Treatment of Severe Decompensated Heart Failure With High-Dose Intravenous Nitroglycerin: A Feasibility and Outcome Analysis

Phillip Levy, MD, MPH
Scott Compton, PhD
Robert Welch, MD, MS
George Delgado, PharmD
Alison Jennett, PharmD
Neelima Penugonda, MD
Robert Dunne, MD
Robert Zalenski, MD

From the Department of Emergency Medicine, Wayne State University, Detroit, MI.

Study objective: We perform a feasibility and outcome assessment of the treatment of severe decompensated heart failure with high-dose nitroglycerin.

Methods: This study was designed as a nonrandomized, open-label, single-arm study of high-dose nitroglycerin. Patients with hypertension (systolic blood pressure ≥160 mm Hg or mean arterial pressure ≥120 mm Hg) who were refractory to initial therapy were eligible for inclusion. Enrolled patients began receiving a titratable nitroglycerin infusion and were given a bolus of high-dose nitroglycerin (2 mg). Repeated administration of high-dose nitroglycerin was allowed every 3 minutes, up to a total of 10 doses. Predefined effectiveness and safety outcomes were tracked throughout hospital admission. To provide a frame of reference for these outcomes, data were retrospectively compiled for similar patients with severe decompensated heart failure who did not receive high-dose nitroglycerin.

Results: Twenty-nine patients received high-dose nitroglycerin. Endotracheal intubation was required in 13.8% of patients, bilevel positive airway pressure (BiPAP) ventilation in 6.9%, and ICU admission in 37.9%. Symptomatic hypotension developed in 1 patient (3.4%), and biomarker evidence of myocardial infarction was found in 17.2% of patients. The mean dose of high-dose nitroglycerin was 6.5 mg (±3.4). For patients who were treated without high-dose nitroglycerin (n=45), endotracheal intubation occurred in 26.7%, BiPAP in 20.0%, and ICU admission in 80.0%. None of these patients developed symptomatic hypotension, and biomarker evidence of myocardial infarction was observed in 28.9% of patients.

Conclusion: In this nonrandomized, open-label trial, high-dose nitroglycerin was associated with endotracheal intubation, BiPAP, and ICU admission less frequently than expected to occur without high-dose nitroglycerin, and adverse events were uncommon. Treatment of hypertensive, severely decompensated heart failure patients with high-dose nitroglycerin seems promising, but a randomized, blinded study is needed to more completely define its clinical utility. According to this trial, such a study seems feasible. [Ann Emerg Med. 2007;50:144-152.]
Editor’s Capsule Summary

What is already known on this topic
Occasional reports have suggested that high-dose intravenous nitrates can be safe and effective in patients with decompensated heart failure.

What question this study addressed
Can emergency department patients with severe decompensated heart failure be safely and effectively treated with repeated 2-mg boluses of intravenous nitroglycerin?

What this study adds to our knowledge
In this 29-patient nonrandomized open-label trial, the mean dose of nitroglycerin was 6.5 mg. Adverse effects were few, and outcomes appeared comparable to or better than those observed in historical controls.

How this might change clinical practice
High-dose intravenous nitroglycerin seems promising in the treatment of severe decompensated heart failure; however, randomized trials are needed to confirm and quantify the benefit.

Importance
Early use of intravenous vasoactive medications can have significant impact on the hospital course of patients admitted with decompensated heart failure.1,14,15 Nitrates (either nitroglycerin or isosorbide dinitrate) have been shown to produce a substantial decrease in pulmonary artery pressure (30% to 50%) and significant clinical improvement in most individuals with decompensated heart failure, but their use at standard doses may be inadequate, resulting in respiratory failure and the need for accessory ventilatory support.1,11-13

Goals of This Investigation
The primary objective of this study was to investigate clinically important outcomes associated with addition of high-dose nitroglycerin to standard therapy for the treatment of severe decompensated heart failure. Specifically, we sought to ascertain the following 2 critical event rates in the treatment of eligible patients: (1) the rates of the primary outcome variable of endotracheal intubation with and without high-dose nitroglycerin therapy and (2) the incidence of adverse effects associated with use of high-dose nitroglycerin. Additionally, a general assessment of feasibility was sought according to our ability to enroll patients who met eligibility criteria for the clinical trial.

