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Low- versus high-dose nitroglycerin infusion in the management of acute pulmonary edema

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ABSTRACT

Background: Nitroglycerin (NTG) is commonly used for the management of pulmonary edema in acute heart failure presentations. Although commonly initiated at low infusion rates, higher infusion rates have favorable pharmacodynamic properties and may improve outcomes in the management of acute pulmonary edema.
Objectives: To characterize the clinical outcomes including the time to resolution of severe hypertension when using an initial low dose (<100 μg/min) versus high-dose (≥100 μg/min) strategy.
Methods: This was a retrospective study performed at a single, tertiary academic emergency department in Atlanta, GA. We describe the blood pressure effects and key safety outcomes (intubation, hypotension, intensive care unit admissions) during the first hour of treatment of acute pulmonary edema.
Results: 41 patients were included in the final sample. 27 (66%) received low dose NTG and 14 (34%) received high dose NTG. The high dose group reached their blood pressure faster on average (hazard ratio = 3.5, 95% CI: 1.2–10.1). 8/14 (57%) of patients in the high dose group reached their BP target within the first hour of treatment, compared to 6/27 (22%) in the low dose group. Observed incidence of safety outcomes were similar between the two groups.
Conclusions: Higher initial NTG doses may be an effective way to decrease times to achieve blood pressure targets and should be the focus of future trials.

1. Introduction

Acute pulmonary edema is a life-threatening manifestation of heart failure that is commonly precipitated by severely elevated blood pressure. Heart failure-related presentations account for approximately one million ED visits per year in the United States [1]. One of the mainstays of resuscitative care is rapid, controlled lowering of blood pressure with vasodilators. Nitroglycerin (NTG) is commonly used for this purpose in emergency departments (ED). Clinical practice guidelines recommend a reduction in blood pressure by 25% within the first hour when treating pulmonary edema that is precipitated by severe hypertension [2]. In the most acute forms, this condition is described as flash pulmonary edema or sympathetic crashing acute pulmonary edema (SCAPE). Despite its widespread use, the optimal dosing strategy for NTG remains investigational and there are no universal recommendations for its use in the treatment of hypertensive emergencies.

NTG infusions are typically used in a dosing range of 5–200 μg/min [2-5], with serial titrations until the desired clinical effect is achieved. NTG has utility in treatment of acute pulmonary edema by means of smooth muscle dilation of capacitance vessels at lower doses, and arterial vasodilation with afterload reduction at higher doses, with the latter effect being observed at higher infusion [6,7]. These effects cause preload reduction and decrease in cardiac filling pressures, which the patient in turn experiences as relief of dyspnea [3]. Alternative dosing strategies that use high dose NTG regimens have been described in small-scale trials and case series. These studies have reported favorable outcomes including decreased mortality, decreased need for endotracheal intubation, decreased need for intensive care unit (ICU) admissions, and without any observed increase in critical adverse events (e.g. hypotension) [7-9]. High dose regimens are characterized by the use of bolus doses of NTG, higher infusion rates, or both. There are considerable dosing differences among studies of IV bolus and continuous infusion of high-dose NTG which limit generalizability [10].

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The purpose of this present study is to examine the impact of the initial NTG infusion dose on clinical outcomes in the treatment of acute pulmonary edema in the ED. The American College of Emergency Physicians recently updated their clinical policy guideline on acute heart failure syndromes to include a Class C recommendation of "consider using high-dose nitroglycerin as a safe and effective treatment option when administered to patients with acute heart failure syndrome and elevated blood pressure." [5,11] Drawing on published data and our local experience with using high dose NTG, we anticipated that a high dose strategy (≥100 μg/min) will have favorable outcomes compared to lower doses without any observed increase in adverse outcomes.

2. Materials and methods

This was a retrospective study performed at the Emory University Hospital Midtown, which is an academic, tertiary care hospital in the downtown area of Atlanta, GA. Our emergency department sees an annual volume of approximately 70,000 patients and has an inpatient capacity of 531 beds. The standard NTG infusion protocol approved by the hospital's pharmacy and therapeutics committee starts at 10 μg/min with a dosing range of 10–400 μg/min. Titration is recommended in steps of 10 μg/min every 3–5 min until clinical effect or blood pressure targets are achieved. The bedside physicians may elect to initiate the NTG infusion at a higher rate than the P&T-approved protocol based on the needs of the clinical scenario and perceived benefit to the patient. The institutional review board approved the study protocol with a waiver of informed consent.

