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# Prehospital Nitroglycerin Safety in Inferior ST Elevation Myocardial Infarction

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Abstract

Patients with inferior ST elevation myocardial infarction (STEMI), associated with right ventricular infarction, are thought to be at higher risk of developing hypotension when administered nitroglycerin (NTG). However, current basic life support (BLS) protocols do not differentiate location of STEMI prior to NTG administration. We sought to determine if NTG administration is more likely to be associated with hypotension (systolic blood pressure < 90 mmHg) in inferior STEMI compared to non-inferior STEMI. We conducted a retrospective chart review of prehospital patients with chest pain of suspected cardiac origin and computer-interpreted prehospital ECGs indicating "ACUTE MI." We included all local STEMI cases identified as part of our STEMI registry. Univariate analysis was used to compare differences in proportions of hypotension and drop in systolic blood pressure ≥ 30 mmHg after nitroglycerin administration between patients with inferior wall STEMI and those with STEMI in another region (non-inferior). Multiple variable logistic regression analysis was also used to assess the study outcomes while controlling for various factors. Over a 29-month period, we identified 1,466 STEMI cases. Of those, 821 (56.0%) received NTG. We excluded 16 cases because of missing data. Hypotension occurred post NTG in 38/466 inferior STEMIs and 30/339 non-inferior STEMIs, 8.2% vs. 8.9%, $p = 0.73$. A drop in systolic blood pressure ≥ 30 mmHg post NTG occurred in 23.4% of inferior STEMIs and 23.9% of non-inferior STEMIs, $p = 0.87$. Interrater agreement for chart review of the primary outcome was excellent ($\kappa = 0.94$). NTG administration to patients with chest pain and inferior STEMI on their computer-interpreted electrocardiogram is not associated with a higher rate of hypotension compared to patients with STEMI in other territories. Computer interpretation of inferior STEMI cannot be used as the sole predictor for patients who may be at higher risk for hypotension following NTG administration. **Key words:** emergency medical services, blood pressure, myocardial infarction, nitroglycerin

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## Introduction

Nitroglycerin is a well-established treatment modality for improving coronary artery blood flow and symptom management in acute coronary syndrome (ACS).[1] Although sublingual nitroglycerin is a relatively safe and effective drug for the treatment of ischemic chest pain, it has never been shown to diminish mortality in ST elevation myocardial infarction (STEMI). Its use may also be associated with some risk. The American Heart Association (AHA) guidelines advise extreme caution with nitroglycerin administration to patients with inferior ST elevation myocardial infarction.[1–3] Right ventricular infarction (RVI) is described to be present in up to 50% of all inferior STEMI and these patients are at high risk of developing hypotension following nitroglycerin administration.[4–6]

Current EMS guidelines recommend a 12-lead electrocardiogram (ECG) for all patients exhibiting signs and symptoms of ACS.[7] Basic life support (BLS) EMS protocols also routinely recommend sublingual nitroglycerin administration to patients with persistent chest pain, aside from those with certain exclusion criteria. However, current BLS protocols do not differentiate location of STEMI prior to nitroglycerin administration. As nitroglycerin could precipitate hypotension in patients with acute inferior wall STEMI and associated RVI, its routine prehospital administration might not be safe. Although it is widely recommended in the medical literature to use caution when administering

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nitroglycerin, very few studies have examined its effects in patients with acute inferior STEMI.[5,6,8–10] To our knowledge, there are no studies demonstrating the safety of nitroglycerin in STEMI patients in the prehospital setting.

The objective of this study was to determine if nitroglycerin administration was more likely to be associated with hypotension (systolic BP < 90 mmHg) in inferior STEMI compared to non-inferior STEMI. We also sought to determine if patients with inferior STEMI were at higher risk of having a drop in systolic BP ≥ 30 mmHg after nitroglycerin administration.

# METHODS

## Study Design and Setting

We retrospectively reviewed prehospital medical records from Urgences-santé, the sole emergency medical services (EMS) provider for the cities of Montreal and Laval in the province of Quebec, Canada. Urgences-santé covers a 744-km$^2$ urban territory with 2.3 million people and conducts 225,000 scene responses per year. The majority (99%) of providers at Urgences-santé are trained to the BLS-D level.

We reviewed all consecutive local STEMI cases from February 2010 to July 2012, identified as part of Urgences-santé's STEMI registry. Our protocol was approved by the Research Ethics Office of the Jewish General Hospital (Montreal, Quebec, CA).

