Prehospital Emergency Care

ISSN: 1090-3127 (Print) 1545-0066 (Online) Journal homepage: https://www.tandfonline.com/loi/ipec20

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To cite this article: Casey Patrick, Brad Ward, Jordan Anderson, Kelly Rogers Keene, Elizabeth Adams, Rebecca E. Cash, Ashish R. Panchal & Robert Dickson (2020): Feasibility, Effectiveness and Safety of Prehospital Intravenous Bolus Dose Nitroglycerin in Patients with Acute Pulmonary Edema, Prehospital Emergency Care, DOI: 10.1080/10903127.2020.1711834

To link to this article: https://doi.org/10.1080/10903127.2020.1711834

Accepted author version posted online: 03 Jan 2020.
Published online: 27 Jan 2020.

Feasibility, Effectiveness and Safety of Prehospital Intravenous Bolus Dose Nitroglycerin in Patients with Acute Pulmonary Edema

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Abstract

Introduction: The necessity of rapid preload and afterload reduction in patients with decompensated congestive heart failure (CHF) and acute pulmonary edema (APE) is well established. In the hospital setting, intravenous (IV) nitroglycerin demonstrates improved patient morbidity and mortality. However, prehospital treatment is typically limited to sublingual nitroglycerin at doses that often do not affect afterload. In this study, we assessed feasibility, safety and effectiveness of prehospital IV bolus nitroglycerin in decompensated CHF patients with APE. **Methods:** This was a retrospective chart review of all emergency medical services (EMS) and ED patient care records of subjects treated for presumed decompensated CHF with APE with bolus-dose IV nitroglycerin between March 15, 2018 and March 15, 2019 by a large, suburban, county-based EMS service in Texas. Inclusion criteria for treatment included both hypertension (systolic blood pressure [SBP] > 160 mmHg) and acute respiratory distress with a paramedic clinical impression of decompensated CHF with APE. Treatment consisted of a 1 mg nitroglycerin bolus, repeated in 5 minutes if SBP > 160 mmHg. **Results:** During the study period, 48 patients were treated with IV bolus nitroglycerin. Initially, the median (IQR) SBP was 211.0 mmHg (190.0–229.5), 5-minutes post IV NTG was 177.0 mmHg (155.0–199.0), and upon ED arrival was 181.5 mmHg (157.0–207.0). 5 minutes after IV nitroglycerin, the median pulse decreased from 113 (96–124) to 103 (85–117) beats per minute and the median oxygen saturation increased from 86% (74–89) to 98% (96–99). Based on hospital records review, 45/48 (94%) of patients treated with IV nitroglycerin were found to have CHF with APE. A single episode of transient hypotension, which resolved without treatment, did occur during EMS transport. **Conclusion**: This case series found that patients who were treated by paramedics with IV NTG had improved systolic blood pressure and oxygen saturation upon ED arrival as compared to their initial presentation. Over 90% of these patients were correctly identified by paramedics as having CHF with APE based on ED evaluation. Only one patient had an adverse event, which was transient hypotension that did not require intervention. **Key words:** congestive heart failure; acute pulmonary edema; prehospital; emergency medical services; nitroglycerin

PREHOSPITAL EMERGENCY CARE 2020;00:000–000

Introduction

Congestive heart failure (CHF) affects 6.6 million patients in the United States with a projected 25% increase over the next two decades (1). The associated morbidity and mortality from CHF are high with approximately one quarter of admitted CHF patients dying within 6 months of hospital discharge (2). There is limited data on the incidence of true decompensated CHF with acute pulmonary edema (APE), however the best estimates indicate a 16% prevalence of APE in admitted decompensated heart failure patients (3).