MATERIALS AND METHODS
Setting and Selection of Participants
Detroit Receiving Hospital and Sinai-Grace Hospital are tertiary care facilities operating within a large urban environment and are affiliated with the Wayne State University School of Medicine. The emergency departments (EDs) have a combined annual census of approximately 160,000 patient visits. Within the community, there is a high degree of baseline hypertension and its associated cardiorenal complications.

The eligible population included all adult patients presenting to the ED of either study site with severe decompensated heart failure. The diagnosis of severe decompensated heart failure was clinical and based on the presence of pulmonary rales, a portable chest radiograph determined by the treating physician to be consistent with pulmonary edema, and 1 or more of the following: a history of heart failure, tachypnea (respiratory rate [RR] > 30 breaths/min), significant dyspnea (use of accessory muscles of respiration or obvious air hunger), and significant hypoxia (defined as oxygen saturation [SpO2] ≤ 90% on room air or ≤ 95% on supplemental oxygen) or hypoxemia (partial pressure of arterial oxygen [PaO2] < 50 mm Hg on room air).

To be considered for study inclusion, all of the following criteria had to be met: age greater than 18 years, a systolic blood pressure (SBP) greater than or equal to 160 mm Hg or mean arterial pressure greater than or equal to 120 mm Hg, and ability to obtain written informed consent from the patient or a close family member. Patients were excluded from study participation if they had any of the following: noncardiogenic pulmonary edema, requirement for immediate intubation or cardiopulmonary resuscitation, an inability to obtain informed consent because of alteration in cognition or consciousness or no family or alternative consenting source available, known or suspected pregnancy, acute ST-segment elevation myocardial infarction, suspected right-sided ventricular ischemia (ST-segment depression or new T-wave inversions in leads V1 or V2), or known sensitivity or intolerance to sublingual, transdermal, or intravenous nitroglycerin. The study was approved by the Wayne State University institutional review board and human investigational committee.

Patients who met the enrollment criteria were given a trial of initial therapy, which consisted of the following class I recommendations from the American Heart Association’s 2000 “Guidelines for the Evaluation and Management of Heart Failure”: high-flow oxygen with a 100% nonrebreather mask, sublingual nitroglycerin tablets or oral mucosal spray at a dose of 0.4 mg every 5 minutes (maximum 4 treatments), and furosemide 60 to 80 mg by intravenous push. Morphine sulfate...
3- to 5-mg intravenous push was allowed but not required. Patients who improved in response to this regimen were no longer considered eligible for study inclusion. Patients who failed to improve and were believed to require intravenous nitroglycerin by the treating physician were approached and asked to participate by study personnel. All willing participants (or their family members) were informed of the study protocol, and written informed consent was obtained before study enrollment.

Active patient screening was conducted for 18 consecutive months, from February 2003 through August 2004. During this time, a convenience sample of patients was recruited, the majority of whom (23 of 29) were enrolled at 1 site (Detroit Receiving Hospital) during the final 12 months (between July 2003 and August 2004).

All enrolled patients had standard baseline information, including age, sex, underlying medical conditions, previous exacerbations or hospitalizations, cause of heart failure (if known), baseline New York Heart Association classification, and all current medications obtained and recorded. All patients underwent a routine physical examination, with particular attention on the presence and degree of rales on lung auscultation, presence of jugular venous distention, and the subjective level of dyspnea.

Baseline automated SBP and diastolic blood pressure, mean arterial pressure, and pulse rate were obtained; pulse oximetry (SpO₂) and RR were also recorded. An ECG and a chest radiograph were performed, and blood samples were collected for routine analysis (including basic chemistry panel, CBC count, and cardiac biomarkers). The protocol also called for point-of-care brain-type natriuretic peptide testing (Triage brain-type natriuretic peptide; Biosite Diagnostics, San Diego, CA) for all patients, but because of logistic constraints, not all patients were tested.

