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Brief Reports

High-Dose Nitroglycerin Bolus for Sympathetic Crashing Acute Pulmonary Edema: A Prospective Observational Pilot Study

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□ **Abstract—Background: Sympathetic crashing acute pulmonary edema (SCAPE) is a severe form of hypertensive acute heart failure with a dramatic presentation. Rapid identification and management in the emergency department (ED) is key to saving these patients and preventing morbidity associated with endotracheal intubation and intensive care treatment. Use of high-dose nitroglycerin (NTG) and noninvasive ventilation (NIV) has been advocated in management of such patients. Objective: To study the feasibility and safety of high-dose NTG combined with NIV in SCAPE. Methods: This was a prospective observational pilot study done in the ED of a tertiary care hospital. All patients were treated with high-dose NTG and NIV. The primary objective was to study the feasibility and safety of the SCAPE management protocol in terms of the outcome of the patient. Resolution of symptoms in 6 h and need for intubation were recorded as endpoints. Any complications associated with high-dose NTG were also recorded. Results: A total of 25 patients were recruited. The mean bolus dose of NTG given was 872 μg, and mean cumulative dose, 35 mg. There was no incidence of hypotension after the bolus dose of nitroglycerin. Eleven patients had resolution of symptoms at 3 h of therapy. Twenty-four patients were discharged from the ED itself after a brief period of observation, and one patient was intubated and shifted to the intensive care unit. Conclusion: Use of our specific SCAPE treatment algorithm, which included high-dose NTG and NIV, was safe and provided rapid resolution of symptoms. © 2021 Elsevier Inc. All rights reserved.**

□ **Keywords—Flash pulmonary edema; SCAPE; High-dose nitroglycerin; Noninvasive ventilation; Sympathetic crashing acute pulmonary edema**

Introduction

Acute heart failure (AHF) is a common emergency routinely seen in clinical practice. The timely recognition and intervention by an emergency physician (EP) is important to prevent mortality and further morbidity in such patients. Hypertensive AHF is a distinct subgroup where there is increase in afterload and decrease in venous capacitance, leading to a shift of fluid from splanchnic circulation to pulmonary circulation (1). Sympathetic crashing acute pulmonary edema (SCAPE) is a severe form of hypertensive AHF with rapid progression of respiratory symptoms, sympathetic surge, and agitation due to hypoxia. Respiratory symptoms include severe respiratory distress with tachypnea, use of accessory muscles, and orthopnea. The hyperacute presentation of this illness leaves EPs with a very narrow window for intervention (2).

Rapid identification and management in the emergency department (ED) is key to prevent deterioration and morbidity associated with endotracheal intubation and intensive care. The recognition of SCAPE is clinical, and immediate management with high-dose nitroglycerin (NTG) and noninvasive ventilation (NIV) should be instituted. Effective management yields positive results within hours and is extremely satisfying for EPs.

Vasodilators have remained the mainstay of treatment in hypertensive AHF by reducing the preload and afterload and thus, relieving the pulmonary congestion (3,4). Although lower doses of NTG ($<$ 50 μg/min) have