The necessity of rapid preload and afterload reduction in patients with decompensated CHF with APE is well established (4–6) and has been shown to improve patient morbidity and mortality (7–11). In the prehospital setting, this has most commonly been accomplished via nitroglycerin, given primarily sublingually. However, the afterload reducing effects of nitroglycerin are only evident following larger doses than are typically used sublingually

Received July 15, 2019 from Montgomery County Hospital District EMS Service, Conroe, Texas (CP, BW, JA, RD); Baylor College of Medicine, Department of Emergency Medicine, Houston, Texas (KRE, RD); Baylor College of Medicine, Houston, Texas (EA); National Registry of Emergency Medical Technicians, Columbus, Ohio (REC, ARP); Division of Epidemiology, The Ohio State University College of Public Health, Columbus, Ohio (REC, ARP); Department of Emergency Medicine, The Ohio State University Wexner Medical Center, Columbus, Ohio (ARP). Revision received December 20, 2019; accepted for publication December 28, 2019.

Thanks to Dr. Kevin Rodgers for the inspiration for this study.

No conflicts of interest to report.

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/ipec.

doi:10.1080/10903127.2020.1711834

(12, 13). Complicating this approach, decompensated CHF patients with APE are often concurrently receiving noninvasive positive pressure ventilation (NIPPV). This makes sublingual drug administration suboptimal, as the mask seal must be repeatedly disrupted to deliver the medication, and their oral mucosa is often dry from non-humidified air delivered by prehospital PAP devices.

Recent emergency department (ED) data suggests that intravenous (IV), bolus dose nitroglycerin decreases the need for intubation, ICU admission rate and hospital length of stay in patients who present with decompensated CHF with APE (7, 8, 14, 15). Additionally, sublingual nitroglycerin has proven effectiveness in the prehospital setting when treating decompensated CHF patients with APE (16). However, the safety of high dose bolus administration of intravenous nitroglycerin has not been evaluated in the prehospital patient population.

In this study, we assessed the feasibility, effectiveness and safety of prehospital IV bolus nitroglycerin use in decompensated CHF patients with APE by paramedics within a single, high-volume, ground based EMS agency.

METHODS

Study Design and Setting

This was a retrospective chart review of all EMS and ED patient care records of subjects treated for presumed decompensated CHF with APE using bolus-dose IV nitroglycerin between March 15, 2018 and March 15, 2019 by a large, suburban, county-based EMS service in Texas. The data review was a part of a quality improvement evaluation of a previously implemented EMS protocol for the treatment of decompensated CHF with APE. The EMS agency employs approximately 220 advanced life support providers and over 1,000 emergency medical technicians (EMTs) in 13 first responder organizations. The service area covers 1,100 square miles and responds to more than 65,000 annual calls for service. This study was approved by The Baylor College of Medicine Institutional Review Board with a waiver of informed consent.

The EMS protocol for acute CHF with APE used in this study is shown in Figure 1. Paramedics initially identified CHF with APE within their clinical management scope and then had the option to administer sublingual nitroglycerin (0.4 mg tablets) while IV or intraosseous (IO) access was being obtained. Following this, an initial dose of 1 mg IV nitroglycerin was administered slowly and repeated in 5 minutes if the SBP remained greater than 160 mmHg. A maximum total dose of 2 mg of IV nitroglycerin was allowed within this protocol. Noninvasive positive pressure ventilation (NIPPV) was also available and encouraged, but not absolutely required, along with a progression to delayed sequence intubation for definitive airway management, if indicated by patient status.

Prior to protocol implementation, 220 paramedics underwent an initial, mandatory 2-hour training session that included a review of nitroglycerin pharmacology, focused didactic instruction on the pathophysiology and clinical findings in acute decompensated CHF with APE, and specifics of the treatment protocol (Figure 1). The training sessions occurred approximately one month prior to protocol deployment. This knowledge was then reinforced by two podcasts, produced in-house, which were available and promoted for the duration of the study period. Providers demonstrated an understanding of acute decompensated CHF and the treatment protocol through both written and psychomotor examinations at the conclusion of the mandatory training session.