**Interventions**

On initiation of the study protocol, all patients began receiving an intravenous nitroglycerin infusion at a starting dose of 0.3 to 0.5 μg/kg per minute. Titration of the nitroglycerin infusion was allowed in increments of 20 μg per minute every 1 to 3 minutes thereafter at the discretion of the treating emergency physician. The maximum rate of intravenous nitroglycerin infusion was fixed at 400 μg per minute. Blood pressure (SBP, diastolic blood pressure, and mean arterial pressure), pulse rate, RR, and SpO₂ were recorded at the initiation of the trial and monitored continually throughout using either manual or automated devices. SBP less than 90 mm Hg was considered an absolute contraindication to intravenous nitroglycerin advancement, with abatement or termination of the infusion if hypotension persisted.

Concurrent with the initiation of the nitroglycerin infusion, all patients received an initial 2-mg intravenous bolus of high-dose nitroglycerin, which was prepared by diluting a standard nitroglycerin solution (American Reagent Laboratories, Inc, Shirley, NY) in 5% dextrose/water to a concentration of 1 mg/mL. Subsequent 2-mg boluses of high-dose nitroglycerin were permitted every 3 to 5 minutes at the discretion of the treating emergency physician. Repeated administration of high-dose nitroglycerin was allowed for a period of up to 30 minutes, resulting in a maximum potential dose of 20 mg (2 mg every 3 minutes for 30 minutes). Study medication was administered in an open-label fashion.

Ventilatory support with either endotracheal intubation or bilevel positive airway pressure (BiPAP) was permitted at any point during patient treatment. The decision to perform either endotracheal intubation or BiPAP was at the discretion of the treating emergency physician. Excessive decrease in blood pressure (defined as a reduction in SBP or mean arterial pressure >30%) was considered an indication to temporarily discontinue bolus treatment and diminish the rate of nitroglycerin infusion. Any episode that did not resolve spontaneously within 5 minutes or after a fluid bolus (500 mL of 0.9% normal saline solution) resulted in termination of the study protocol. Other indications for protocol termination included bradycardia (defined as a pulse rate <60 beats/min); new onset of chest pain, with ECG changes suggestive of developing myocardial ischemia or infarction (ST-segment elevation >1 mm or depression >2 mm in 2 contiguous leads or new left bundle-branch block) that was not present at protocol initiation; or new onset of neurologic deficits, as noted by the treating physician. Recommended treatment of these conditions was based on standard advanced cardiac life support protocols, but actual care was at the discretion of the treating emergency physician.

Patients requiring further intensive care were admitted to a monitored unit bed, whereas hemodynamically stable and clinically improved patients were admitted to a general medical ward. Performance of an echocardiogram was requested for all enrolled patients during their inhospital stay, as was repeated testing of serum laboratory values at 24 and 48 hours postadmission. Ultimately, however, the treatment of the hospitalized patient was deferred to the admitting physician.

**Outcome Measures**

The primary effectiveness end point was the requirement for endotracheal intubation within the first 6 hours of treatment. The primary safety endpoints were development of either neurologic complications (defined as presence of any new speech, sensory, or movement deficits defined as a transient ischemic attacks or stroke on clinical grounds or by subsequent computed tomography of the brain) or cardiovascular complications, defined as hypotensive episodes requiring intervention or the incidence of acute myocardial infarction, as noted by immediate ECG changes as described or a positive troponin I test result (ArISYM by Abbott Laboratories, Abbott, IL) within 24 hours.

Secondary endpoints included the following: proportion of patients requiring BiPAP, need for ICU admission, total hospital length of stay, interval development or worsening of renal dysfunction (as determined by increase in serum creatinine...
level >0.5 mg/dL at 24 or 48 hours), 30-day ED revisitation rate or hospital admission rate for decompensated heart failure, and interval changes in blood pressure (summatied using mean arterial pressure), pulse rate, SpO₂, and RR.

