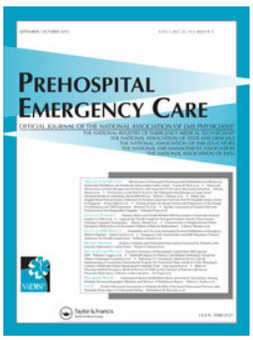

Prehospital Emergency Care

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

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To cite this article: Nichole Bosson, Benjamin Isakson, Jayson A. Morgan, Amy H. Kaji, Atilla Uner, Katherine Hurley, Timothy D. Henry & James T. Niemann (2019) Safety and Effectiveness of Field Nitroglycerin in Patients with Suspected ST Elevation Myocardial Infarction, Prehospital Emergency Care, 23:5, 603-611, DOI: 10.1080/10903127.2018.1558318

To link to this article: https://doi.org/10.1080/10903127.2018.1558318

Accepted author version posted online: 17 Dec 2018.
Published online: 28 Jan 2019.

Safety and Effectiveness of Field Nitroglycerin in Patients with Suspected ST Elevation Myocardial Infarction

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Abstract

Objective: While widely used in the treatment of cardiac conditions, only limited data characterize out-of-hospital nitroglycerin (NTG) use. We sought to determine the safety of out-of-hospital sublingual NTG administered for suspected ST-segment elevation myocardial infarction (STEMI) and its effect on the patient's pain score. **Methods**: We prospectively identified adult patients with suspected STEMI transported by paramedics to three percutaneous Coronary Intervention PCI-capable hospitals in a large urban-suburban emergency medical services (EMS) system. We compared patients who received field NTG to those who did not. The primary outcome was the change in systolic blood pressure (SBP) between initial EMS measurement and emergency department (ED) triage vital signs. Secondary outcomes included the frequency of hypotension (SBP < 100 mmHg) and bradycardia (HR < 60) on ED arrival, drop in SBP ≥ 30 mmHg, out-of-hospital cardiac arrest (OHCA), and the change in pain score compared to an a priori threshold of -1.39. **Results**: Among 940 EMS transports for suspected STEMI, we excluded 160 for initial SBP < 100 mmHg, leaving 780 subjects for the analysis. Median age was 67 with 61% male. NTG was administered to 340 (44%) patients. The median change in SBP was -10 mmHg (IQR -27, 2) and -3 mmHg (IQR -20, 9) in patients treated with and without NTG, respectively. The median difference in the decrease in SBP was 6 mmHg (95% CI 3, 9 mmHg). The frequencies of ED hypotension and bradycardia, the drop in SBP ≥ 30 mmHg, and the OHCA did not differ between groups. For patients with an initial pain score > 0, the average change in pain score for patients treated with NTG was -2.6 (95% CI -3.0, -2.2), while patients who did not receive NTG had a change in pain score of -1.4 (95% CI -1.8, -1.0). **Conclusion**: In this cohort, field NTG did not result in a clinically significant decrease in blood pressure when compared with patients who did not receive NTG. However, NTG did cause a clinically significant reduction in pain.
Key words: ST elevation myocardial infarction; emergency medical services; nitrates; pharmacology

PREHOSPITAL EMERGENCY CARE 2019;23:603–611

Introduction

Nitroglycerin (NTG) is widely used for treatment of chest pain of suspected cardiac etiology. Due to its vasodilatory effect, NTG is presumed to be beneficial in acute coronary syndrome (ACS) by increasing blood flow to the injured myocardium and reducing cardiac workload. There have been no studies evaluating outcomes from ACS after out-of-hospital treatment with NTG.

NTG is not without potential risk. By vasodilating all blood vessels, and the venous system in particular, it causes a drop in blood pressure and preload. Thus, there is concern for precipitating hypotension in ACS involving the right ventricle (1–3). Contraindications to the use of NTG, as outlined by the American Heart Association (AHA) Guidelines on the treatment of ACS, include right ventricular infarction (4). This raises concern for use in inferior ST-segment elevation myocardial infarction (STEMI) in the prehospital setting, since many inferior

Received September 27, 2018 from The Los Angeles County Emergency Medical Services Agency, Los Angeles, California, USA (NB); Department of Emergency Medicine, Harbor-UCLA Medical Center and Los Angeles Biomedical Institute, Torrance, California, USA (NB, BI, AHK, JTN); The David Geffen School of Medicine at UCLA, Los Angeles, California, USA (NB, AHK, AU, JTN); Department of Cardiology, Cedars-Sinai Medical Center, Los Angeles, California, USA (JAM, TDH); Department of Emergency Medicine, Ronald Regan UCLA Medical Center, Los Angeles, California, USA (AU, KH). Revision received December 5, 2018; accepted for publication December 7, 2018.