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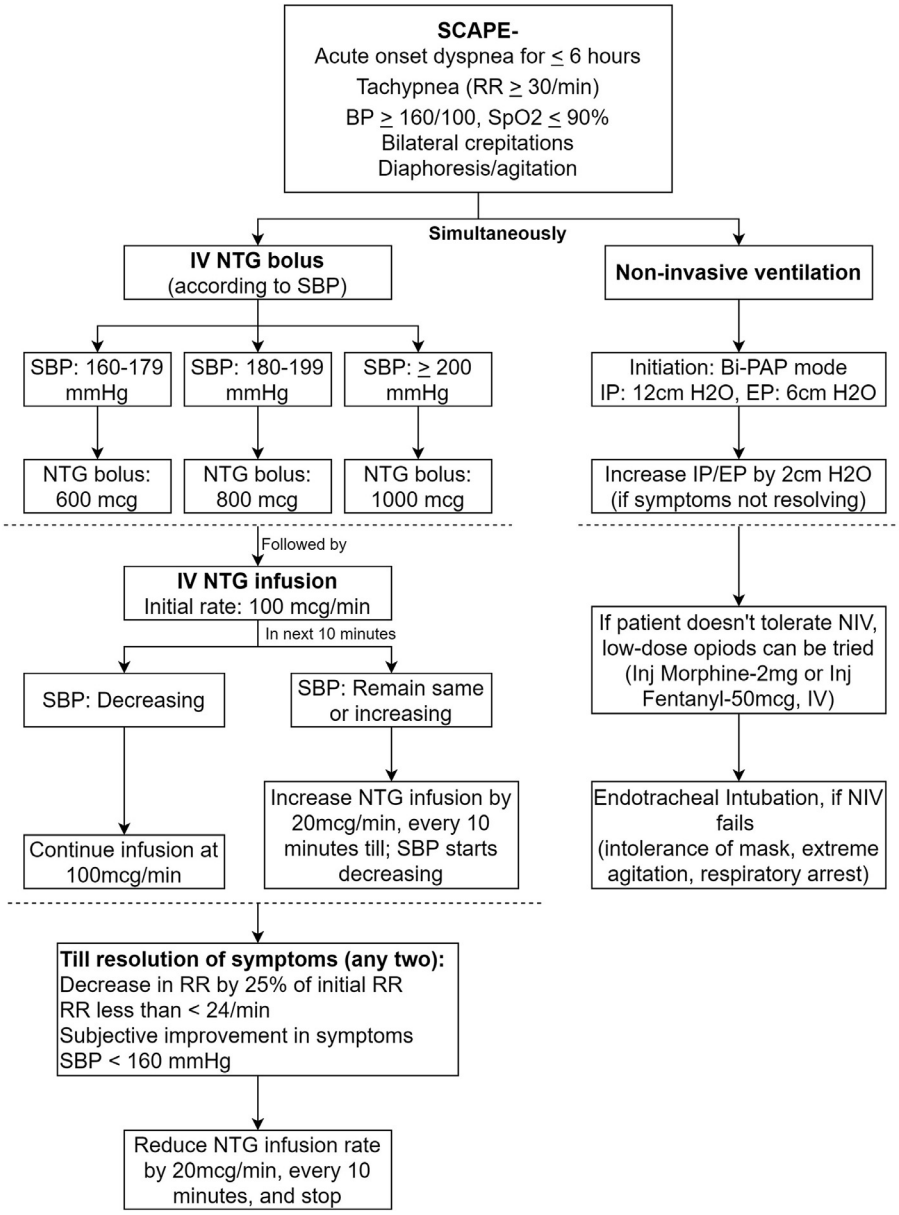

Figure 1. Protocol for SCAPE ED Management – SCAPE Treatment Protocol (STP).
SCAPE = sympathetic crashing acute pulmonary edema; ED = emergency department; IV = intravenous; NTG = nitroglycerin; SBP = systolic blood pressure; Bi-PAP = bilevel positive airway pressure; IP = injection pressure; EP = epidural pressure; NIV = noninvasive ventilation; RR = respiratory rate.

not shown significant improvement in symptoms, higher doses (50–250 μg/min) have shown better resolution of symptoms and hence, obviated the need for an intensive care unit (ICU) bed (5–8). Noninvasive positive pressure ventilation (NIPPV) has a class I recommendation in acute pulmonary edema. NIV in addition to high-dose NTG helps in reducing the work of breathing, decreasing preload and afterload, and preventing endotracheal intubation and ventilation in these patients (9,10). At our department, we developed a specific SCAPE Treatment Protocol (STP) (Figure 1), which includes high-dose NTG bolus followed by tapering doses and NIV.

Although there is a paucity of literature with regards to use of high-dose NTG in SCAPE patients, it is now being routinely used in many EDs. The objective of our study was to assess the feasibility and safety of STP.