## Study Population

We included all adult (≥ 18 years old) prehospital patients with chest pain of suspected cardiac origin and computer-interpreted STEMI on their prehospital 12-lead ECG who received sublingual nitroglycerin by Urgences-santé's primary care paramedics (PCPs) as part of the provincial nitroglycerin protocol for patients with suspected ACS. Quebec's PCPs are trained at the BLS-D level and are trained in ECG acquisition but not in ECG interpretation.

The protocol definition of chest pain of suspected cardiac origin is presented in Table 1. Briefly, the protocol indicates that patients with ongoing chest pain of suspected cardiac origin who are hemodynamically stable (including a systolic BP ≥ 100 mmHg) receive sublingual nitroglycerin 0.4 mg/spray with no maximum of doses allowable, as long as their chest pain continues and their repeat vital signs remain stable (systolic BP ≥ 100 mmHg and HR > 50 bpm and < 150 bpm). Other exclusion criteria for nitroglycerin include bradycardia or tachycardia (< 50 bpm or ≥ 150 bpm), pregnancy, pain of traumatic origin, allergy to nitrates, or recent ingestion of PDE-5 inhibitor medications.

## Outcome Measures

The primary outcome was hypotension, defined as a systolic blood pressure < 90 mmHg, after NTG administration. The secondary outcome was a drop in systolic blood pressure ≥ 30 mmHg after administration of NTG. We also analyzed the proportion of patients with inferior STEMIs who received NTG and became hypotensive who also had greater elevation in lead III than in lead II as well as the proportion who had ST elevation in lead V1, which may be indicators of right ventricular involvement and a greater risk of hypotension with NTG administration.

Blood pressure was recorded by PCPs with either a manual sphygmomanometer or a non-invasive blood pressure monitor. It was recorded on the initial assessment of the patient and then repeated prior to each sublingual nitroglycerin administration as well as upon arrival at the hospital. All prehospital ECGs were acquired from ZOLL E Series monitors/defibrillators (Zoll GE Medical Systems Marquette 12SL Analysis Program version 14). Since Quebec PCPs are not trained in ECG interpretation, the automated computer interpretation is used in the field. All cases that had a prehospital ECG with interpretation code "***ACUTE MI***" were included in this dataset. The computer-generated ECG interpretation was used to evaluate the primary and secondary outcomes.

Two investigators (D.R. and E.S.) who are emergency physicians, each with over 10 years experience in clinical practice, retrospectively and independently analyzed all prehospital ECGs to assess if they met the American Heart Association (AHA) criteria for STEMI and inferior STEMI. They were blinded to the computer interpretation. Since physician interpretation may not always concur with computer interpretation concerning the diagnosis of STEMI, we

TABLE 1. Definition of chest pain of suspected cardiac origin – Quebec's Provincial Primary Care Paramedics Protocol for Chest Pain

| Chest pain of suspected cardiac origin is defined as: |
|---|
| • Non–trauma-related chest pain or discomfort between the umbilicus and the jaw, including back and arms |
| • The pain must be originating from the anterior chest (including retrosternal), may be in the form of a tightness, pressure, vise-like, squeezing, choking, punching, or indigestion, and be less than 12 hours duration if continuous |
| • Should not be epigastric, subcostal, or located only in the arms or jaw; is not felt as a shock, a needle, a burn, a cut, a knife, a pinch; and is not increased with inspiration or movement |
| • In a patient with known coronary artery disease, the pain may be different from that described above if it matches the patient's usual angina symptoms |

recalculated the primary outcome using the physician interpretation of the presence and territory of STEMI. The physician interpretation of the prehospital ECGs (physician-interpreted ECGs) was also used to analyze the proportion of post-NTG hypotensive patients with inferior STEMIs who also had greater elevation in Lead III than in Lead II as well as the proportion who had ST elevation in lead V1.

Acute STEMI were categorized as inferior (ST elevation $\geq$ 0.1 mV in leads II, III, and aVF) and non-inferior (ST elevation $\geq$ 0.2 mV in men or $\geq$ 0.15 mV in women in leads V2–V3 and/or $\geq$ 0.1 mV in the remaining leads).[11] Patients with multiregion infarcts that include the inferior territory were included in the inferior STEMI group. Patients with left bundle branch block were not included in the study unless they demonstrated ST elevation concordant with the QRS complex. Prehospital ECG transmission did not occur, and there was no physician overread of the ECGs on the scene. As PCPs in Quebec do not interpret ECGs, the territory of injury in a suspected STEMI was not a factor in actual NTG use.