This data was previously presented, in part, at the American College of Emergency Physicians Research Symposium in Washington, DC, October 2017.

The authors have no conflicts of interest to report.

This work was completed without external funding.

A.H. Kaji, J.T. Niemann, and N. Bosson conceived of the study and designed the trial. N. Bosson created the data collection instrument. A. Uner, N. Bosson, and T.D. Henry supervised the enrollment and data abstraction at each site. B. Isakson, J.A. Morgan, and K. Hurley collected the data. A. Uner and N. Bosson performed the data abstraction for inter-rater reliability. N. Bosson performed the analysis, with the assistance of A.H. Kaji. N. Bosson drafted the manuscript and all authors contributed substantially to its revision.

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doi:10.1080/10903127.2018.1558318

STEMI result from proximal right coronary artery (RCA) occlusion and 50% involve the right ventricle (3). Traditional 12-lead ECG is focused mainly on the left side of the heart and typically emergency medical systems (EMS) protocols do not include acquisition of right-sided ECG leads. Furthermore, in many systems, Basic Life Support (BLS) protocols allow for administration of NTG without differentiating the location of STEMI. There is also risk of other adverse events including bradycardia and cardiac arrest (5–9).

Despite the theoretical risk, the limited retrospective studies of NTG in the prehospital setting for multiple indications suggest that the medication is safe (10–13). However, with regard to NTG use for STEMI, the AHA International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care concluded that there was not enough evidence to determine the benefit or harm of out-of-hospital use of NTG (14). Given the high false positive rates for STEMI identified in the field, an additional concern is that many patients treated with NTG for presumed STEMI will ultimately have an alternate etiology for their pain (15, 16). Therefore, it is not clear that the benefits outweigh the risks of administering NTG to all patients with suspected STEMI in the field.

We sought to determine the association of out-of-hospital NTG administration with changes in blood pressure, heart rate, and pain scores in patients treated by EMS for suspected STEMI.

METHODS

Study Design

This is a retrospective chart review of prospectively identified patients with suspected STEMI transported by EMS to one of three participating PCI-capable hospitals within the Los Angeles County (LAC) regional cardiac care system from July 1, 2015 to December 31, 2016. The Institutional Review Board at each of the participating centers reviewed and approved the study with exemption of informed consent.

Population and Setting

The LAC regional cardiac system includes seventy-three 911-receiving centers, of which 36 are STEMI Receiving Centers (SRC). Emergency Medical Services are provided by 30 fire-based provider agencies with approximately 4000 paramedics. The system serves a population of greater than 10 million distributed over more than 4000 square miles. All SRC are capable of providing immediate cardiac catheterization 24 hours per day, 7 days per week with cardiovascular surgeons available (17). For patients with STEMI who access 911, paramedics transport directly to the closest SRC for primary PCI. Prehospital management throughout LAC is standardized via field treatment protocols. All adult patients with suspected cardiac chest pain receive an immediate 12-lead ECG to evaluate for STEMI and a complete assessment with documentation of vital signs including pain score. We define "suspected STEMI" as a provider impression of STEMI as determined by the software and/or paramedic interpretation of the ECG along with the patient's clinical presentation and, when needed, assistance of online medical control. All patients without an aspirin allergy receive aspirin. Patients with persistent chest pain on EMS arrival receive sublingual NTG 0.4 mg as the primary treatment, unless contraindicated. NTG administration may be repeated twice for persistent pain. Contraindications to NTG include systolic blood pressure (SBP) less than 100 mmHg or use of a phosphodiesterase 5 inhibitor within the previous 48 hours. Opiate analgesia is also contraindicated for SBP less than 100 mmHg, but may be administered if NTG must be avoided for other reasons, or in addition to NTG, if the pain is not relieved after 3 doses of NTG. Intravenous fluids are authorized for any patient with signs of poor perfusion, which includes but is not limited to hypotension, bradycardia or tachycardia, altered mental status, delayed capillary refill, and skin pallor, cyanosis, or mottling.

