood pressure is marginal (17–19). The dual arteriolar and venous effects of SNP appear to contribute to the immediate hemodynamic response of the drug (20). Dilation of the arterial resistance vessels reduces LV afterload and allows the severely compromised LV to eject more blood. The venodilator effect increases venous capacitance and reduces congestion. Both effects lead to an increase in cardiac output in patients with heart failure and often reduce the basal tachycardia. We expect there is a reluctance of physicians to use SNP in hospitalized ADHF patients with low cardiac output or marginal blood pressure. This stems from the misguided belief that vasodilation could potentially be risky if systemic vascular resistance is reduced without any compensatory increase in cardiac output, leading to significant hypotension and downward spiraling of detrimental hemodynamic support. This concept, however, is an oversimplification of the usual cardiac hemodynamics observed, typically in patients with severe LV systolic dysfunction with increased ventricular volumes. The substantial improvement in cardiac output more than offsets any fall in blood pressure under most circumstances. As a result, a reduction in afterload or wall stress during SNP administration usually leads to a marked increase in cardiac output, preventing the development of significant hypotension. Our data corroborate this hypothesis, as we observed that the SNP-treated patients had a statistically greater increase in cardiac index without substantial reduction in MAP when compared with the non–SNP-treated control cohort.

Alternative treatment strategies in these critically ill hospitalized ADHF patients include intravenous infusion of inotropic therapy. These drugs can lead to symptomatic and hemodynamic improvement, but at the cost of increased risk for ischemic events, tachyarrhythmias, and long-term mortality (14,21). In contrast to inotropic therapies, SNP is energetically neutral and reduces myocardial oxygen consumption by a reduction in LV wall tension. Furthermore, increased coronary perfusion pressure via coronary vasodilation can lead to a protective effect on the already compromised myocytes (22–24). It is likely that SNP improves cardiac output but not at the expense of increased myocardial oxygen demand.

The presence of a low cardiac output and elevated intracardiac filling pressures in the setting of ADHF represents a very high-risk individual, and the ability to safely add SNP to standard optimal medical therapy is of great reassurance. It is important to emphasize that the profile of our patient population has important differences from recent large-scale clinical registries such as ADHERE (Acute Decompensated Heart Failure National Registry) and from the recently published ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial (12,25). With an annual mortality plus cardiac transplant rate as high as 50%, our patient cohort likely has far more advanced disease than those in the ADHERE registry or even the ESCAPE trial. Although the ESCAPE trial has raised concerns about the risk-benefit ratio of *routine* invasive hemodynamic monitoring in patients hospitalized with ADHF, our study at least lends some credit to using invasive monitoring when adding intravenous vasoactive drug therapy in this advanced heart failure population. Of particular importance, we observed no greater incidence of hypotension or worsening renal dysfunction during hospitalization. Furthermore, there was a trend toward less use of inotropic drugs in the SNP-treated group. However, because selection bias may have entered the decision to use SNP, this difference might also be the result of the nontreated SNP patients being "sicker."

Recent reports have also highlighted the important prognostic value of systemic blood pressure in ADHF (12,26). The use of SNP versus inotropic agents may have been biased in part because of a higher MAP or systolic blood pressures at baseline, a known predictor of better outcomes in the setting of ADHF. Additionally, patients with higher blood pressure are assumed to be more tolerant of SNP. However, as we excluded patients with low MAPs, and the

presence of equivalent post-treatment hemodynamics and MAPs between both patient groups, our findings suggest that the administration of vasodilator therapy primarily targets any potentially "reversible" contributions of hemodynamic alteration. Also, subanalysis of the patients with MAP ≤85 mm Hg still demonstrated a better outcome in the SNP-treated group, thus suggesting that low blood pressure per se should not necessarily dissuade physicians from using SNP.

The early and continuous separation of the mortality curves for the 2 cohorts implies a continued and increasing benefit of vasodilator therapy throughout the follow-up period. We hypothesize that this is secondary to the ability to establish an early optimal hemodynamic balance with SNP, allowing the institution of longer-term oral vasodilator therapy bridged by SNP titration. Thus, use of early intravenous and late oral vasodilators exerts an improved short-term hemodynamic benefit and a long-term survival benefit. The fact that this benefit was observed in patients already treated with maximal neurohormonal blockade lends credence to the suggestion that the combination of agents is exerting an effect via mechanisms incremental to neurohormonal antagonism. Indeed oral vasodilators have been proven to enhance nitric oxide bioavailability (27), myocardial metabolism (28) and energy regulation (29), to have potent antioxidant effects (30), and reduce LV hypertrophy (31) and remodeling (32), in addition to significant morbidity and mortality benefits when used in African Americans with advanced heart failure (33). Our results provide additional support for the beneficial use of these vasodilators (hydralazine and nitrates) in patients with advanced heart failure, independent of race (33–35).