Patient inclusion criteria for initial EMS chart review included a free text ePCR search for all patients who were given IV bolus nitroglycerin as well as all patients who presented to the EMS agency with dyspnea (e.g. NIPPV use) and the presence of hypertension (systolic blood pressure (SBP) >160 mmHg). These parameters were chosen in effort to capture all patients who could have potentially been treated for decompensated CHF with APE using the bolus IV NTG protocol during the study period. A three-person expert review panel (two physicians and one paramedic) then reviewed these charts to identify if the patients should have been identified as decompensated CHF with APE and possibly treated under the protocol. Data sources included evaluation of the EMS records followed by the receiving hospital electronic medical records for patient outcome data. Hospital records were reviewed for all patients who were treated under the protocol during the study period and included in the final analysis.

Measures

Data were abstracted with a standardized data collection form following a complete EMS and ED chart review as described above. The study variables included demographic information, past medical history, hemodynamic data, initial emergency department chest x-ray results, and final emergency department diagnoses. Nitroglycerin routes of administration and dosages given by EMS were compiled from the ePCR as well. Additional information collected included EMS albuterol administration, 12-lead

ACUTE CHF/ACUTE PULMONARY EDEMA TREATMENT PROTOCOL

Historical Findings	Physical Findings
▪ Prior history of CHF ▪ Orthopnea ▪ Paroxysmal nocturnal dyspnea ▪ Cocaine/Methamphetamine use	▪ Rales ▪ Pedal edema ▪ History of A-fib or A-fib on EKG

Assessment:

- Cardiac Assessment
- DDX: Ischemia, HTN crisis, renal (fluid overload), non-cardiogenic (drowning, inhalational, drug-induced)

Clinical Management Options:

Interventions	Pharmacology
▪ Noninvasive ventilation ▪ 12-Lead ECG ▪ Vascular Access o Consider IO on urgent/critical patient	▪ **NTG** 0.4 mg sublingual o If systolic >100mmHg o May repeat q 3-5 min x 3 prior to vascular access o May repeat q 3-5 min PRN following vascular access **AND IF MODERATE/SEVERE RESPIRATORY DISTRESS:** ▪ **NTG** 1mg Slow IVP o Only if Systolic >160 o May repeat x 1 q 5 minutes o Consider IV NTG in tandem with NIPPV

Consult:

- If DSI is needed

Figure 1. MCHD acute CHF/APE protocol.

electrocardiogram assessment, and EMS on-scene time and patient transport times. Hemodynamic data such as blood pressure measurements and heart rate during EMS transport and blood pressure values at emergency department arrival were also collected. Additionally, emergency department troponin, creatinine, and B-Naturetic peptide (BNP) levels were also collected when available. Finally, the incidence of both EMS and ED intubation were collected.

Analysis

All analyses were completed using Microsoft Excel (Microsoft Corporation, Redmond, WA) and Stata IC Version 15.1 (StataCorp LLC, College Station, TX). Descriptive statistics are reported as median (IQR) for continuous variables and as frequencies (%) for categorical variables.

Results

A total of 250 EMS patient charts were identified and reviewed that satisfied the inclusion criteria. From these charts, 162 patients were determined to not qualify since an alternate diagnosis was more likely than decompensated CHF with APE (Figure 2). Chronic obstructive pulmonary disease and pneumonia were the most common alternate paramedic impressions in this group. 88 patients were found to have clinical and hemodynamic characteristics consistent with decompensated CHF with APE.

Of the 88 patients identified by chart review with CHF with APE, 18/88 (20%) patients had no prehospital IV access due to inability to place a peripheral IV. IO access was not attempted in any of the study patients. An additional 22/88 (25%) untreated patients were a result of paramedic decision to not