Selection of Participants

We included consecutive adult patients transported for suspected STEMI to one of three high-volume SRCs: Cedars-Sinai Medical Center, Harbor-UCLA Medical Center, and Ronald Reagan UCLA Medical Center. Mobile Intensive Care Nurses (MICNs) at each site prospectively identified patients 24/7 and maintained a log during the 18 month study period. We included patients who were 18 years of age or older without a primary complaint of trauma or cardiac arrest on EMS arrival and excluded those who had an SBP less than 100 mmHg on initial EMS vital signs.

Measurements

Depending on the study site, hospitals stored the prehospital records as paper charts or uploaded them into the electronic medical record. Using the log to identify patients, a study investigator reviewed prehospital and hospital records for initial

field and emergency department (ED) vital signs; field NTG treatment; in-hospital management including immediate or delayed coronary angiography and PCI; prehospital and ED ECG findings; final diagnosis; and patient outcomes. Investigators determined the final diagnosis as STEMI, non-STEMI, or angina (collectively ACS) based on the documentation of an International Statistical Classification of Disease (ICD) 9 or 10 in one of these categories at hospital discharge. If none was present, the diagnosis was classified as "other." Investigators classified the location of PCI per the documentation in the cardiac catheterization report. At each study site, one investigator performed the data abstraction. A second investigator then independently confirmed key data elements. Using the kappa statistic, inter-rater reliability was assessed on a random 10% sample of records.

Key Outcome Measures

The primary safety outcome was the change in blood pressure in patients who received field NTG compared to those who did not. Secondary safety outcomes were the frequencies of ED hypotension (defined as a triage systolic blood pressure (SBP) $<$ 100 mmHg), drop in SBP $\geq$ 30 mmHg, bradycardia (defined as heart rate $<$ 60 beats per minute), and out-of-hospital cardiac arrest (OHCA). Efficacy was evaluated primarily with the change in chest pain score among patients who received NTG, and secondarily with in-hospital mortality. We selected the SBP threshold of 100 mmHg for hypotension, because this is the SBP below which NTG is contraindicated by LAC treatment protocols. We selected a drop in SBP $\geq$ 30 mmHg based on prior literature (13). LAC paramedics and hospital personnel assess chest pain on an 11-point Numeric Rating Scale (NRS) by querying the patient on their level of pain from 0–10. We evaluated the change in pain score in patients who received field NTG and those who did not among patients with chest pain on EMS arrival (initial pain score $>$ 0). A priori, we determined the minimum clinically important difference (MCID) in pain score after treatment with NTG as 1.39 (18–20).

We conducted several planned subgroup analyses. We performed the same comparisons described above in the subgroup of patients with a final diagnosis of STEMI. Additionally, we compared the frequency of the safety outcomes in patients who received PCI to a mid or proximal right coronary artery (RCA) lesion compared to patients who received PCI at any other location.

Analytical Methods

Study investigators entered data into a secure online data collection tool SherlockMD (SherlockMD, Santa Monica, CA). At the completion of the study, data were downloaded as a Microsoft Excel file (Microsoft Corporation, Redmond, WA) and transferred to SAS 9.4 (SAS Institute, Cary, NC) for analysis. We describe the two groups with frequencies and proportions or medians with interquartile range (IQR). We assessed the differences in the change in SBP and mean arterial blood pressure (MAP) with Hodges-Lehmann's median difference. We calculated the risk differences and used the Cochran-Mantel-Haenszel chi square test to compare drop in SBP $\geq$ 30 mmHg, ED hypotension, and bradycardia between the two groups. Given the rarity of OHCA, we used the Fischer's exact test. We use the one side t-test to compare the change in pain score among patients treated with NTG and among those not treated with NTG to the a priori MCID of 1.39. We performed multivariable logistic regression to further explore the association of field NTG with the risk of drop in SBP $\geq$ 30 mmHg and ED hypotension, adjusting for patient factors (age, gender, vital signs, and final diagnosis). To account for confounding by indication (e.g., paramedics may administer NTG to those who appear to be "less sick"), we performed a propensity-score adjusted analysis to assess the association of field NTG with in-hospital mortality. A propensity-score was calculated based on factors that could influence treatment with NTG: age, gender, vital signs, and hospital diagnosis (as a surrogate for paramedic impression).