2.1. Selection of patients

Inclusion criteria were age ≥ 18 years, a clinical diagnosis of acute pulmonary edema, at least one severely elevated blood pressure reading (≥180 mmHg systolic or ≥ 120 mmHg diastolic), and initiation of a NTG infusion while the patient was in the ED. [2] A clinical diagnosis of acute pulmonary edema was inferred if any of the following were present in the documentation from the index ED encounter: explicit physician documentation of a suspicion for acute pulmonary edema, respiratory rate ≥ 30/min, new or increased supplemental oxygen requirement, presence of rales on auscultation, presence of B-lines on lung sonography, or a chest X-ray interpreted as having a pulmonary edema pattern. Exclusion criteria included any clinical syndrome with defined blood pressure goals (e.g. aortic dissection, pre-eclampsia/eclampsia, intracranial hemorrhage), pregnancy, concurrent or previous use of a non-NTG vasoactive medication during the index ED visit (e.g. nicardipine), and clinical suspicion of non-cardiogenic pulmonary edema (e.g. ARDS, rapid opioid-reversal, transfusion-associated, etc. as recorded by either the emergency physician or the admitting team). Patients who had incompletely recorded vital signs were also excluded. Patients without a vital sign recording or NTG titration at least every 15 min during the initial hour of NTG infusion were considered to have inadequate vital sign documentation.

The primary data sources were the hospital electronic medical record (EMR) and emergency medical services (EMS) documentation. We identified potential charts by the charge capture generated when an order for intravenous NTG is placed. Data abstraction was performed by two study team members. We collected basic demographic and clinical information including age, sex, date of service, comorbid conditions (congestive heart failure [CHF], hypertension [HTN], coronary artery disease [CAD], history of myocardial infarction [MI], end stage renal disease [ESRD], and diabetes mellitus [DM]), outpatient medication usage (diuretics, nitrates, calcium channel blockers [CCB], beta blockers [BB]), the use of non-invasive positive pressure ventilation (NIPPV), and use of sublingual or topical NTG prior to the start of the infusion (recorded as a binary variable). We collected relevant data about the NTG infusions including the starting dose, titrations, and effects on blood pressure (systolic blood pressure [SBP], diastolic blood pressure [DBP], and mean arterial pressure [MAP]) at 5-min intervals. A standardized data abstraction form was used for this purpose. Consecutive charts were reviewed from January 1, 2020 until the enrollment target was reached.

2.2. Variables

Our primary outcome was the time until a blood pressure reduction of 25% was achieved. Our interest was in assessing the first hour of therapy, and therefore outcomes were censored at 60 min following the initiation of NTG infusion. The blood pressure "goal" was individualized for each patient based on their presenting blood pressure (MAP). All blood pressures measurements refer to non-invasive, oscillometric readings as invasive blood pressure monitoring is uncommonly used in our ED for this indication. If multiple values were recorded prior to the NTG infusion, an average of the three most recent pressures was used to define the patient's "goal" blood pressure. Secondary outcomes included key safety outcomes such as the need for endotracheal intubation, hypotension, and rate of ICU admission. The primary exposure variable for the study was the initial dose of NTG infusion (μg/min). Covariates for the adjusted comparison were selected a priori based on expert opinion and the extant literature. These included age, gender, initial SBP, initial DBP, medical history (including CAD, CHF, ERSD, prior MI), home medications (beta blockers, calcium channel blockers, and diuretics), NIPPV usage, and NTG received in any form prior to the start of the infusion.