Study limitations. Obvious limitations inherent to the retrospective study design should be considered when findings are interpreted. Comprehensive follow-up, review of events, and centralized adjudication minimized the potential for missed or misclassified outcomes. However, selection bias probably entered the decision to treat or not treat patients with SNP, which trended toward the use of SNP in patients with higher systemic, right- and left-sided filling pressures, and lower cardiac output. This may suggest that the SNP group was more hemodynamically compromised, "tipping the scales" in favor of standard therapy. Also, only one-half of the patients had implantable cardioverter defibrillator or cardiac resynchronization therapy with defibrillator because widespread use of the devices only started after 2002. The mechanism of death could not be ascertained, but other studies of advanced heart failure suggest that a majority of patients die of progressive pump failure (36). Accurate estimates about duration of vasoactive therapies administered, medication doses, and how many patients achieved hemodynamic goals in both treatment arms could not be retrieved due to logistic limitations. It should also be emphasized that our patient population was younger than the overall heart failure population thereby explaining the higher cardiac transplant rate. Lastly, our single-center data was achieved while patients were hospitalized in a specialized heart failure intensive care unit, which included medical and nursing staff that are experienced in the use of SNP. Recognizing all the aforementioned limitations, we believe that the information provided in this study is a well-balanced description of our long-standing, in general, positive experience with use of SNP in advanced decompensated heart failure patients. Together with the ongoing controversy with another vasodilator, nesiritide (37), and potential detrimental effects of inotropic agents, we hope our data will provide some insights into the potential for reviving an age-old concept of a vasodilator-based approach to low cardiac output in carefully selected patients who may tolerate such strategy. Careful interpretation of our findings should be based on the applicability of our protocols, and further studies are needed to examine the safety and efficacy of SNP-based intensive medical therapy in this vulnerable population.

Conclusions

In our single-center study, we demonstrated that intravenous SNP could be safely administered in selected patients admitted with advanced low-output heart failure to achieve an optimal hemodynamic profile. The use of SNP as part of intensive medical therapy and the transition to oral vasodilators in patients already treated with neurohormonal antagonists was associated with improved long-term clinical outcomes irrespective of inotropic drug usage or renal dysfunction during admission.

Reprint requests and correspondence: Dr. W. H. Wilson Tang, Section of Heart Failure and Cardiac Transplantation Medicine, Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Avenue, Desk F25, Cleveland, Ohio 44195. E-mail: tangw@ccf.org.

REFERENCES

1. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303–10.
2. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293–302.
3. Pitt B, Zannad F, Remme WJ, et al. Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709–17.
4. Packer M, Coats AJ, Fowler MB, et al. Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651–8.
5. Cleland JG, Daubert JC, Erdmann E, et al., Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539–49.
6. O'Connor CM, Gattis WA, Uretsky BF, et al., the FIRST Investigators. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). Am Heart J 1999;138:78–86.