We used the same analytical methods for the univariate comparisons within the subgroup of patients with a final diagnosis of STEMI. Finally, we calculated the relative risk for ED hypotension for those who received PCI to a mid or proximal RCA lesion as compared to patients with documented PCI at any other location.

RESULTS

Among 940 EMS transports for suspected STEMI, we excluded 160 for initial SBP $<$ 100 mmHg, leaving 780 subjects for the analysis. (Figure 1) Median age was 67 (IQR 56–80) with 61% male. Table 1 provides the patient characteristics by treatment group. NTG was administered by EMS to 340 (44%) patients; inter-rater reliability for its administration was excellent, kappa 0.92 (95% CI 0.82, 1.0). The median change in SBP was -10 mmHg (IQR -27, 2) vs -3 mmHg (IQR -20, 9) in patients treated with and without NTG respectively. The median

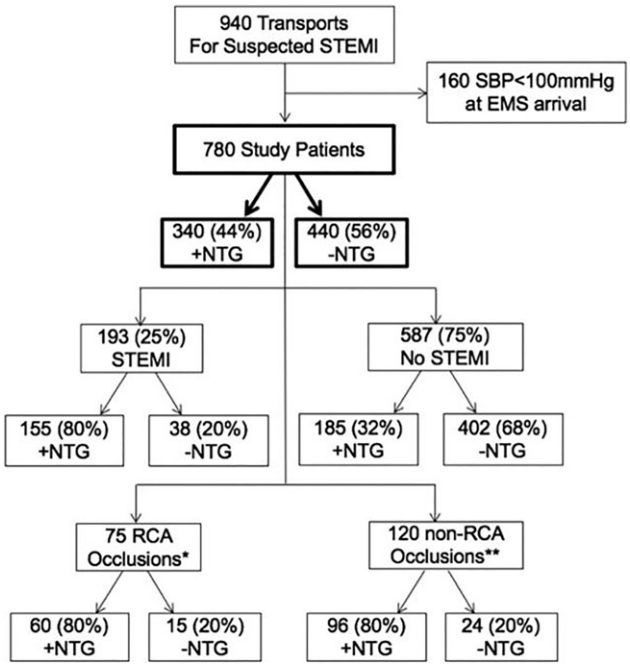

FIGURE 1. Patient flow diagram. Bold represents primary cohort. * PCI to a proximal or mid RCA lesion. ** PCI to a lesion, not proximal or mid RCA. STEMI = *ST-segment Elevation Myocardial Infarction*; SBP = *Systolic Blood Pressure*; EMS = *Emergency Medical Services*; NTG = *Nitroglycerin*; PCI = *Percutaneous Coronary Intervention*; RCA = *Right Coronary Artery*.

TABLE 1. Patient characteristics by nitroglycerin (NTG) treatment group

	Received NTG (340)		No Field NTG (440)	
	N	%	*N*	%
Male Sex	234	69	245	56
Age, median (IQR)	63	(54–75)	70	(58–82)
Race/Ethnicity				
Asian	18	5	34	8
Black	119	35	155	35
Hispanic	42	12	43	10
Pacific Islander/Hawaiian	3	1	2	0.5
White	123	36	167	38
Other	35	10	39	9
Initial Field Vital Signs, median (IQR)				
Systolic Blood Pressure, mmHg	144	(128–167)	140	(115–160)
Diastolic Blood Pressure, mmHg	87	(75–100)	80	(70–95)
Mean Arterial Pressure, mmHg	107	(94–120)	101	(86–116)
Heart Rate	88	(72–104)	88	(70–108)
Initial Pain Score, median (IQR)	8	(5–9)	0	(0–0)
Final Diagnosis				
STEMI	155	46	38	9
NSTEMI	35	10	28	6
Angina	10	3	7	2
Other	139	41	366	83