## Data Collection

Trained data extractors aware of the study's objectives reviewed all consecutive cases of patients with STEMI as identified in the STEMI registry. They extracted data concerning baseline demographics, blood pressures, medications administered, nitroglycerin protocol use from the paper-based prehospital medical records and the ECG from the ZOLL E Series monitors/defibrillators. Using a predefined instruction list, they entered all collected data in a secure database specifically designed for this study. If a case had insufficient data from the prehospital record or the ZOLL E Series monitors/defibrillators to calculate the primary outcome, we excluded the specific case.

Using a standardized data entry form, the emergency physician reviewers reported their respective analysis of prehospital ECGs, including the presence of STEMI (yes/no), the territory of infarction (inferior/non-inferior), the presence of ST elevation in lead V1 (yes/no), and ST elevation in lead III more than lead II (yes/no). Disagreement between the reviewers was resolved by consensus. Trained data extractors then entered the physicians' interpretation data in the study database.

In order to establish interrater variability of the data extraction for the primary outcome, another data extractor reexamined a 5% random sample of cases in the database and we calculated agreement using kappa.

## Data Analysis

We collected a sample over a 29-month period, which were all the prehospital ECGs with STEMI available since the commencement of the comprehensive prehospital ECG program. We calculated a sample size of approximately 725 patients (362 per group), based on an expected 15% hypotension rate in inferior STEMI patients receiving nitroglycerin[6] with an 80% power to detect a 40% relative (6% absolute) lower rate of the occurrence of hypotension in the non-inferior STEMI group. We used descriptive statistics (means $\pm$ standard deviations and proportions) to describe the demographic and clinical characteristics of the study population. We used a chi-square test to evaluate differences between inferior STEMI and non-inferior STEMI groups in terms of patient characteristics and study outcomes (hypotension post NTG administration and decrease in systolic BP $\geq$ 30 mmHg). We also used multiple variable logistic regression analysis to assess the association between area of STEMI and hypotension while controlling for other factors (age, gender, past medical history, including coronary artery disease (CAD), diabetes, dyslipidemia, hypertension). All analyses were performed using the statistical software package SAS 9.3 (SAS Institute, Cary, NC). We calculated and reported the 95% confidence intervals for all outcomes.

# RESULTS

Over a 29-month period, we identified 1,466 STEMI cases. Initial hypotension (pre-NTG administration) was present more frequently in the inferior STEMI group compared to the non-inferior STEMI group, 84/849 (9.9%) vs. 30/607 (4.9%). Of those 1,466 cases, 821 (56.0%) received NTG, while complete data were available for 805. Table 2 summarizes the baseline characteristics of patients with inferior STEMI and non-inferior STEMI. Age, gender, and initial systolic blood pressure were very similar between cohorts. Of note, the inferior STEMI cohort had a higher incidence of diabetes mellitus, dyslipidemia, and previous history of coronary artery disease. This cohort also had higher initial heart rate and diastolic blood pressure.

Hypotension occurred post NTG administration in 38/466 inferior STEMIs and 30/339 non-inferior STEMIs (computer-interpreted ECGs), 8.2% vs. 8.9%, $p = 0.73$. A drop in systolic blood pressure $\geq$ 30 mmHg occurred in 109/466 of inferior STEMIs and 81/339 of non-inferior STEMIs, 23.4% vs. 23.9%, $p = 0.87$ (Table 3).

Using physician-interpreted prehospital ECGs, hypotension post NTG administration was noted in 25/282 inferior STEMIs and 26/314 non-inferior STEMIs, 8.9% vs. 8.3%, $p = 0.80$ (Table 4). ST elevation in lead III > lead II was present in 56.1% (CI 52–60%) of inferior STEMI patients, while ST elevation in lead V1 was noted in 6.8% (CI 4.4–9.2%) of patients with STEMI in the inferior territory. There was no difference in the rate of hypotension post NTG administration in

TABLE 2. Clinical data of STEMI patients who received nitroglycerin

| | STEMI inferior ($n = 474$) | STEMI other territory ($n = 347$) |
|---|---|---|
| Age, mean (SD), years | 64.1(14.5) | 63.5(15.1) |
| Male sex, *n* (%) | 325/474(68.6) | 247/347(71.2) |
| Systolic blood pressure | | |
| Median (IQR), mmHg | 138(122–156) | 138(121–159) |
| *n* (%) with ≤ 90 mmHg | 5/474(1.1) | 2/347(0.6) |
| Diastolic blood pressure | | |
| Median (IQR), mmHg | 86(76–98) | 82(72–94) |
| Heart rate | | |
| Median (IQR), beats/min | 83(70–98) | 76(65–92) |
| *n* (%) with < 50 beats/min | 5/474(1.1) | 0/347(0) |
| *n* (%) with ≥ 150 beats/min | 4/474(0.8) | 4/347(1.2) |
| Past medical history | | |
| CAD (%) | 165/463(35.6) | 105/338(31.1) |
| Diabetes (%) | 93/463(20.1) | 50/338(14.8) |
| Dyslipidemia (%) | 143/463(30.1) | 84/338(24.9) |
| Hypertension (%) | 193/463(41.7) | 138/338(40.1) |