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Methods

Study Design and Patient Selection

A prospective observational study was planned in the ED of our tertiary care hospital between June and December 2019. Our ED caters to around 100,000 patients per year, with about 10% of patients presenting with acute dyspnea. Ethical clearance was taken from the institutional ethics committee (IEC/234/05.04.2019). All consecutive patients aged > 18 years who presented with hypertensive AHF were screened for eligibility. Management for SCAPE was started as per the department protocol in all patients who were eligible (Figure 1). The recruitment and data collection were done by the treating physician. Due to the acuity of symptoms, informed consent was obtained from the patient after the resolution of symptoms. We used the inclusion criteria similar to the one described in the paper by Paone et al. (11). The case definition of SCAPE included a patient presenting with acute-onset respiratory distress of < 6 h, with a respiratory rate of more than 30 breaths/min, bilateral coarse crepitations, and saturation of < 90% on room air or < 95% on oxygen associated with sympathetic surge (diaphoresis, tachycardia and agitation) andblood pressure of > 160/100 mm Hg. . Patients who required immediate intubation or cardiopulmonary resuscitation and had a contraindication to NTG (allergic to NTG, aortic stenosis, hypertrophic cardiomyopathy, and use of sildenafil within 24 h or tadalafil within 48 h) were excluded. Patients with acute coronary syndromes were excluded as they were immediately shifted for percutaneous intervention.

SCAPE Treatment Protocol (STP)

The eligible patients were given a bolus dose of nitroglycerin (600–1000 μg over 2 min) followed by initiation of high-dose infusion (100 μg/min) and up-titrated, depending on patient's response and blood pressure levels. The dose of the bolus NTG was based on the initial systolic blood pressure (SBP) of the patient, if SBP was 160–179 mm Hg, a bolus of 600 μg was given; if SBP was 180–199 mm Hg, a bolus of 800 μg; and if SBP was ≥ 200 mm Hg, a bolus of 1000 μg was given. After the infusion was started at 100 μg/min and the SBP remained the same or increased after 10 min, the infusion rate was up-titrated by 20 μg/min every 10 min until there was a decreasing trend in SBP. The infusion was maintained at that rate until the resolution of symptoms. In patients with clinical improvement, the infusion rate was slowly reduced at the rate of 20 μg/min every 10 min. All patients on NTG were simultaneously commenced on NIV with bilevel positive pressure ventilation with inspiratory pressures (inspiratory positive airway pressure) of 12 cm H_2O and expiratory pressures (expiratory positive airway pressure) of 6 cm H_2O. Both inspiratory and expiratory pressures were increased by 2 cm H_2O each time the patient did not show improvement. If patients did not tolerate an NIV mask, low-dose opioid (intravenous fentanyl 50 μg/morphine 2 mg) was given to relay anxiety and improve tolerability. Despite opioid therapy, if patient did not tolerate the NIV mask and remained overtly agitated, delayed sequence intubation technique was used to intubate these patients (12). All eligible patients were managed in a high-dependency unit of the ED, which is a four-bedded area with ventilators, monitors, and other equipment to resuscitate a patient. There are six such high-dependency units in our ED that are each manned by a resident and a nursing staff. The patients were closely monitored with frequent vitals assessment. Data recording included vitals at presentation and at 10 min, and then hourly until 6 h. Blood pressure was measured noninvasively. Point-of-care ultrasound was performed immediately on arrival of the patient to assess the lung (looking for B-profile), inferior vena cava (collapsible or distended), and cardiac contractility. Adverse effects reported during the protocol were also recorded. Excessive decrease in blood pressure (defined as a reduction in SBP or mean arterial pressure of 30%), was considered as an indication to reduce the rate of nitroglycerin infusion (8). In cases when the drop in blood pressure resulted in sudden hypotension, the study protocol was terminated and the patient was given a fluid bolus of 500 mL of 0.9% normal saline. Other indications for protocol termination included bradycardia (defined as a pulse rate of 60 beats/min), new onset of chest pain, and new-onset neurologic deficits, as noted by the treating physician. Recommended treatment of these conditions was based on standard advanced cardiac life support protocols. Once there was resolution of symptoms, the patients were given oral antihypertensives, which they were already taking at home, to maintain their blood pressure levels. In those who had no history of oral antihypertensive intake, angiotensin receptor blockers were started in consultation with the cardiologist. They were observed in the ED for a minimum of 2 h of resolution to look for any rebound symptoms. Resolution was defined by any two of the following—a decrease in respiratory rate (RR) by 25% of initial reading, RR ≤ 24 breaths/min with patient maintaining saturations on pulse oximetry (SpO_2 ≥ 90% on room air or ≥ 95% on supplemental oxygen), subjective improvement in dyspnea and use of accessory muscles, systolic blood pressure of < 160 mm Hg, and disappearance of coarse crepitations in all lung auscultation fields (or disappearance of B-profile on lung ultrasound) (11).