IQR = *Inter-quartile Range*; STEMI = *ST-segment Elevation Myocardial Infarction*; NSTEMI = *Non-ST-segment Elevation Myocardial Infarction*.

difference in the decrease in SBP was −6 mmHg (95% CI −9, −3 mmHg). (Table 2) The frequencies of ED hypotension and bradycardia, drop in SBP ≥ 30 mmHg, and OHCA, did not differ between groups. Inter-rater reliability for ED hypotension was 0.93 (95% CI 0.80, 1.0). Individual patient data for change in SBP, MAP and heart rate are depicted in Figure 2. Among patients who received NTG, the lowest recorded heart rate at ED triage was 39 in one patient. In both groups, bradycardia was most

TABLE 2. Safety outcomes by nitroglycerin (NTG) treatment group

	Received NTG (340)		No Field NTG (440)		Measure of Difference
	Median	*IQR*	*Median*	*IQR*	
Systolic Blood Pressure	−10	(−27, 2)	−3	(−20, 9)	−6 mmHg (95% CI −9, −3)*
Mean Arterial Pressure	−9	(−20, 3)	−4	(−17, 6)	−4 mmHg (95% CI −7, −1)*
	N	%	N	%	
Drop in SBP ≥ 30 mmHg	18	5.3	29	6.7	1.4% (95% CI −2.0, 4.8)†
ED Hypotension	32	9.1	54	12.1	2.9% (95% CI −1.4, 7.2)†
ED Bradycardia	24‡	7.2	41‡	9.7	2.5% (95% CI −1.5, 6.4)†
Out-of-hospital Cardiac Arrest	1	0.3	4	0.9	Fischer exact, p = 0.2

*Hodges-Lehmann's Median Difference.
†Risk Difference.
‡Including newly bradycardic patients: Received NTG $N = 10$, No Field NTG $N = 17$.

often mild with HR 50–59 in 75% of bradycardic patients. The frequency of hypotension and bradycardia did not differ by the number of NTG doses administered. (Table 3) In multivariable logistic regression models, adjusting for patient age, gender, initial bradycardia, and final diagnosis of ACS, there was no association of field NTG with a drop in SBP ≥ 30 mmHg or with ED hypotension. (Table 4).

For patients with an initial pain score greater than 0, the average change in pain score for patients treated with NTG (N = 300) was −2.6 (95% CI −3.0, −2.2), while patients not treated with NTG (N = 96) had an average change in pain score of −1.4 (95% CI −1.8, −1.0). Compared with the MCID of −1.39, the p value for a greater decrease in pain was <0.0001 for those treated with NTG and 0.5 for those without NTG in the field. Ten patients (3%) treated with NTG died in the hospital compared with 39 patients (9%) who did not receive NTG. In the propensity-score adjusted model, patients who received NTG had decreased odds of in-hospital mortality, OR 0.3 (95% CI 0.1, 0.8).

Of 193 patients with confirmed STEMI, 155 (80%) received NTG. In this subgroup, the median change in SBP was −11 mmHg (IQR −26, 0) and 0 mmHg (IQR −18, 12) in patients treated with and without NTG respectively; median difference −9 mmHg (95% CI −17, 0 mmHg).(Table 5) The average change in pain score was −2.4 (95% CI −2.9, −1.9) with NTG ($N = 145$), compared with the MCID p = 0.0002. Five patients (4%) who received NTG died in hospital versus 6 patients (16%) who did not receive NTG. Among 75 patients with mid- or proximal-RCA lesions, 60 (80%) received NTG. Compared to patients treated with PCI in any other location, the occurrence of ED hypotension and bradycardia on ED triage vital signs after NTG among patients with RCA lesions was similar, RR 0.64 (95% CI 0.21, 1.95) and RR 1.30 (95% CI 0.57, 2.94), respectively.