SD, standard deviation; IRQ, interquartile range; CAD, coronary artery disease.



patients with inferior STEMIs who had either elevation in lead III > lead II or ST elevation in lead V1 compared to patients with inferior STEMIs without those findings. Both univariate and multivariable regression analysis did not identify variables that are significantly associated with hypotension post NTG. As the multivariable regression analysis did not identify variables that were significantly associated with hypotension post NTG, only the unadjusted results from the univariate analysis are presented. Interrater agreement for chart review of the primary outcome was excellent ($\kappa = 0.94$).

## DISCUSSION

Our results suggest that patients with inferior STEMI on the computed ECG interpretation who receive prehospital nitroglycerin for persistent chest pain are not at higher risk of hypotension than patients with STEMI in other territories. This finding was consistent when the physician interpretation of prehospital ECG was used to evaluate our primary outcome. These results are surprising, yet reassuring. The purpose of this study was to determine if Quebec's current protocol for nitroglycerin administration was safe. As the administration of nitroglycerin to inferior STEMI patients in the emergency department is usually avoided, we were concerned about the consequences of its routine administration for chest pain in the prehospital setting to patients who may have undiagnosed inferior STEMIs. Quebec's PCPs do not insert intravenous lines, and thus cannot intervene with a fluid bolus if hypotension occurs. The results of our study suggest there is no need to change our current EMS nitroglycerin protocol for safety concerns.

The results of our study also question the legitimacy of avoiding nitrates in inferior STEMI. Although it is widely recommended in the medical literature to use caution when administering nitroglycerin to patients with inferior STEMI, the only study supporting this statement is a retrospective cohort study published in 1989 by Ferguson et al. The authors concluded that in the setting of an inferior STEMI, a marked hypotensive response to nitrates—defined as a decrease in systolic BP ≥ 30 mmHg and associated symptoms—suggests the presence of RV involvement, and in such patients, nitrates should be administered carefully.[6] Of note, the results of our study did not reveal a difference in the rate of decrease in systolic BP ≥ 30 mmHg between patients with inferior and non-inferior STEMI after NTG administration, although we noticed 25% of patients in both cohorts had a decrease in systolic BP ≥ 30 mmHg. As it would have been very challenging to extract from the medical records the clinical findings that would have made a drop in blood pressure worrisome, we opted to choose hypotension (systolic BP < 90 mmHg) as our primary outcome. A few case reports have also described hypotension and bradycardia following

TABLE 3. Hypotension (systolic blood pressure < 90 mmHg) and drop in systolic blood pressure ≥ 30 mmHg post nitroglycerin according to STEMI territory (computer-interpreted ECG)

| | STEMI inferior ($n = 466$) | STEMI other territory ($n = 339$) | *p*-value |
|---|---|---|---|
| Hypotension (systolic blood pressure < 90 mmHg) | 38/466 (8.2%)<br>CI 5.7–10.6% | 30/339 (8.9%)<br>CI 5.8–11.9% | 0.73 |
| Drop in systolic blood pressure ≥ 30 mmHg | 109/466 (23.4%)<br>CI 19.6%–27.2% | 81/339 (23.9%)<br>CI 19.4%–28.4% | 0.87 |

CI, confidence interval.

TABLE 4. Hypotension post nitroglycerin (systolic blood pressure < 90 mmHg) according to STEMI territory (physician-interpreted ECG)

| | STEMI inferior ($n = 282$) | STEMI other territory ($n = 314$) | $p$-value |
|---|---|---|---|
| Hypotension (systolic blood pressure < 90 mmHg) | 25/282 (8.9%)<br>CI 5.8–12.8% | 26/314 (8.3%)<br>CI 5.5–11.9% | 0.80 |

CI, confidence interval.

nitroglycerin administration, but only one involves patients with acute inferior wall MI.[8–10] To our knowledge, prior to this investigation, there were no studies showing mortality/morbidity benefits, or demonstrating the effects of nitroglycerin in STEMI patients in the prehospital setting.

