

ADVANCES

Chest pain in emergency department patients: If the pain is relieved by nitroglycerin, is it more likely to be cardiac chest pain?

Robert Steele, MD; Timothy McNaughton, MD; Melissa McConahy, John Lam

ABSTRACT

Introduction: It is often believed that chest pain relieved by nitroglycerin is indicative of coronary artery disease origin.

Objective: To determine if relief of chest pain with nitroglycerin can be used as a diagnostic test to help differentiate cardiac chest pain and non-cardiac chest pain.

Design: Prospective observational cohort study with a 4-week follow-up of patients enrolled.

Setting: Academic tertiary care hospital, with 60 000 visits/year.

Inclusion criteria: Adult patients presenting to the emergency department with active chest pain who received nitroglycerin and were admitted for chest pain.

Exclusion criteria: Patients with acute myocardial infarction diagnosed after obtaining an ECG, patients whose chest pain could not be quantified, those for whom no cardiac work-up was done, or those who received emergent cardiac catheterization.

Results: 270 patients were enrolled. Nitroglycerin relieved chest pain in 66% of the subjects. The diagnostic sensitivity of nitroglycerin to determine cardiac chest pain was 72% (64%–80%), and the specificity was 37% (34%–41%). The positive likelihood ratio for having coronary artery disease if nitroglycerin relieved chest pain was 1.1 (0.96–1.34). Telephone follow-up at 4 weeks was performed, with a 95% follow-up rate.

Conclusions: Relief of chest pain with nitroglycerin is not a reliable diagnostic test and does not distinguish between cardiac and non-cardiac chest pain.

Key words: chest pain; nitroglycerin

RÉSUMÉ

Introduction : On croit souvent que la douleur thoracique soulagée par la nitroglycérine indique que cette douleur est attribuable à une insuffisance coronarienne.

Objectif : Déterminer si le soulagement de la douleur thoracique à l'aide de la nitroglycérine peut servir de test diagnostique permettant de différencier la douleur thoracique d'origine cardiaque de la douleur d'origine non cardiaque.

Méthodologie : Étude prospective par observation de cohortes avec un suivi après 4 semaines des patients inclus dans l'étude.

Cadre : Hôpital universitaire de soins tertiaires recevant 60 000 visites/année.

Critères d'inclusion : Les patients adultes s'étant présentés à l'urgence pour une douleur tho-

Loma Linda University Medical Center, Loma Linda, Calif.

Received: July 29, 2005; revisions submitted: Mar. 22, 2006; accepted: Mar. 27, 2006

This article has been peer reviewed.

Can J Emerg Med 2006;8(3):164-9

racique active qui avaient reçu de la nitroglycérine et qui furent hospitalisés pour une douleur thoracique.

Critères d'exclusion : Les patients chez qui un infarctus du myocarde avait été diagnostiqué après un ECG, les patients dont la douleur thoracique ne pouvait être quantifiée, ceux chez qui aucun bilan cardiaque n'avait été fait ou ceux qui avaient reçu un cathétérisme cardiaque d'urgence.

Résultats : Deux cent soixante-dix patients furent inclus. La nitroglycérine soulagea la douleur thoracique chez 66 % des sujets. La sensibilité diagnostique de la nitroglycérine pour déterminer la douleur thoracique d'origine cardiaque était de 72 % (64 %–80 %) et la spécificité était de 37 % (34 %–41 %). Le rapport de probabilité positif d'avoir une insuffisance coronarienne si la nitroglycérine soulageait la douleur thoracique était de 1,1 (0,96–1,34). Un suivi téléphonique après 4 semaines fut effectué, avec un taux de suivi de 95 %.

Conclusions : Le soulagement de la douleur thoracique à l'aide de nitroglycérine n'est pas une épreuve diagnostique fiable et ne permet pas de distinguer la douleur thoracique d'origine cardiaque de la douleur d'origine non cardiaque.