DISCUSSION

The administration of NTG for suspected STEMI in the field appears to be safe and to result in clinically significant pain relief. Although there was a statistically significant decrease in SBP in patients who received field NTG compared to patients who did not receive field NTG in our cohort, this did not result in a clinically meaningful decline in status as evidenced by the ED triage vital signs. Normal circadian variation of SBP in both healthy individuals and patients with diagnosed hypertension has been shown to be quite large, with a standard deviation of 15.1 mmHg and 13.6 mmHg, respectively, and an average range over the course of a day of up to 70 mmHg (21). Therefore, our observed 6 mmHg increase in the drop in SBP after field NTG administration compared to those who did not receive the drug is not likely to be clinically significant. Furthermore, administration of NTG by EMS was not associated with an increased risk of hypotension or bradycardia at ED arrival and there was no increase in the rare event of OHCA during EMS field care.

The frequency of hypotension after NTG in our study was 9%. This is similar to the 8.4% reported by Robichaud et al. among patients with STEMI treated with NTG in the field (13). In that study, the authors evaluated the frequency of hypotension after administration of NTG in patients with inferior STEMI compared to patients with STEMI in other territories, but did not include a comparative group of patients without field NTG (13). Our results comparing NTG administration to no NTG in all patients with suspected STEMI further support the safety of NTG use in the field. While Robichaud et al. (13) found that 23% of patients had a drop in SBP ≥ 30 mmHg after NTG, in our cohort this was much lower at 5.3%. Prior studies of undifferentiated patients presenting with chest pain or dyspnea, have also found hypotension to be rare after field NTG (10, 11).

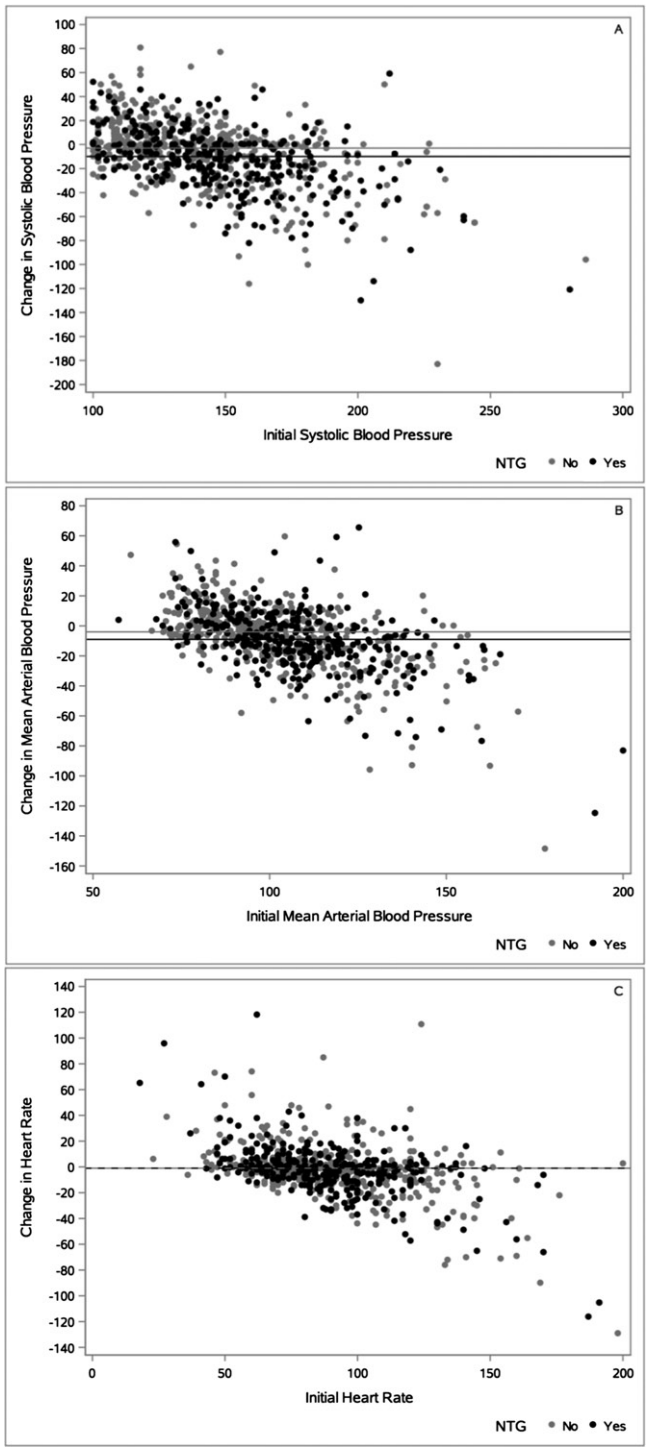

FIGURE 2. Change in vital signs by initial measurement. Reference lines represent the median change by group. (A) Systolic Blood Pressure; (B) Mean Arterial Blood Pressure; (C) Heart Rate.