7. Stevenson LW. Clinical use of inotropic therapy for heart failure: looking backward or forward? Part I: inotropic infusions during hospitalization. Circulation 2003;108:367–72.
8. Butler J, Forman DE, Abraham WT, et al. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients, Am Heart J 2004;147:331–8.
9. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. Circulation 2005;111:1487–91.
10. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. JAMA 2005;293:1900–5.
11. Mebazaa A, Nieminen MS, Packer M, et al., SURVIVE Investigators. Levosimendan vs. dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. JAMA 2007;297: 1883–91.
12. Adams KF Jr., Fonarow GC, Emerman CL, et al., ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J 2005;149:209–16.
13. Heart Failure Society of America. Executive summary: HFSA 2006 comprehensive heart failure practice guideline. J Card Fail 2006;12: 10–38.
14. Abraham WT, Adams KF, Fonarow GC, et al., ADHERE Scientific Advisory Committee and Investigators, ADHERE Study Group. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). J Am Coll Cardiol 2005;46:57–64.
15. Binkley PF, Starling RC, Hammer DF, Leier CV. Usefulness of hydralazine to withdraw from dobutamine in severe congestive heart failure. Am J Cardiol 1991;68:1103–6.
16. Steimle AE, Stevenson LW, Chelimsky-Fallick C, et al. Sustained hemodynamic efficacy of therapy tailored to reduce filling pressures in survivors with advanced heart failure. Circulation 1997;96:1165–72.
17. Guiha NH, Cohn JN, Mikulic E, Franciosa JA, Limas CJ. Treatment of refractory heart failure with infusion of nitroprusside. N Engl J Med 1974;291:587–92.
18. Franciosa JA, Cohn JN. Hemodynamic responsiveness to short- and long-acting vasodilators in left ventricular failure. Am J Med 1978;65: 126–33.
19. Cohn JN, Burke LP. Nitroprusside. Ann Intern Med 1979;91:752–7.
20. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration cooperative study. N Engl J Med 1986;314:1547–52.
21. Cuffe MS, Califf RM, Adams KF Jr., et al., Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Investigators. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA 2002;287:1541–7.
22. Schlant RC, Tsagaris TS, Robertson RJ Jr. Studies on the acute cardiovascular effects of intravenous sodium nitroprusside. Am J Cardiol 1962;9:51–9.
23. Rowe GG, Henderson RH. Systemic and coronary hemodynamic effects of sodium nitroprusside. Am Heart J 1974;87:83–7.
24. Franciosa JA, Akhtar N, Notargiacomo A. Hemodynamic and metabolic response to nitroprusside infusion in experimental acute myocardial infarction. Circulation 1973;48 Suppl 4:165.
25. Binanay C, Califf RM, Hasselblad V, et al., ESCAPE Investigators and ESCAPE Study Coordinators. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. JAMA 2005;294:1625–33.
26. Gheorghiade M, Abraham WT, Albert NM, et al., OPTIMIZE-HF Investigators and coordinators. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. JAMA 2006;296:2217–26.
27. Ignarro L, Napoli C, Loscalzo J. Nitric oxide donors and cardiovascular agents modulating the bioactivity of nitric oxide. Circ Res 2002;90:21–8.
28. Munzel T, Kurz S, Rajagopalan S, et al. Hydralazine prevents nitroglycerine tolerance by inhibiting activation of a membrane-bound NADH oxidase. J Clin Invest 1996;98:1465–70.
29. Recchia FA, Osorio JC, Chandler MP, et al. Reduced synthesis of NO causes marked alterations in myocardial substrate metabolism in conscious dogs. Am J Physiol Endocrinol Metab 2002;282:197–206.
30. Loke KE, Laycock SK, Mital S, et al. Nitric oxide modulates mitochondrial respiration in failing human heart. Circulation 1999; 100:1291–7.
31. Janssens S, Pokreisz P, Schoonjans L, et al. Cardiomyocyte-specific overexpression of nitric oxide synthase improves left ventricular performance and reduces compensatory hypertrophy after myocardial infarction. Circ Res 2004:94;1256–62.
32. Prabhu SD. Nitric oxide protects against pathological ventricular remodeling: reconsideration of the role of NO in the failing heart. Circ Res 2004;94:1155–7.
33. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 2004;351:2049–57.
34. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration cooperative study. N Engl J Med 1986;314:1547–52.
35. Taylor AL, Ziesche S, Yancy C, et al., African-American Heart Failure Trial Investigators. Early and sustained benefit on event-free survival and heart failure hospitalization from fixed-dose combination of isosorbide dinitrate/hydralazine: consistency across subgroups in the African-American Heart Failure Trial. Circulation 2007;115:1747–53.
36. Teuteberg JJ, Lewis EF, Nohria A, et al. Characteristics of patients who die with heart failure and a low ejection fraction in the new millennium. J Card Fail 2006;12:47–53.
37. Witteles RM, Kao D, Christopherson D, et al. Impact of nesiritide on renal function in patients with acute decompensated heart failure and pre-existing renal dysfunction a randomized, double-blind, placebo-controlled clinical trial. J Am Coll Cardiol 2007;50:1835–40.

Key Words: heart failure ■ hemodynamics ■ cardiac output ■ inotropic agents ■ vasodilation.