Introduction

Chest pain is a common presenting emergency department (ED) symptom that may be caused by one of several conditions.¹ It is routinely divided into cardiac (e.g., angina, myocardial infarction, myocardial ischemia) and non-cardiac (e.g., musculoskeletal, esophageal spasm, pleurisy, pneumonia, pulmonary embolism, aortic dissection) chest pain. Patients with chest pain relieved by nitroglycerin (NTG) are more likely to be admitted.²

Chest pain relieved by NTG has been used as a diagnostic clue, suggesting the cause is secondary to active coronary artery disease (CAD).^{3,4} Many studies have used “chest pain relieved by nitroglycerin” as an element to help define angina.^{5,6} NTG-relieved chest pain has been used as a marker of intermediate myocardial risk and to help determine if the source of pain is cardiac or non-cardiac.^{7,8}

Chest pain may often create a diagnostic challenge for emergency physicians (EPs). This study included patients who represented the EP conundrum (i.e., chest pain with no objective signs of ischemia). In such cases, the EP must decide whether the pain represents active CAD or whether it is related to some other process. Each year, between 2%–8% of patients with acute myocardial infarctions (AMIs) are discharged, resulting in adverse malpractice outcomes for physicians and adverse clinical outcomes for patients.^{9,10} In attempts to lower this risk and to decide whether the chest pain is CAD or non-cardiac, EPs employ every test available to make their decision.^{11–13} One of the interventions frequently used as part of the work-up is the response to NTG,¹³ which is known to induce venous dilation and to enhance pooling. It is uncertain that such a strategy aids in differentiating between cardiac and non-cardiac chest pain.¹⁴

Recent studies have failed to show the diagnostic utility

of NTG.^{15–17} By more clearly defining NTG pain relief, avoiding the use of confounding pain medications (e.g., morphine) and by ensuring a more rigorous patient follow-up, this study aims to confirm the danger of relying on pain relief with NTG as a diagnostic strategy.

Methods

Study design and setting

This was a prospective observational cohort study that took place in an academic urban ED with approximately 60 000 annual visits per year, including 3500 patients with chest pain. The hospital's Institutional Review Board approved this study, and all subjects gave informed written consent.

Inclusion criteria

Patients who presented to the ED with the active chief complaint of chest pain and who received NTG were prospectively enrolled. NTG had to be given sublingually in the ED by a medical professional (nurse or physician). The standard protocol for patients who present to this institution who have suspected cardiac-related chest pain is to administer 1 dose of 400 mcg NTG every 5 minutes, up to 3 doses or until the pain has resolved. The NTG can be given by nurse per protocol or by the physician at the bedside. The treating physician was not blinded to the patient's response to NTG. All tests were ordered as routinely indicated. A trained study investigator who was not involved in patient care enrolled the study subjects.

Exclusion criteria

Patients with chest pain who had an obvious diagnosis of myocardial ischemia were not approached to be in the study (e.g., cardiogenic shock). Patients with ECG evidence of AMI on their initial ECG or patients emergently

going to the cardiac catheterization laboratory were excluded. Patients who could not quantify their chest pain, and those who had chest pain but did not complete a standard cardiac work-up (consisting of at least 2 ECGs, 2 troponin tests and a chest x-ray) were excluded.

Data collection

A standardized form was used to record chest pain severity. Over a 9-month period, trained study investigators enrolled patients meeting the inclusion criteria who presented to the ED between the hours of 0700 and 2400, 7 days a week. The investigators recorded the patient's pain score before and after each NTG dose, the latter recording occurring within 5 minutes of the patient receiving the drug. The patient was asked to report his or her pain, based on a 1–10 score (1 = very mild; 10 = severe). A visual analog score with happy to sad faces was also used.

Patient characteristics, including demographic data, were recorded. The board-certified EP working in the ED during subject enrollment interpreted the ECG. Laboratory results, final disposition and final diagnosis were determined by the EP caring for the patient. Final diagnosis at hospital discharge was also reviewed. Patients were classified into risk categories based on a Thrombolysis in Myocardial Infarction (TIMI) Risk Score (see Table 1).¹⁸

Definitions

Positive response to NTG — defined a priori as a reduction of 3 points or more in the pain scale or complete pain relief from chest pain if the initial pain was 3 or less.

Negative response to NTG — defined as failure to achieve the above pain reductions.

Cardiac chest pain — defined for this study as chest pain associated with 1 of the following: 1) new ECG changes of 1 mm in 2 contiguous leads, 2) positive cardiac troponin T >0.3 mcg/L (normal level <0.3 mcg/L), 3) cardiac catheterization showing >70% stenosis, or 4) a positive provocative test (myocardial scintigraphy, treadmill or dobutamine echocardiography) as interpreted by a board-certified cardiologist. If the provocative test led to a cardiac catheterization, then the cardiac catheterization was considered the gold standard.