To provide an estimate of baseline outcomes in our study population, data were abstracted for a group of similar patients (n=45) who were treated for severe decompensated heart failure during the study recruitment period but were not enrolled in the trial (ie, did not receive high-dose nitroglycerin).

Institutional review board approval with waiver of informed consent was obtained for retrospective analysis of the hospital records of these individuals, and only those patients who completely satisfied the inclusion/exclusion criteria were included. These data were abstracted by 2 study investigators, with double data entry to minimize entry errors. Because of sporadic enrollment during the initial 6 months of screening and an overall low rate of enrollment at one study site (Sinai-Grace Hospital), all nonintervention patients were derived from the cohort of individuals treated for severe decompensated heart failure without high-dose nitroglycerin at Detroit Receiving Hospital during the final 12 months of recruitment. Reasons for nonenrollment of these patients were not available. An outline of the patient recruitment scheme with more complete representation of group derivation is presented in Figure 1.

Primary Data Analysis

Baseline, treatment, and outcome variables are presented as means or proportions, with corresponding SDs, interquartile ranges, or 95% confidence intervals (CIs) where appropriate. Statistical analysis was performed with SPSS (version 13.0.1; SPSS, Inc., Chicago, IL).

Figure 1. Overview of patient recruitment. ADHF, Acute decompensated heart failure; DRH, Detroit Receiving Hospital; ETI, endotracheal intubation; SGH, Sinai-Grace Hospital.
**RESULTS**

Characteristics of Study Subjects

Baseline characteristics are presented in the Table. There was a high degree of preexisting hypertension in high-dose nitroglycerin (89.7% [95% CI 74.9% to 97.0%]) and nonintervention patients (80.0%; 95% CI 66.7% to 89.6%), but a history of coronary artery disease was relatively less common in both groups (37.9% [95% CI 22.1% to 56.1%] and 26.7% [95% CI 15.5% to 40.8%], respectively).

Underlying heart failure was seen in a greater proportion of high-dose nitroglycerin patients (89.7% [95% CI 74.9% to 97.0%]) than nonintervention patients (57.8% [95% CI 43.2% to 71.4%]), with a suggestion of more advanced disease, as noted by a higher prevalence of New York Heart Association III or IV classification (79.3% [95% CI 62.2% to 90.9%] versus 57.8% [95% CI 43.2% to 71.4%]) and a lower mean ejection fraction (35.7% [95% CI 28.7% to 42.7%] versus 40.2% [95% CI 35.1% to 45.3%]). Patients in the high-dose nitroglycerin group were also receiving diuretics more frequently at baseline (65.5% [95% CI 47.4% to 80.7%] versus 42.2% [95% CI 28.7% to 56.8%]), but other baseline medications, including angiotensin-converting enzyme inhibitors and β-blockers, were similar. Initial vital signs, including mean arterial pressure, pulse rate, RR, and SpO₂, were markedly abnormal in both intervention and nonintervention patients.

**Main Results**

The majority (34.5%) of patients received 3 boluses of high-dose nitroglycerin (Figure 2), and the mean dose of high-dose nitroglycerin administered was 6.5 mg (95% CI 5.2 to 7.8 mg). The mean initial and final intravenous nitroglycerin infusion rates were 23.6 µg/min (95% CI 15.4 to 31.9 µg/min) and 50.2 µg/min (95% CI 37.9 to 62.5 µg/min) for patients who received high-dose nitroglycerin. The mean initial intravenous nitroglycerin infusion rate for the nonintervention group was 31.7 µg/min (95% CI 26.0 to 37.3 µg/min); the final intravenous nitroglycerin rate for nonintervention patients was not available. Mean furosemide dosing was 85.5 mg (95% CI 76.5 to 94.6 mg) in the high-dose nitroglycerin group and 82.1 mg (95% CI 72.8 to 91.4 mg) in the nonintervention group. β-Blockers, angiotensin-converting enzyme inhibitors, and morphine were used in 10.3% (95% CI 3.0% to 25.1%), 34.5% (95% CI 19.3% to 52.6%), and 37.9% (95% CI 22.1% to 56.1%) of high-dose nitroglycerin patients and 11.1% (95% CI 4.4% to 22.7%), 11.1% (95% CI 4.4% to 22.7%), and 11.1% (95% CI 4.4% to 22.7%) of the nonintervention patients.