Finally, we did not find an association between hypotension after NTG administration and the previously described standard 12-lead ECG features suggestive of right ventricular involvement in inferior STEMI. In the context of inferior wall STEMI, ST segment elevation of greatest magnitude in lead III (compared with leads II and aVF) and ST segment elevation in lead V1 suggest right ventricular involvement.[12] The presence of ST elevation in lead III > II has been shown to be highly sensitive for diagnosing right ventricular involvement, with a high negative predictive value and low negative likelihood ratio.[13] These criteria would theoretically have been useful in the prehospital setting as a screening tool. However, from our study results, they cannot be used to identify patients with inferior STEMI who are at risk for hypotension following nitroglycerin administration.

## LIMITATIONS

While the automated computerized interpretation has a high sensitivity and specificity for STEMI identification, it is limited by a low positive predictive value.[14,15] Nevertheless, our findings were consistent when the physician interpretation of prehospital ECG was used to evaluate our primary outcome.

Although we used a sample of all consecutive prehospital ECGs available to us, we were not able to reach our initial estimated sample size due to a higher than expected number of excluded cases. Over the 29-month period, we collected 1,466 STEMI cases. However, not all received NTG. We had 466 inferior STEMIs and 339 non-inferior STEMIs, instead of the 362 per group originally estimated. In addition, the hypotension rate was only half expected, 8.2% instead of 15%. Recalculating the sample size with the observed rate of hypotension, we would have needed to collect ~38,000 cases to demonstrate the same relative difference in groups with a power of 80%. Given the small difference actually observed, we believe it is unlikely we would be making a type II error.

We noted that among the 1,466 STEMI cases, only 821 received NTG as per protocol. Explanations for this finding are multiple: patients could have a STEMI without chest pain, resolved chest pain on evaluation by paramedics, or contraindications to NTG administration. Moreover, one of the contraindications of Urgences-santé nitroglycerin protocol is a systolic blood pressure < 100 mmHg. There is thus a subset of patients with blood pressure between 90 and 100



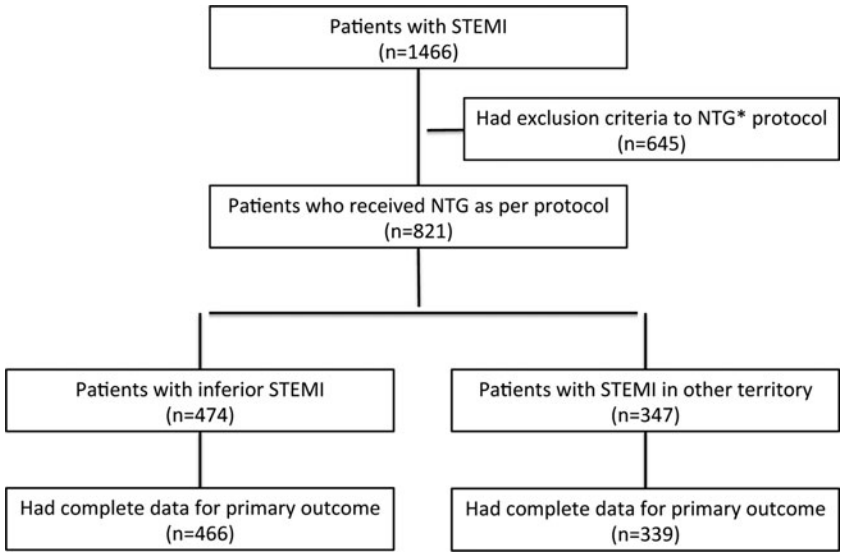


FIGURE 1. Flow diagram of the study. NTG, nitroglycerin.

mmHg who were not included in the analysis. Another potential limitation is that paramedics may have been more reluctant to give NTG to patients with inferior STEMI and elected to do so only in patients who were stable in their opinion, leading to a selection bias. However, since our paramedics are not trained in ECG interpretation, this is unlikely to have occurred.

Finally, given the retrospective nature of the study, we cannot draw any frank conclusion from our results with respect to safety of nitroglycerin administration in inferior STEMI. A prospective study evaluating the effect of nitroglycerin administration in patients with STEMI in the prehospital setting would be required.

## Conclusion

Our study suggests that nitroglycerin administration to patients with chest pain and inferior STEMI on their computer-interpreted ECG is not associated with a higher rate of hypotension compared to patients with STEMI in other territories. Computer-interpreted prehospital ECGs indicating an inferior STEMI cannot be used as the sole predictor for patients who may be at higher risk for hypotension following NTG administration.



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