2.3. Statistical analysis

Continuous variables (e.g. age, initial BP) were described using medians and interquartile ranges. Categorical variables were described using frequencies and percentages. For the primary outcome, time to BP goal, Kaplan-Meier curves and Cox proportional hazard models were used to evaluate the role of initial NTG dose. We dichotomized patients on the basis of their initial NTG dose: Low Dose (< 100 μg/min) and High Dose (≥ 100 μg/min). This cutoff was chosen to align with the definitions used in similar studies to ours, well as to reflect the changing pharmacologic effects of nitroglycerin when given at higher doses, i.e. increased afterload reduction via arterial vasodilation [3,6,7,12]. Hazard ratios and 95% confidence intervals from the Cox model are presented both unadjusted as well as adjusted for age, gender, initial SBP, initial DBP, comorbid conditions, medications, and prior NTG administration. Non-linear effects of age, SBP, and DBP were incorporated using natural cubic splines. Both a visual inspection of the Schoenfeld residuals and Grambsch-Therneau test ($p = .67$) indicate that the proportional hazard assumption was met [13,14]. Secondary outcomes, including hypotension, the need for intubation, and ICU admission, were evaluated using the χ^2 and exact tests. Because the NTG dichotomization cut point was arbitrary, a sensitivity analysis was conducted such that the Cox proportional hazard models were repeated using initial NTG dose in μg/min. Historical data from the study site suggest approximately 25% of patients with a standard dose reach the BP target within 60 min (25% event rate/75% censoring) and a of 2:1 ratio of low dose to high dose patients. Using these parameters, we estimated a sample size of 38 patients would be necessary to detect an absolute reduction of 50%. Statistical analyses were conducted using R v4.2 (R Core Team, 2022). We strived to adhere to the STROBE guidelines for reporting observational studies (Appendix 1) [15].

3. Results

Forty-one patients met all inclusion criteria. Two hundred and fifty-one charts were excluded. The reasons for exclusion were as follows: inadequate vital sign documentation (118), indication for NTG other than pulmonary edema (75), blood pressures not meeting criteria for hypertensive emergency (21), no NTG titration data in the medication administration record (6), pregnancy (4), and concurrent use of another

Table 1
Patient characteristics as a function of dosing group.

Characteristic	Low Dose (< 100 μg/min) $N = 27$		High Dose (≥ 100 μg/min) $N = 14$	
	N or M	% or IQR	N or M	% or IQR
Age, M / IQR	64	56–74	64.5	47–72
Gender, N / %				
Female	14	51.9%	14	100.0%
Male	13	48.1%	0	0%
Initial SBP, M / IQR	214	199–230	210	198–223
Initial DBP, M / IQR	118	107–130	112.5	99–125
Past Medical History, N / %				
CHF	19	70.4%	12	85.7%
HTN	27	100.0%	14	100.0%
ESRD	11	40.7%	8	57.1%
CAD	4	14.8%	3	21.4%
DM	17	62.9%	3	21.4%
Medications, N / %				
Nitrates	11	40.7%	8	57.1%
CCB	20	74.1%	9	64.3%
BB	23	85.2%	10	71.4%
NIPPV	19	70.4%	11	78.6%
Prior Nitro administration, N / %	11	40.7%	6	42.9%
Initial NTG Dose (μg/min), M / IQR	10	10–10	120	100–200

vasoactive medication (1). In the final sample of 41 patients, 27 (66%) received low dose NTG and 14 (34%) received high dose NTG. Overall, the sample was 31.7% male ($N = 13$), 68.3% female ($N = 28$) and had a median age of 64 years (IQR: 54–71.5). The sample had a median initial SBP of 211 mmHg (IQR: 198.5–229.5) and a median initial DBP of 116 mmHg (105–125). Table 1 presents patient characteristics stratified by NTG dosing group.

Outcomes are presented in Table 2 as a function of dosing group and Kaplan-Meier curves are shown in Fig. 1. The Cox model indicated that the high dose group reached their BP faster on average (hazard ratio = 3.5, 95% CI: 1.2–10.1). This finding remained significant in the adjusted model (hazard ratio = 7.7, 95% CI: 1.7–34.4). In the sensitivity analysis, dosing (μg/min) was associated BP goal achievement in both the unadjusted (hazard ratio = 1.004, 95% CI: 1.0003–1.009) and adjusted analyses (hazard ratio = 1.01, 95% CI: 1.004–1.020). Note that the magnitude of the hazard ratios differs between the main analysis and sensitivity analysis due to a unit change from a group difference to μg/min. Thus, across all analyses, higher starting dose is associated with meeting BP goals faster.

Secondary outcomes are also described in Table 2. Overall, 6 patients (14.6%) were intubated, 34 (82.9%) were admitted to the ICU, and 0 patients developed hypotension. Neither intubation ($p = 1$) nor ICU admission ($p = .67$) differed across dosing groups. No comparison was conducted for hypotension because it did not occur in any patient.