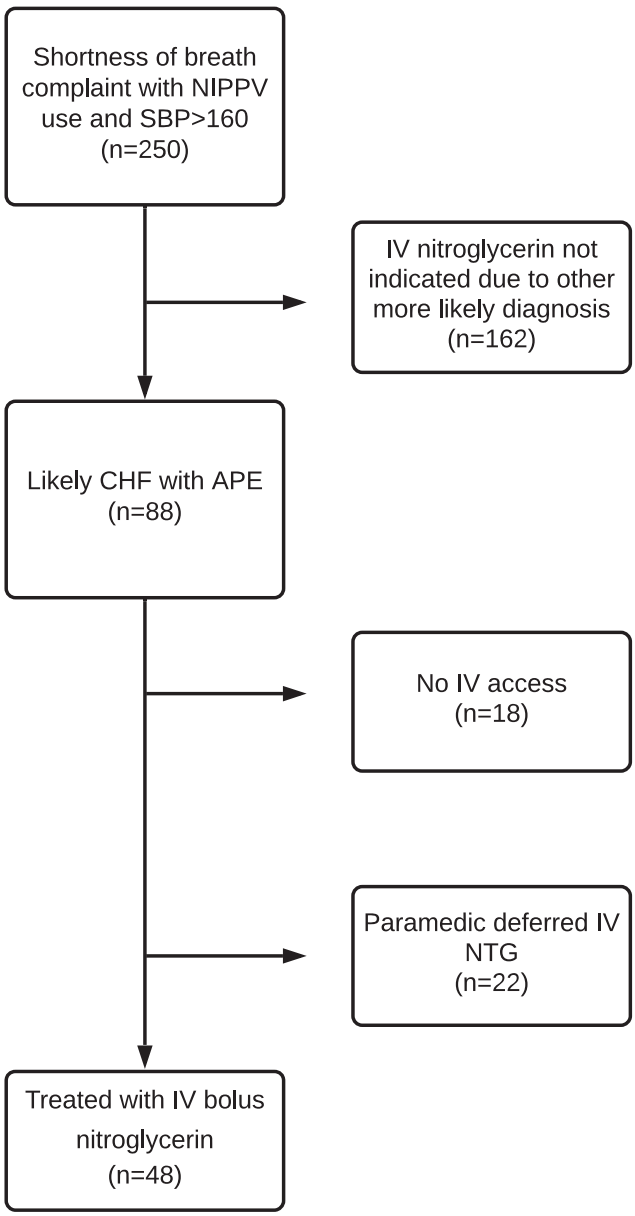

FIGURE 2. Patient exclusion/inclusion flowchart.

TABLE 1. Demographic characteristics of patients treated with IV NTG (N = 48)

	Frequency (%)
Age, years	
Mean (SD)	70.4 (14.3)
Median (IQR)	72 (61.5–79)
Range	33–100
Sex	
Male	35 (73)
Female	13 (27)
Race/ethnicity	
White	37 (77)
Black	1 (2)
Hispanic	10 (21)
Past Medical History	
Congestive heart failure	30 (63)
Hypertension	37 (77)
Diabetes mellitus	18 (38)
End stage renal disease	5 (10)

TABLE 2. Description of prehospital care provided to patients treated with IV NTG (N = 48)

	Frequency (%)
Placed on NIPPV	42 (88)
Intubated by EMS	4 (8)
Received albuterol	14 (29)
Received prehospital 12-lead ECG	46 (96)
STEMI	0
Missing	*2*
Scene time, median (IQR)	19.5 minutes (13.0–23.0)
Transport time, median (IQR)	18.0 minutes (12.5–23.0)
Nitroglycerin dosage	
IV	48 (100)
1 mg	33 (69)
2 mg	15 (31)
Sublingual (prior to IV)	16 (33)
0.04 mg	13 (81)
0.08 mg	3 (19)

Abbreviations: NIPPV – noninvasive positive pressure ventilation; EMS – emergency medical services; ECG – electrocardiogram; STEMI – ST elevation MI; IV – intravenous.

administer IV bolus nitroglycerin (Figure 2). Finally, 48/88 (55%) patients were treated under the protocol with bolus dose IV nitroglycerin. These patients had a mean age of 70 years-old, most were male, white and had past medical histories of hypertension and CHF (Table 1).

The median on-scene EMS time for these patients was 19.5 (13.0–23.0) minutes with a median transport time of 18.0 (12.5–23.0) minutes. These times are similar to the overall EMS system scene and transport times. Other treatments included nebulized albuterol in 14/48 (29%), 42/48 (88%) of the patients were maintained on NIPPV and 4/48 (8%) required EMS intubation. Prior to treatment with IV bolus nitroglycerin, 16/48 (33%) were treated with sublingual nitroglycerin. Of the patients treated with bolus dose IV nitroglycerin, 33/48 (69%) received a single 1 mg dose and 15 patients 15/48 (31%) received a second 1 mg dose (Table 2).