Non-cardiac chest pain — defined as a patient who had no positive findings in relation to their cardiac work-up. All patients received at least 2 troponin tests, and results of 2 ECGs had to be normal.

Follow-up

Patients were followed up at 4 weeks after discharge from

the hospital. The investigators asked about repeat hospitalizations, cardiac studies, cardiac events, death, or new medical diagnoses since discharge. Twelve subjects (4.4%) were lost to follow-up, even though the investigators contacted surrounding hospitals and the county coroner's office.

Results

A total of 278 patients were enrolled. Eight subjects were excluded after initial entry into the study, leaving 270 subjects studied (Fig. 1). One hundred and seventy-seven of 270 patients showed a positive response to NTG (66%), and 93/270 (34%) showed a negative response (Fig. 1).

Of those patients who experienced relief with NTG, 60/177 (34%) had defined cardiac chest pain and 117/177 (66%) had non-cardiac chest pain. For those who had no relief with NTG, 23/93 (25%) were found to have cardiac chest pain and 70/93 (75%) were found to have non-cardiac chest pain. There were 35 AMIs, based on troponin levels in the study population. Of those diagnosed with AMI, 20 experienced relief with NTG and 15 did not ob-

Table 1. Demographic data for the 270 patients who presented to the emergency department (ED) with an active chief complaint of chest pain, were treated with nitroglycerin, and prospectively enrolled in the study

Variable	No. (and %) of patients*	
	Chest pain relieved (n = 177)	Chest pain not relieved (n = 93)
Mean age in years	65	62
Male	52	51
Estimated TIMI Risk Score		
<1	0 (0)	1 (1)
<2	48 (27)	23 (25)
2–4	80 (45)	40 (43)
>4	49 (28)	27 (29)
Patient history		
Hypertension	115 (65)	59 (63)
Hypercholesterolemia	65 (37)	40 (43)
Family history of CAD	64 (36)	37 (40)
Current smoker	64 (36)	33 (35)
Prior known CAD	62 (36)	36 (45)
Diabetes mellitus	50 (28)	24 (26)
Myocardial infarction	20 (11)	15 (16)
Procedures performed		
PTCA	20 (11)	12 (13)
CABG	12 (7)	8 (9)
Discharged from ED	3 (2)	5 (5)

*Except where otherwise indicated.

TIMI = Thrombolysis in Myocardial Infarction; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass graft; CAD = coronary artery disease

tain relief. There were 9 deaths, 3 in the group that did respond to NTG and 6 in the group that did not.

The sensitivity of NTG as a diagnostic test for chest pain was 72% (confidence interval [CI] 64%–80%). The specificity was 37% (CI 34%–41%). The positive likelihood ratio of determining if a patient whose chest pain is relieved following the administration of NTG has cardiac chest pain was 1.1 (CI 0.96–1.34). Using a Pearson χ^2 , NTG was found not to be statistically significant ($p = 0.12$) when differentiating between patients with CAD and those without CAD as a cause of their chest pain.

Thirteen patients (5%) were admitted to the hospital but did not undergo a cardiac test (stress echo, treadmill, cardiolyte, cardiac catheterization). Five of these subjects experienced relief with NTG, and 8 did not. There were no cardiac events at 4 weeks in any of these patients.

Eight patients were excluded from the study because they were discharged home from the ED. Three of these patients were diagnosed as stable cardiac chest pain requiring medical management only and were discharged from the ED following relief of pain through the administration of NTG. The 5 patients who were discharged from the ED without relief from NTG had a diagnosis of non-cardiac chest pain. Their inclusion would have changed the sensitivity and specificity by a value of 1% and 2%, respectively, creating an insignificant change. All 8 of the ED-discharged patients had follow-up with no cardiac events at 4 weeks. There were 12 (4.4%) subjects who were lost to follow-up; none were in the discharge group.

Statistical analysis

This study compared 2 groups, those with a positive response to NTG and those with a negative response. A Student's t test was performed for continuous data. A χ^2

analysis was performed for categorical variables. Likelihood ratios were calculated using the delta method.¹⁸ All statistical analysis was done using Stata 9.0 (Stata Corporation, College Station, Tex.)