4. Discussion

In this retrospective study comparing initial low-dose vs high-dose NTG infusions in the treatment of acute pulmonary edema, the high-dose group achieved guideline-recommended MAP reduction target more frequently and faster than in the low-dose group. These results

Table 2
Outcomes as a function of dosing group.

Outcome	Low Dose (< 100 μg/min) N = 27		High Dose (≥ 100 μg/min) N = 14	
	N or M	%	N or M	%
BP Goal Reached w/in 60 mins, N / %	6	22.2%	8	57.1%
Mean Time to Goal Being Met	54.0	–	40.4	–
Intubation, N / %	4	14.8%	2	14.3%
Hypotension, N / %	0	0%	0	0%
ICU, N / %	23	85.2%	11	78.6%

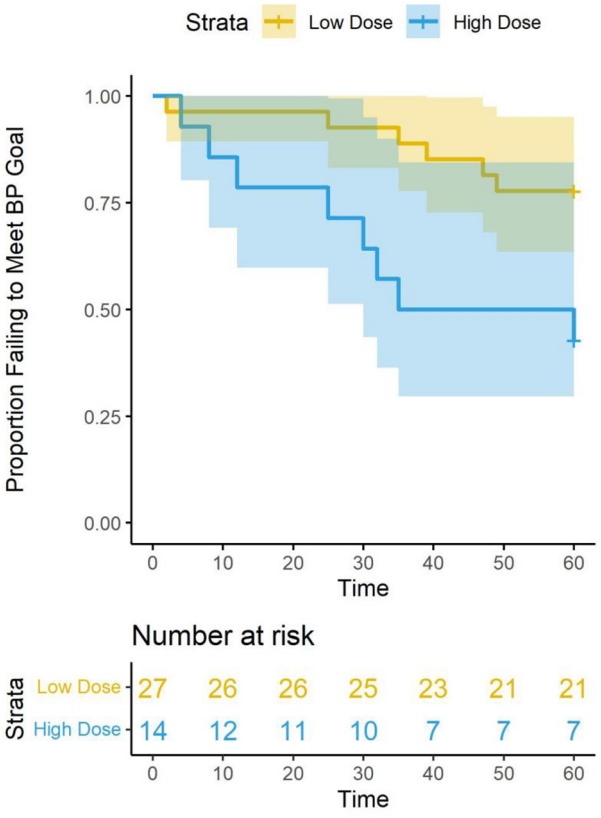

Fig. 1. Kaplan-Meier curves as a function of dosing group. Shaded regions depict 95% confidence intervals.

remained significant when adjusting for covariates including age, gender, initial BP, comorbid conditions, and home medication usage. The frequency of key safety outcomes including need for intubation and ICU admission were similar between the two groups and importantly, no episodes of hypotension were observed in either arm.

The use of high-dose IV NTG for the treatment of acute pulmonary edema in the emergency department has gained popularity in literature and open access forums, however the adoption of recommendations regarding high-dose strategies in guidelines had been lacking prior to the updated ACEP clinical practice guideline [2,3,5,11]. Guidelines suggest starting a NTG continuous infusion at a rate of 5 μg /min with titration in increments of 5 μg/min every 3–5 min. The recommended blood pressure target for acute pulmonary edema precipitated by severe hypertension (SBP ≥180 mmHg or DBP ≥120 mmHg) is a 25% reduction in SBP within the first hour [2]. Criteria for resolution of acute pulmonary edema includes improvement in at least two of the following: tachypnea, dyspnea, hypoxia, and SBP or MAP [2,7,10]. The titration of IV vasodilators for rapid blood pressure control provides a feasible framework for the resolution of symptoms of pulmonary edema and is easily protocolized.

Conventional low-dose NTG infusion (5–10 μg/min) seems comparatively ineffective for acute pulmonary edema and is less likely to achieve rapid blood pressure reduction compared to high-dose NTG infusions. This leads to delays in the resolution of respiratory embarrassment and more time that the patient is exposed to the hypertensive end-organ damage manifesting as pulmonary edema. Treatment of acute pulmonary edema is time-sensitive in nature and requires an aggressive and structured approach to provide rapid correction of hemodynamic abnormalities.