The primary effectiveness endpoint of endotracheal intubation within 6 hours occurred in 13.8% (95% CI 4.8% to 29.5%) of patients treated with high-dose nitroglycerin and 26.7% (95% CI 15.5% to 40.8%) of the nonintervention patients. The primary safety endpoint of cardiovascular complications was 20.7% (95% CI 9.1% to 37.8%) in the high-dose nitroglycerin group (17.2% [95% CI 6.9% to 33.7%]) with myocardial infarction and 3.5% (95% CI 0.4% to 15.0%) with symptomatic hypotension) and 28.9% (95% CI 17.3% to 43.1%) of the nonintervention patients (all due to myocardial infarction, with no episodes of symptomatic hypotension). There were no patients in either group who developed immediate ECG changes suggestive of cardiac ischemia during treatment, and all myocardial infarction diagnoses were based on interval development of biomarker positivity. Additionally, the occurrence of symptomatic hypotension in the high-dose nitroglycerin group corresponded to a single instance that developed after administration of one 2-mg dose and resolved with a 500-mL fluid bolus, without evidence of further complications. The other primary safety endpoint of adverse neurologic events was not witnessed in either group, and there were no inhospital deaths.

Use of BiPAP occurred in 6.9% (95% CI 1.5% to 20.3%) of the high-dose nitroglycerin patients and 20.0% (95% CI 10.4% to 33.3%) of the nonintervention patients. The ICU admission rate was 37.9% (95% CI 22.1% to 56.1%) in the high-dose nitroglycerin group.
nitroglycerin group and 80.0% (95% CI 66.7% to 89.6%) in the nonintervention group. Mean total hospital length of stay was 4.1 days (95% CI 1.8 to 5.5 days) in high-dose nitroglycerin patients and 6.2 days (95% CI 3.9 to 8.6 days) in nonintervention patients. There was a similar degree of baseline renal dysfunction by mean serum creatinine level (normal at our institution ≤1.2 mg/dL) in both groups (high-dose nitroglycerin 3.5 mg/dL [95% CI 1.9 to 5.0 mg/dL]; nonintervention 2.8 mg/dL [95% CI 1.7 to 3.8 mg/dL]), with a similar incidence of creatinine increase within 48 hours (13.8% [95% CI 4.8% to 29.5%] for the high-dose nitroglycerin group and 15.6% [95% CI 7.2% to 28.1%] for the nonintervention group). Mean 30-day ED return visits for decompensated heart failure were also similar, occurring in 27.6% (95% CI 14.0% to 45.4%) and 22.2% (95% CI 12.0% to 35.9%) of high-dose nitroglycerin and nonintervention patients, respectively.

Graphic display of the hemodynamic and respiratory response to high-dose nitroglycerin is presented in Figure 3A-D. Observations were available for the majority of patients during the first hour of treatment (median time from arrival [interquartile range] 55.0 minutes [48.0 to 121.0 minutes]), with demonstrable improvements in mean arterial pressure, pulse rate, RR, and SpO2. Though fewer data were available at points beyond this period, a continuation of the same trend was visible. The median (interquartile range) change between initial and final measurements for mean arterial pressure, pulse rate, RR, and SpO2 were 50.0 mm Hg (33.2 to 75.0 mm Hg), 18 beats/min (7.5 to 37.0 beats/min), 8.0 beats/min (3.0 to 11.0 beats/min), and 3.0% (0.0% to 8.5%), respectively. Because we did not specify reassessment times for the nonintervention patients, similar data for that group were not available.