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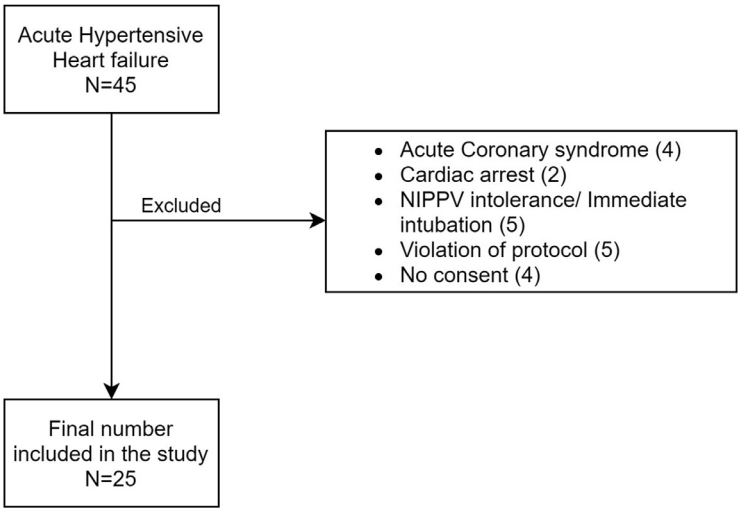

Figure 2. Plot for patient enrollment.
NIPPV = noninvasive positive pressure ventilation.

Outcome Measure

The primary objective of the study was to report the feasibility and safety of high-dose NTG combined with NIV in SCAPE. The proportion of SCAPE patients who had resolution of symptoms at 6 h and proportion of patients who developed adverse events due to the use of STP were calculated. The secondary objectives were to report mean bolus of NTG given, infusion/hour doses of NTG, and its correlation with systolic blood pressure.

Primary Data Analysis

All the observations were entered in proforma for further statistical analysis. Categorical variables were presented in numbers and percentages (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected, then nonparametric test (Friedman test) was used. A p-value of < 0.05 was considered statistically significant. Statistical analysis was performed with SPSS (version 25; SPSS, Inc., Chicago, IL).

Results

Characteristics of Study Subject

A total of 25 patients met the eligibly criteria for SCAPE during the study period (Figure 2). The basic characteristic of the patients are presented in Table 1.

Out of the 25 patients, a majority (16/25) presented during the night between 12 AM and 6 AM. All patients were agitated and diaphoretic at time of presentation.

Table 1. Basic Characteristics

Characteristics	
Age*	44.2 (18.8)
Sex†	
Male	12 (48)
Female	13 (52)
Duration of symptoms (hours)*	3.2 (1.4)
Comorbidities†	
Hypertensive	19 (76)
Diabetic	10 (40)
Chronic kidney disease	15 (60)
Coronary heart disease	3 (12)
Rheumatic heart disease	2 (8)
Dilated cardiomyopathy	2 (8)
Others‡	4 (16)

* Mean (SD).
† Frequency (%).
‡ One case each of tuberculosis, chronic obstructive pulmonary disease, chronic lymphocytic leukemia, and systemic lupus erythematosus.