There have been numerous case reports and case series that raise concern about NTG precipitating severe bradycardia (5–8). In our cohort, there was no association of field NTG with bradycardia upon ED arrival. While profound bradycardia can occur in patients with cardiac ischemia, our data suggests that this is uncommon and may not be associated with sublingual NTG. Our findings are similar to those of Engelberg et al. who reported a single patient with significant bradycardia in a cohort of 1662 patients treated with field NTG for chest pain (11).

TABLE 3. Frequency of ED hypotension and bradycardia by doses of nitroglycerin (NTG) administered

Doses of NTG	Total *N*	Hypotension*		Bradycardia†	
0	440	54	(12%)	41	(10%)
1	115	13	(11%)	9	(8%)
2	108	10	(9%)	5	(6%)
3	117	9	(8%)	10	(9%)

*Hypotension p value for difference = 0.1.
†Bradycardia p value for difference = 0.3.

Forty-one percent of patients in whom paramedics administered NTG ultimately did not have a diagnosis of ACS. The high frequency of false-positive STEMI in the LAC EMS system has been described previously and is largely due to a reliance on software ECG interpretation for routing of suspected STEMI patients (16). Still, based on Table 1, paramedics administered NTG to nearly three-quarters of patients with ACS and avoided this therapy in a similar proportion without ACS. It is reassuring that despite the high false-positive rate, the administration of field NTG was not associated with increased adverse events in the heterogeneous population treated by EMS for suspected STEMI, as well as within the subgroup of patients with confirmed STEMI. Our study results support the safety of field use of NTG, though it may be administered incorrectly to some patients with potential STEMI mimics, such as aortic dissection, and other non-cardiac diagnoses. Notably, in our cohort, the frequency of hypotension and bradycardia did not increase with additional doses of NTG. While it is possible that some patients had transient events in the field, we chose to focus our outcome on the patient's status at ED arrival, since transient events were not likely to be clinically meaningful, particularly given the short transport times in our system (average 11 minutes).

Furthermore, we did not find an increased risk of hypotension among patients with proximal or mid-RCA occlusions confirmed on coronary angiography. There are several possible reasons for our findings. While right ventricular involvement in inferior STEMI is common, hemodynamic instability is actually rare due to the right ventricle's more favorable oxygen supply-demand ratio compared to the left heart and more extensive collateral flow (3, 22). In addition, left heart occlusions may also

TABLE 4. Multivariable logistic regression models for drop in systolic blood pressure after field nitroglycerin (NTG) treatment, OR (95% CI)

	Drop in SBP ≥ 30 mmHg ($N = 750$)		ED Hypotension, SBP < 100 mmHg ($N = 762$)	
Nitroglycerin treatment	0.9	(0.5, 1.8)	0.8	(0.5, 1.4)
Age (year)	1.0	(1.0, 1.0)	1.0	(1.0, 1.0)
Gender (ref = male)	1.0	(0.5, 2.0)	1.4	(0.8, 2.2)
Initial field bradycardia (HR < 60)	0.9	(0.3, 2.7)	1.4	(0.7, 2.8)
Acute Coronary Syndrome diagnosis	0.9	(0.4, 1.8)	0.9	(0.5, 1.5)

Hosmer-Lemeshow fit statistic p = 0.3 and p = 0.2, respectively.