LIMITATIONS

Our study was limited by several important methodologic considerations. Foremost among these was the absence of a randomized design, which introduced the potential for selection bias and imbalances in group composition and disallowed powering the trial for clinical outcomes. Additionally, the retrospective nature of nonintervention group data collection precluded standardization and further limited our ability to perform direct comparison with high-dose nitroglycerin patients. Though retrospective analysis also increases the risk of recall bias and abstraction errors, our primary and secondary outcome measures were largely dichotomous and readily available from medical records, minimizing the potential for subjective interpretation. Furthermore, because the nonintervention patients were derived from a concurrent treatment pool, likelihood of confounding from seasonal or temporal variation in decompensated heart failure management was greatly reduced.

Use of an open-label intervention was another important limitation that may have increased the potential for treatment bias. To partially account for this, we did follow patients throughout their hospital stay, during which time subsequent care was rendered by clinicians who had no vested interest in the study itself. Because patient enrollment was based in large part on the willingness of the noninvestigator ED staff to participate, it was thought that an open-label design would be appropriate for this preliminary study, enabling data collection for justification of a subsequent randomized, blinded trial.

Last, this study had a relatively small sample size, with skewed ethnic representation. The limited number of patients enrolled is consistent with the preliminary nature of the trial, however, and, given the inherent difficulty of consenting procedures in the critically ill, was not entirely unanticipated. That nearly 90% of all those who participated in the study were blacks was also not surprising and is representative of the ethnic composition of the city of Detroit. Although this may limit the generalizability of our findings, it does add to the importance of our results because this is the only investigation of high-dose nitroglycerin...
nitrates to be conducted in a predominantly black patient population.

**DISCUSSION**

In this nonrandomized, open-label trial of treatment for hypertensive patients with severe decompensated heart failure, patients who received high-dose nitroglycerin required endotracheal intubation, BiPAP, or ICU admission with less frequency than patients who did not. Myocardial infarction was also less common among patients treated with high-dose nitroglycerin, but it is not clear whether this was an effect of the intervention or a result of baseline variability in group composition. Of particular importance, only 1 patient who received high-dose nitroglycerin developed symptomatic hypotension, and the incidence of induced renal impairment was low.

This study was designed as a preliminary evaluation of high-dose nitroglycerin, with a single treatment arm; direct comparison with nonintervention patients therefore is not appropriate. Nonetheless, provision of data for patients treated

---

**Figure 3.** Hemodynamic and respiratory response to high-dose nitroglycerin over time. **A,** Mean arterial pressure. **B,** Pulse rate. **C,** RR. **D,** SpO₂.
without high-dose nitroglycerin provides some measure of baseline outcomes in our study population and enables estimation of an effect size that can be used to power a future, methodologically more rigorous investigation. That we were able to enroll patients in this trial despite the critical nature of their illness is encouraging and implies that further research involving high-dose nitroglycerin is feasible.

The pharmacologic basis for the proposed benefit of high-dose nitroglycerin lies in the dose-dependent nature of the vascular response to nitrare therapy. At infusion doses of less than 250 µg/minute, the effect of nitroglycerin is predominantly venodilatory, resulting in preload reduction. For those patients with primarily systolic dysfunction, this may be helpful in restoring optimal cardiac contractile response to fluid overload. In markedly hypertensive patients, however, transient exacerbation of diastolic dysfunction may be the principal mechanism responsible for decompenstation.

This may be due, at least in part, to a physiologic increase in end-diastolic volume, which, in the setting of impaired ventricular compliance, results in an increase of diastolic pressure and fluid backflow into the lungs (ie, cardiogenic pulmonary edema). In this setting, both preload and afterload reduction may be required to improve ventricular distensibility and ease the pressure gradient impeding forward flow. Higher doses of intravenous nitroglycerin (≥250 µg/minute) are known to induce both venous and arterial dilation, which may result in an augmented clinical response that exceeds either isolated effect. Because the arterial response to nitroglycerin is more pronounced in patients with excessive vascular resistance, high-dose nitroglycerin may be particularly advantageous for the treatment of severe decompensated heart failure patients with profound hypertension.