Discussion

In our study, NTG did not appear to be useful in the diagnostic algorithm of cardiac versus non-cardiac chest pain in ED patients. Showing both a low sensitivity and an even lower specificity, our study revealed the diagnostic value of NTG relief in ED chest pain patients to be more myth than science. The positive likelihood ratio was approximately 1, suggesting that the pretest probability of disease was equivalent to the post-test probability of disease.

This study corroborates recent work done by Shry and colleagues,¹⁵ Henrikson and coworkers,¹⁶ and Diercks and associates¹⁷ (Table 2). Several important differences exist between those studies and ours. We did not have morphine as a confounding variable in relief of pain. Our locked medication dispensing system and our NTG protocol did not allow the nurse time to get the morphine before giving 3 doses of NTG. If a patient has cardiac-related chest pain, the focus in our institution is to try to relieve the pain with NTG, obtain an ECG, give ASA and obtain intravenous access. Medication is not released from the medication dispensing system until the patient is registered at the bedside, which generally takes 15 minutes. In the event that the patient is *in extremis*, or having obvious ischemia with grossly abnormal vitals, or an ECG diagnostic of an AMI, the nurse can override the registration process and open the medication dispensing system with a special code.

Shry and colleagues were unable to rely on objective measures for all of their patients: in 12% of their study

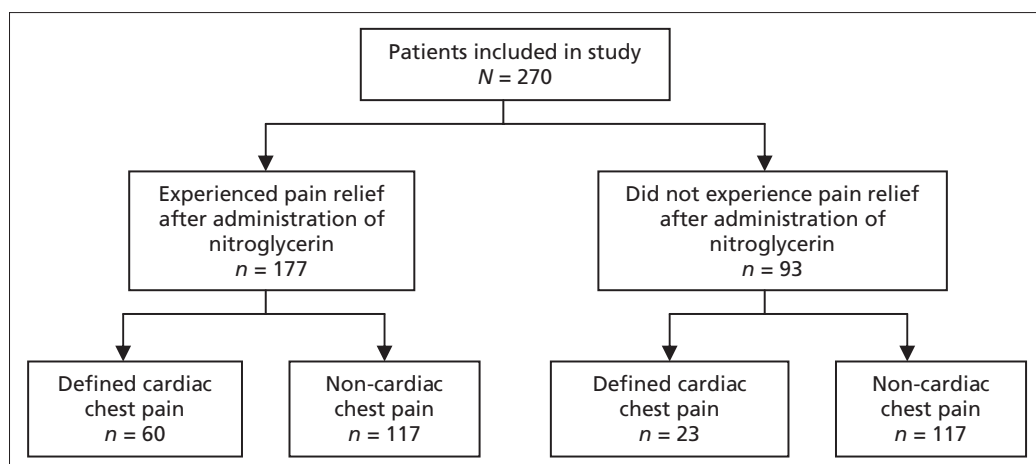


Fig. 1. Comparison of outcomes for 270 patients who presented to the emergency department during the study period with an active chief complaint of chest pain.

subjects a cardiac origin was based on cardiologist subjective impression.¹⁵ Henrikson and coworkers noted problems when patients reported pain of 3/10 or less.¹⁶ They had defined a positive response to NTG as a 50% reduction in pain, making it difficult to interpret pain changes in those with lower pain scores. Our 3-point system was chosen because it seemed to be relevant in terms of being a clinically important reduction of pain, yet simple and reproducible if repeated at other institutions.

NTG use at home or by emergency medical services was not documented. It was felt that timing, patient selection and pain scale recording would all be adversely affected, decreasing the accuracy of NTG as a diagnostic test. In addition, because of the short half-life of NTG, we felt that NTG use before ED arrival in a patient with active chest pain would be unlikely to be a confounding variable.

Work-up bias was not considered to be a major factor in

this study. All admitted patients had a cardiology evaluation that included at least 2 troponin tests, and 95% underwent additional investigations. Of the 13 (5%) who were admitted to the hospital but did not undergo a definitive cardiac test (stress echo, treadmill, cardiolyte, cardiac catheterization), all were followed up, with none having an event at 4 weeks. The percutaneous transluminal coronary angioplasty and coronary artery bypass grafting rates on the in-patient side were not statistically different between those who received relief and those who did not. Patients admitted for chest pain received a work-up regardless of NTG status, although theoretically, the scope or intensity of the work-up chosen by the physician could have been influenced by NTG.