TABLE 5. Safety outcomes for the subgroup of patients with confirmed STEMI by nitroglycerin (NTG) treatment group

	Received NTG (155)		No Field NTG (38)		Measure of Difference
	Median	IQR	Median	IQR	
Systolic Blood Pressure	−11	(−26, 0)	0	(−18, 12)	−9 mmHg (95% CI −17, 0)*
Mean Arterial Pressure	−9	(−18, 3)	−1	(−13, 9)	−8 mmHg (95% CI −15, −1)*
	N	%	*N*	%	
Drop in SBP ≥ 30 mmHg	6	3.9	3	8.1	−4.2% (95% CI −13.5, 5.1)†
ED Hypotension	14	9.0	4	10.5	−1.5% (95% CI −12.2, 9.2)†
Bradycardia	20	13.0	7	18.9	−5.9% (95% CI −19.6, 7.7)†
Out-of-hospital Cardiac Arrest	1	0.7	1	2.6	Fischer exact, p = 0.4

*Hodges-Lehmann's Median Difference.
†Risk Difference.

involve the right ventricle and result in a preload dependent condition (23–25). While limited by sample size, our results suggests that specifically avoiding NTG use in inferior STEMI, which is common in EMS systems, may be misguided. One quarter of the local EMS agencies in the state of California, for example, currently prohibit the use of NTG in inferior STEMI (26). This analysis would benefit from additional study with a larger sample size and specific information about the infarct territory. Further studies are needed to determine which patients, in particular, are at increased risk for hypotension when treated with NTG.

Our results demonstrate safety of NTG for treatment of suspected STEMI in the field. We also found a clinically meaningful reduction in pain score for a majority of patients following NTG administration, based on our a priori MCID. In contrast and as expected, the majority of STEMI patients who did not receive field NTG did not have a clinically meaningful reduction in their pain. Larger studies will be important to evaluate patient-centered outcomes to determine if there is a measurable long-term benefit to field NTG treatment. While the benefits of NTG to reduce morbidity and mortality in STEMI remain uncertain, the importance of NTG as an effective non-opiate analgesic for ischemic chest pain cannot be discounted. Given the side effect profile of opiate analgesics, NTG offers an excellent alternative. Furthermore, the effect of opiate analgesics on outcome for patients with ACS is also unknown (26), with one large registry study demonstrating harm (27). In a Class I recommendation, the AHA limits the indication for opiate analgesia to patients in whom chest pain is unresponsive to nitrates (4). The results of our analysis lend further support to the recommendation for NTG as the preferred medication for initial pain management in patients with suspected ACS, including STEMI. We suggest EMS protocols include NTG as the first-line field treatment for presumed ischemic chest pain.

When considering these results, there are several notable limitations. Although patients were identified prospectively, data were gathered via chart review and, therefore, incur all of the limitations of a retrospective analysis, including the inability to determine causality. We attempted to mitigate the risk of bias as much as possible by adhering to recommendations for reducing bias in chart review studies (28). Still, there are likely other unknown differences between the groups, which may influence the association of NTG with our measured outcomes. In particular, mortality is influenced by many factors. Despite our propensity score-adjusted analysis, the mortality difference we found most likely reflects a difference between the groups from unmeasured confounders, rather than a true

association with NTG. The majority of patients who did not receive NTG had a documented pain score of zero. However, paramedic judgment may also influence the decision to treat with NTG. While a limitation, we feel this is also a strength with respect to the ability to measure the effectiveness (e.g., akin more to pragmatic trial) or beneficial effect of NTG under "real world" conditions, rather than NTG's efficacy, measured under ideal conditions. We did not collect data on additional interventions in the field, including administration of opiate analgesics, which may have reduced our ability to assess a difference in pain relief from NTG. Furthermore, we were not able to detect transient episodes of hypotension in the field that resolved either spontaneously or with intravenous fluid administration prior to ED arrival. In particular, the subgroup analyses were limited by small sample sizes. Only 25% of the study population had a confirmed hospital diagnosis of STEMI, so this limited our ability to assess the differences in hemodynamic effects of NTG in this group. Although proximal RCA occlusions are associated with RV infarction, we did not have anatomic studies to confirm the infarct territory. Finally, this study only included patients treated at three hospitals within a single regional urban/suburban EMS system. Our results may, therefore, not be generalizable to other systems, particularly rural settings where EMS transport times are prolonged.

CONCLUSION

In this cohort of suspected or confirmed STEMI patients, field NTG resulted in pain reduction and did not result in a clinically significant decrease in blood pressure when compared with patients who did not receive NTG, nor an increased frequency of hypotension or bradycardia on ED arrival.

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