Main Results

The mean bolus dose of NTG given was 872 μg; the mean cumulative dose of NTG received was 35 mg. There was no incidence of hypotension post bolus dose of nitroglycerin. In 2 patients there was a transient episode of hypotension during the infusion, which responded to a small bolus of fluid, and the infusion was restarted after 10 min. No other complication due to high-dose nitroglyc-

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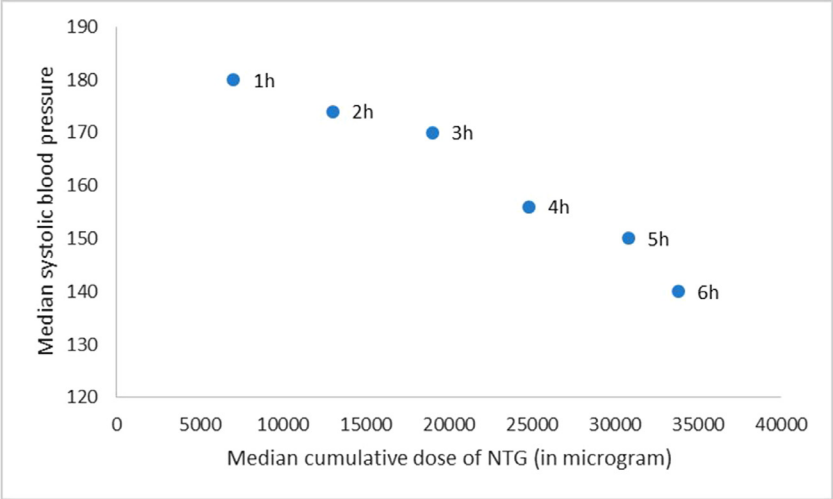

Figure 3. Hemodynamic response (Systolic Blood Pressure) to high-dose nitroglycerin (NTG) over time.

Table 2. Vitals in Different Timelines – Median (Interquartile Range)

	At Arrival	At 1 Hour	At 3 Hours	At 6 Hours	At Discharge	*p* Value
Respiratory rate	40 (37–42)	28 (27–29.5)	30 (30–32)	24 (22–25)	20 (19–21)	<
SpO_2	80 (76–87)	99 (98–99)	98 (98–99)*	99 (98–99)*	99 (98–99)	0.001†
Heart rate	128 (120–138)	120 (112–123)	106 (100–115)	90 (89–99)	80 (78–88)	
Systolic blood pressure	200 (180–220)	180 (166–196)	170 (150–185)	140 (131–150)	130 (130–136)	
Diastolic blood pressure	111 (108–130)	110(105–119)	100 (98–100)	84 (80–90)	80 (80–82)	

* On noninvasive ventilation support.
† *p*-Value for Friedman's test comparing medians of each hemodynamic parameter at different time points.

erin was seen during the first 6 h. Hemodynamic response to high-dose NTG is summarized in Table 2 and Figure 3.

NIV was started at the initial inspiratory positive airway pressure of 12 cm H_2O, and expiratory positive airway pressure of 6 cm H_2O, and subsequently, pressures were increased or decreased based on patients' tolerance and response. In 6 patients, a maximum inspiratory positive airway pressure of 16 cm H_2O and expiratory positive airway pressure of 10 cm H_2O was given, and in rest, the subjective improvement of symptoms was seen by up-titrating the pressures by only 2 cm H_2O. Twelve patients were given low-dose opioids (fentanyl 50 μg) to improve their mask tolerability. One patient did not tolerate NIV and was subsequently intubated within 6 h. On point-of-care ultrasound, B-profile was seen in all patients, cardiac contractility was reduced in 3 patients, and inferior vena cava (IVC) was > 50% collapsible in 8 patients.

Out of 24 patients who were discharged from ED to home, 11 patients had resolution of symptoms at 3 h and the remaining had symptom resolution within 6 h. Average length of stay for patients discharged to home was 15 h. One patient who was intubated was shifted to the ICU.

Discussion

This observational study included patients presenting with SCAPE. Our study revealed that use of STP resulted in rapid resolution of symptoms among patients presenting in SCAPE and thus, obviating the need for ICU care in most patients.

Out of the 25 patients, 19 were hypertensive on treatment, with 15 of them having underlying chronic kidney disease, predisposing these patients to refractory hypertension (13). These patients are predisposed to nocturnal hypertension due to sympathetic surge, thus precipitating heart failure (14). Sixty-four percent of our patients presented to the ED at night, highlighting the importance of better blood pressure control at night time.