Levy et al. conducted a nonrandomized open-label, single-arm trial of 29 ED patients with severe decompensated heart failure and hypertension comparing a high-dose NTG protocol to conventional therapy

[7]. All patients received IV NTG infusion at a starting rate of 0.3–0.5 μg/kg/min titrated by 20 μg/min to a maximum rate of 400 μg/min. Concurrent with initiation of NTG infusion, patients in the intervention group received a 2 mg IV NTG bolus every 3–5 min up to 30 min. The mean bolus dose was 6.5 mg (95% CI 5.2–7.8 mg). The mean initial and final IV NTG infusion rates were 23.6 μg/min and 50.2 μg/min, respectively, for patients who received high-dose NTG. The non-intervention group had a mean initial rate of 31.7 μg/min, however the final rate was not available. The high-dose NTG group was associated with a lower rate of intubation, BiPAP, and ICU admission compared to conventional therapy.

Wilson et al. conducted a retrospective review of 395 patients who received NTG for acute pulmonary edema in the ED over a 5-year period [9]. Patients were divided into three groups where 124 received intermittent NTG bolus, 182 received NTG continuous infusion, and 89 received bolus plus continuous infusion. The bolus was administered as 2 mg IV every 3–5 min. The median bolus dose was 2 mg (IQR 1–2 mg). The median initial and maximum rates of NTG continuous infusion were 20 μg/min (IQR 10–30 μg /min) and 35 μg/min (IQR 20–50 μg /min), respectively. This study found that intermittent bolus NTG reduced ICU admission and shorter hospital LOS when compared to continuous infusion NTG.

While these studies demonstrate the feasibility and effectiveness of high-dose NTG versus conventional therapy, the continuous infusion rates used in the infusion-only groups were not high enough to achieve the arterial vasodilation necessary for clinically significant afterload reduction. More investigations would be useful to determine if a bolus-based NTG strategy is superior to or comparable to high-dose infusion.

4.1. Limitations

Our study has several limitations which we acknowledge. First, this was a retrospective study and as such, there was no randomization and no systematic means of accounting for why physicians chose to use a low- or high-dose NTG infusion. This may potentially introduce confounding or bias by indication, e.g. if clinicians were selecting higher doses for patients perceived to be more ill or with higher initial blood pressures. However, all recorded baseline characteristics between the low- and high-dose groups were similar with the exceptions of sex and percentage of patients with DM. No male patients received high dose NTG in our study for unclear reasons. Second, we excluded many charts ($n = 118$) for inadequate vital sign documentation. This was necessary since our study outcome required frequent vital sign documentation to discern the effects of NTG infusion but may also represent a source of confounding bias due to the comparatively high number of excluded charts. We only included HF as a binary variable, not the specific phenotype or quantitative ejection fraction. There may be a differential response to NTG doses based on the type of HF, but our study design and sample size were not designed to capture this. For the same reason, it was also necessary to record application of NIPPV as a binary term rather than a specific mode of NIPPV or "doses". Additionally, we collected information on any NTG given prior to the start of an infusion but simplified this to a binary covariate rather than examine the effect of a specific dose or route; only sublingual and topical routes were observed, and no bolus doses of IV NTG were used in any patient. Finally, the rates of safety outcomes observed between the two groups were similar, however our study was not powered to detect small differences in these outcomes.

5. Conclusions

Our retrospective review provides evidence that high dose continuous infusions NTG may be superior to low-dose infusion for achieving timely blood pressure control in acute pulmonary edema. The rate of adverse outcomes was similar between these two strategies, suggesting that high dose strategies are reasonably safe and that risk for treatment-related hypotension may be minimal. Starting at higher doses may allow for the beneficial secondary effects of nitroglycerin (e.g. arterial vasodilation) to occur more quickly, and limit the total time that the patient remains exposed to toxic hypertension. Higher initial NTG doses may be an effective way to decrease times to BP targets and should be the focus of future trials.

Prior presentations

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Author contributions

GSK, LAB, and CDC conceived the study. GSK and NH performed data collection. TPM designed the study statistics and performed the primary analyses. All authors participated in the manuscript preparation and are responsible for the quality and accuracy of the overall paper.

CRediT authorship contribution statement

Geoffrey S. Kelly: Writing – original draft, Validation, Data curation, Conceptualization. **Lindsey A. Branstetter:** Writing – original draft, Validation, Supervision, Methodology, Data curation, Conceptualization. **Tim P. Moran:** Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Nathan Hanzelka:** Validation, Investigation, Data curation. **Claudia D. Cooper:** Writing – original draft, Supervision, Investigation, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2022.12.022.

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