Effective reduction in mean arterial pressure (>5% but <30%) within the first 30 minutes of treatment for patients with cardiogenic pulmonary edema has been shown to correlate with a decreased incidence of death, recurrent pulmonary edema, mechanical ventilation, and myocardial infarction during the subsequent 24 hours of treatment. Our findings are consistent with this and add to the existing body of literature supporting the use of high-dose nitrates for decompensated heart failure. The initial publication, an observational study by Bosc et al, reported improvement in dyspnea and tachypnea in 71% of 35 patients treated with a single 3-mg bolus of intravenous nitroglycerin. Rabacal et al followed this study with an analysis of high-dose isosorbide dinitrate (repeated 5- to 10-mg intravenous boluses) and noted marked symptom resolution in 68% of their patients (n=22), with a statistically significant reduction in blood pressure and increase in arterial pH. Subsequent evaluations by Nashed et al and Nashed and Allegrea used repeated bolus doses of intravenous nitroglycerin (0.8 mg each) and found an 83% improvement in clinical condition in their sample of 24 patients. The largest analysis, by Cotter et al, compared bolus intravenous isosorbide dinitrate (3 mg intravenous every 5 minutes; n=56) with bolus intravenous furosemide treatment (80 mg intravenous every 15 minutes; n=54). An absolute reduction of 21% was reported in the composite endpoint of death, endotracheal intubation, or myocardial infarction and in the nitrate treated group. The mean total dose of isosorbide dinitrate in this study was 11.4 mg (±6.8 mg). In the most recent evaluation, Sharon et al compared high-dose isosorbide dinitrate (4 mg intravenous every 4 minutes; n=20) with BiPAP (n=20) and found a significantly higher incidence of death, endotracheal intubation, or myocardial infarction in the BiPAP group (85% versus 25%; P=.0003). As with our trial, the overall incidence of hypotension in these studies was low (0% to 13%), and there were no reports of additional adverse events.

Although the preponderance of existing data on high-dose nitrates has been collected from patients who received isosorbide dinitrate, nitroglycerin and isosorbide dinitrate appear to function similarly through release of endogenous nitric oxide. Direct comparison of the 2 agents, however, has shown that intravenous nitroglycerin is approximately 8 times more potent than isosorbide dinitrate. The relative nitrate doses used in our study, therefore, are far in excess of those reported from previous investigations. As such, we recommend caution in using high-dose nitroglycerin as described in this trial until more complete safety data are available.

In conclusion, high-dose nitroglycerin was effective in this nonrandomized, open-label trial involving hypertensive, severely decompensated heart failure patients and was associated with a lower rate of endotracheal intubation, BiPAP, and ICU admission than non–high-dose nitroglycerin treatment in clinically similar, retrospectively analyzed patients. A rapid and profound decrease in blood pressure was also observed with use of high-dose nitroglycerin, without an associated increase in adverse events. Though encouraging, these results are preliminary, and the next logical step in the evaluation of high-dose nitroglycerin is an adequately powered, multicenter, prospective, randomized, double-blind, comparison trial. According to our investigation, conduct of such a trial seems feasible.

Supervising editor: Allan B. Wolfson, MD

Author contributions: PL conceived the study, supervised the conduct of the trial and all data collection, and drafted the article. PL, SC, RW, and RZ designed the trial and obtained grant funding. SC, RW, GD, AJ, RD, and RZ revised the article. GD, AJ, and RD assisted with conduct of the trial. GD, AJ, NP, and RD assisted with data collection. PL, SC, RW, NP, and RZ assisted with data analysis. PL takes responsibility for the paper as a whole.

Funding and support: By Annals policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article, that might create any potential conflict of interest. See the Manuscript Submission Agreement in this issue for examples of...
Severe Decompensated Heart Failure Treated With Intravenous Nitroglycerin

Levy et al

specific conflicts covered by this statement. Support provided by the Emergency Medicine Foundation.


Reprints not available from the authors.

Address for correspondence: Phillip Levy, MD, MPH, Wayne State University Department of Emergency Medicine, 4201 St Antoine, UHC-6G, Detroit, MI 48201; 313-993-8558, fax 313-993-7703; E-mail philleyx_2000@yahoo.com.

REFERENCES