Patients treated with IV bolus nitroglycerin had a median initial EMS SBP of 211.0 mmHg (190.0–229.5). The median SBP 5 minutes post EMS IV nitroglycerin administration was 177.0 mmHg (155.0–199.0), and the median initial emergency department (ED) SBP was 181.5 mmHg (157.0–207.0). The median pulse decreased from 113 (96–124) to 103 (85–117) beats per minute and the median oxygen saturation increased from 86% (74–89) to 98% (96–99) 5 minutes post EMS IV nitroglycerin administration (Table 3). Supplemental oxygen was provided in varying concentrations depending on

Table 3. Vital signs before IV NTG administration, after completion of administration, and at presentation to the emergency department. Presented as median (IQR)

	Pre-NTG	5min Post-NTG	Initial ED	Median Reduction (Pre to Post)	Median Reduction (Pre to ED)
Systolic blood pressure, mmHg	211.0 (190.0–229.5)	177.0 (155.0–199.0)	181.5 (157.0–207.0)	33 (10–55)	29 (14–50)
Diastolic blood pressure, mmHg	116.9 (99.5–134.5)	97.8 (82.0–110.0)	98.8 (81.0–110.5)	16 (1–38)	13 (1–33)
Heart rate, bpm	113 (96–124)	103 (85–117)	–	7 (13–+2)	–
Oxygen saturation, %	86 (73.5–89)	98 (96–99)	–	+12 (9–20)	–

Abbreviations: IV – intravenous; NTG – nitroglycerin; ED – emergency department; bpm – beats per minute.

Table 4. Description of care and lab values in the emergency department of patients treated with IV NTG (N = 48)

	Frequency (%)
Final diagnosis of acute CHF/APE	45 (94)
Supported by chest x-ray	37 (84)
Missing	*1*
Intubated within 6 hours of hospital arrival	8 (17)
Admitted to ICU	18 (38)
BNP, median (IQR)	606.5 (331–1396)
Missing	*6*
Troponin	
Positive	8 (18)
Negative	36 (82)
Missing	*4*
Creatinine, median (IQR)	1.3 (1.1–1.8)
Missing	*3*

Abbreviations: CHF – congestive heart failure; APE – acute pulmonary edema; ICU – intensive care unit; BNP – B-natriuretic peptide.

the severity of patient presentation. Of the patients treated, 41/48 (85%) had an improvement in SBP and 45/48 (94%) had improved oxygen saturation following nitroglycerin administration. One patient had hypotension, which resolved without treatment, during EMS transport following a 1 mg dose of nitroglycerin. The blood pressure in this specific patient dropped from 203/88 to 71/38 and improved to 105/73 in 4 minutes without additional treatment. The patient was normotensive upon ED arrival and had no syncope, chest pain or other complaints. There were no other reported adverse events during transport.

Based on hospital EMR review, 45/48 (94%) of the patients treated with IV bolus nitroglycerin were found to have CHF with APE during their ED stay. Two patients who received bolus IV nitroglycerin were diagnosed with pneumonia and the third was diagnosed with COPD. 8/48 (17%) of patients were intubated within 6 hours of hospital arrival and 18/48 (38%) were admitted to the intensive care unit. The median BNP value was 606.5 (331–1396) and the median Creatinine was 1.3 (1.1–1.8). 8/48 (18%) treated patients had positive ED troponin values (Table 4), however, none had ECG findings consistent with ST elevation myocardial infarction.

Discussion

This study reports on the feasibility, effectiveness and safety of prehospital administration of IV NTG for treatment of CHF with APE. A 16% reduction in SBP was noted during EMS transport, which is well within accepted parameters for blood pressure control even in the setting of hypertensive emergency (17). Greater than 90% of all patients treated with IV nitroglycerin were correctly identified as decompensated CHF with APE based on the final ED diagnosis. The 2% rate of hypotension observed following treatment with bolus IV nitroglycerin is consistent with that seen in larger studies (7, 8, 18). The single occurrence of hypotension seen in this study resolved without additional treatment or significant clinical consequences. The results suggest that prehospital administration of high dose IV nitroglycerin may be both safe and effective in the prehospital setting of decompensated CHF with APE.