Paone et al., in their case study, described a protocol to identify and manage SCAPE patients, where they started with an infusion rate of 400 μg/min and then reduced the rates by 50 μg/min every 5 min (11). In contrast, we gave an initial NTG bolus dose of 600–1000 μg (depending on the systolic blood pressure) and started infusion at 100 μg/min, gradually titrating the infusion rate upward

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(2). The maximum rate that the patient required was 200 μg/min. Symptomatic resolution was seen in almost all the patients at 6 h. This helped in better control of patients' hemodynamic status and prevented adverse events associated with high-dose NTG.

In 2 patients there was transient hypotension, which responded to a small bolus of fluid. This could be due to the fact that, though these patients were in obvious pulmonary edema, they were volume depleted when IVC was assessed by ultrasound, which was $>$ 50% collapsible. Systemic hypovolemic state has been described in literature among the hypertensive heart failure patient group due to chronic hypertension and chronic diuretic usage (15). This highlights the value of immediate bedside ultrasound to assess the IVC diameter and collapsibility in such patients, as volume-depleted patients may be at risk of significant hypotension with high-dose NTG. This observation is important to understand the pathophysiology of this acute presentation, as patients of SCAPE are mostly euvolemic, where diuresis may have little role; though a larger study focusing on this aspect will be needed to validate the findings.

Only one patient out of 25 had to be intubated, but the rest of the patients were successfully weaned off NIV and discharged. Wilson et al., in their retrospective study, revealed a higher rate of intubation (15/89) in patients who received a combination of bolus and infusion due to different patient selection criteria (7). A similar study by Mallick et al., using repeated doses of high-dose NTG with NIV, prevented intubation in all patients (16). A larger prospective study using combination therapy of NTG with bilevel positive pressure ventilation in SCAPE will be needed to address the utility of this therapy.

The use of NIV is a class I indication for AHF, but in SCAPE patients the challenge lies in application of mask over the face, as the patient does not tolerate it. The presentation of SCAPE is dramatic as the patient is extremely agitated, restless, and diaphoretic, struggling to breathe. In that instance, it is all about taking leadership, mobilizing resources, and utilizing effective crisis communication techniques (17). One good way to tackle the situation is to stand by the patient's bedside maintaining calm, holding the NIV mask on the patient's face to reduce leak and simultaneously counseling the patient for compliance. Starting with lower NIV pressures and increasing pressures when the patient starts tolerating the mask will also assist adherence to treatment (2). Relaying anxiety by using low-dose opioids (e.g., morphine 2 mg or fentanyl 50 μg) helps improve NIV mask acceptability. Although there is infrequent use of sedatives by physicians across the world, in our experience use of low dose opioids improved tolerability (18,19).

Limitations

Our study was a single-center pilot study with a small sample size. Findings may not be generalizable to the more heterogeneous population of India or around the world. We did not record frequent vital parameters and focused on just the first 6 h. Though we could see a significant improvement in patients with use of NIV and high-dose NTG, the key factor that affected outcome was correct patient selection, which included a subset of AHF patients with extreme clinical presentations (i.e., SCAPE). Also, our study focused only on the short-term adverse effects of high-dose NTG. A lack of longer-term follow-up precludes recognition of recurrent symptoms, subsequent decompensation, and any prolonged effects of NTG.

Conclusion

SCAPE Treatment Protocol used at our center is an effective management strategy for patients presenting to the ED in SCAPE. The combination of high-dose NTG with NIV was well tolerated.

. ARTICLE SUMMARY

1. Why is this topic important?

Sympathetic crashing acute pulmonary edema (SCAPE) is a challenging clinical entity for emergency physicians due to its dramatic presentation and a very narrow window to intervene. There is no uniform protocol across emergency departments for management of SCAPE.

2. What does this study attempt to show?

The study was done to report the feasibility and safety of high-dose nitroglycerin combined with noninvasive ventilation in SCAPE.

3. What are the key findings?

Eleven patients out of the 25 had resolution of symptoms at 3 h, 14 patients had symptom resolution within 6 h, and one patient had to be intubated. No short-term adverse events were seen.

4. How is patient care impacted?

SCAPE Treatment Protocol used at our center provided rapid resolution of symptoms without adverse events.

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