In other settings, bolus dose IV nitroglycerin has improved patient outcomes. Early hospital-based studies demonstrated reduced need for intubation and mechanical ventilation when bolus IV nitroglycerin was added to accepted standard therapies for acute decompensated CHF with APE, such as furosemide and NIPPV (3, 9, 10). Further investigation demonstrated decreased mortality, ICU length of stay (LOS) and hospital LOS with high dose bolus IV nitroglycerin as compared to a continuous IV nitroglycerin drip (7, 8). Although this evidence supported its use, bolus dose IV nitroglycerin is not regularly utilized even in the ED treatment of acute pulmonary edema (19, 20). High dose sublingual nitrates have been studied in the prehospital setting (16), but this study evaluated prehospital bolus IV nitroglycerin in patients diagnosed with decompensated CHF with APE by paramedics.

An important concern is whether prehospital providers can correctly identify patients who should be treated within the IV nitroglycerin protocol. There is existing evidence that EMS providers perform poorly when attempting to diagnose acute pulmonary edema in the field (21). This is often due to the fact that this patient population can be heterogenous

with significant overlap between acute CHF and acute COPD exacerbations. In this evaluation, we noted a high agreement (>90%) between IV nitroglycerin use and a final ED diagnosis of CHF with APE. This may be due to the addition of a focused training curriculum for the paramedics on recognition and treatment of CHF with APE prior to protocol initiation. Specifically, in the curriculum, differentiation between these diagnoses was a focal point of the initial education program and will likely need continued emphasis as the protocol evolves. There were an additional 40 patients who potentially could've been treated with bolus dose nitroglycerin that were not. This was partially due to lack of IV access and a potential solution is to encourage IO placement in this critically ill patient group. The remaining group of 22 untreated patients were a result of paramedic choice which will likely improve with protocol evolution, education and paramedic comfort.

One significant benefit of bolus dose IV nitroglycerin is that it is inexpensive and relatively simple to dose and administer. We utilized a 100 mcg/mL concentration with a final dose volume of 10 mL. Over 2/3 of the patients in our study required only a single 1 mg dose, consistent with prior data from Wilson et al (8) demonstrating the effectiveness of a single bolus dose of IV nitroglycerin. For these reasons, coupled with prior hospital studies (22), the results suggest that prehospital administration of high dose IV nitroglycerin may be both safe and effective and are the first step in evaluating a possible role for bolus dose IV nitroglycerin in prehospital patients with decompensated CHF with APE.

Limitations

This study was limited by its retrospective nature, small sample size and due to the fact that patients were treated within a single ground-based EMS agency. Further, we were unable to study the effects of IV bolus dose nitroglycerin on prehospital airway management. Since no control group was used in this study, we cannot determine additional benefit beyond standard care and treatments such as high dose sublingual nitroglycerin or early NIPPV. Additionally, we are unable to ascertain the impact of the treatment on the use of NIPPV or its association with endotracheal intubation. This is an important consideration since in-hospital studies have demonstrated decreased intubation rates and mechanical ventilation needs (3, 9, 10). Randomized studies with larger sample sizes are needed to further investigate the effects of prehospital bolus dose nitroglycerin on patient morbidity and mortality in patients with decompensated CHF with APE.

CONCLUSION

This case series found that patients who were treated by paramedics with IV NTG had improved systolic blood pressure and oxygen saturation upon ED arrival as compared to their initial presentation. Over 90% of these patients were correctly identified by paramedics as having CHF with APE based on ED evaluation. Only one patient had an adverse event, which was transient hypotension that did not require intervention. Future work must be directed at both confirming safety and effectiveness along with evaluating the possible mortality benefit from prehospital bolus dose IV nitroglycerin administration.

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