There is generally a trade-off between internal validity and external validity in all research. A study that makes tight experimental control over a narrow and homogenous set of subjects a priority is unlikely to produce results that

Table 2. Comparison of recent literature to the present study

Variable	Shry et al, ¹⁵ 2002	Henrikson et al, ¹⁶ 2003	Diercks et al, ¹⁷ 2005	Present study, 2006
Study design	Retrospective review	Prospective observational	Prospective observational	Prospective observational
Patients considered for study*	All admitted ED chest pain patients	Consecutive ED chest pain patients	Convenience sample, ED chest pain patients	Convenience sample, ED chest pain patients
No. of patients excluded	23	659	51	8
Confounding variables, % of excluded patients	Cardiac chest pain based on cardiology evaluation, 12%	Morphine used with nitroglycerin, 9%	Pain medications NR; EMS and home medications NR	EMS and home medications NR
No. of patients included in study	251	459	664	270
Male, % of patients	53	47	48	51
Mean age, yr	60	59	54	64
Pain scale used to determine amount of pain relief	0–10	1–10	0–10	1–10†
Response to administration of nitroglycerin	2-unit reduction	50% reduction	Divided into 4 groups: Significant/Complete; Moderate; Minimal; No change	3-unit reduction
Diagnosis of AMI, % of enrolled patients	NR	18%	10%	13%
Length of follow up (% of patients contacted)	N/A	4 mo (85%)	30 d (89%)	4 wk (95%)
Death, % of enrolled patients	NR	2%	NR	3%

*Nitroglycerin was used as inclusion criteria for all studies.

†Visual Analog Scale.

ED = emergency department; NR = not recorded; EMS = emergency medical services; AMI = acute myocardial infarction

are widely applicable to a large number of other settings or relevant to a more diverse range of human beings. Conversely, a study that tries to capture the unpredictability, uncertainty, diversity and ambiguity of real-world settings is unlikely to find results that are immune from criticisms about poor internal validity. We tried to study a group of ED chest pain patients with uncertain diagnosis while creating a study that was both controlled and reproducible.

Limitations

A selection bias may have occurred from our exclusion criteria. The population we were trying to study was the ED chest pain patient who has diagnostic uncertainty. Diagnostic tests perform better when there is little uncertainty of disease in the patient population (i.e., if you are distinguishing between a group of patients who have either very high or very low likelihood of disease). Here, by excluding all patients with low likelihood of disease (e.g., those discharged from the ED) and those *in extremis*, we may have failed to detect a difference in those subgroups.

The definition of “non-cardiac” was based on the absence of objective findings. The absence of findings does not completely rule out disease. A prospective study limiting the patient population to those who receive NTG and have a cardiac catheterization might offer a gold standard against which to compare NTG as a diagnostic test.

We assumed the initial ECG reading by the attending EP to be accurate. There was no over-read of the ECG performed by a cardiologist.

Conclusion

Based on our study of adult ED patients, relief of chest pain with NTG is not a reliable diagnostic test and does not help physicians to distinguish between cardiac and non-cardiac chest pain.

Competing interests: None declared.

References

1. Fothergill NJ, Hunt MT, Touquet R. Audit of patients with chest pain presenting to an accident and emergency department over a 6-month period. *Arch Emerg Med* 1993;10(3):155-60.
2. Engelberg S, Singer AJ, Moldashel J, et al. Effects of prehospital nitroglycerin on hemodynamics and chest pain intensity. *Prehosp Emerg Care* 2000;4:290-3.
3. Braunwald E, Zipes DP, Libby P, editors. *Heart disease: a textbook of cardiovascular medicine*. 6th ed. Philadelphia: WB Saunders; 2001. p. 27-44.
4. O'Rourke RA, Shaver JA, Salerni R, et al. The history, physical examination, and cardiac auscultation. In: Alexander RW, Schlant RC, Furster V, editors. *Hurst's The heart*. 9th ed. New York: McGraw-Hill; 1998. p. 229-342.

5. Weiner DA, Ryan TJ, McCabe CH, et al. Exercise stress testing: correlations among history of angina, ST-segment response and prevalence of coronary artery disease in the coronary artery surgery study (CASS). *N Engl J Med* 1979;301:230-5.
6. Diamond GA, Forrester JS, Hirsch M, et al. Application of conditional probability analysis to the clinical diagnosis of coronary artery disease. *J Clin Invest* 1980;65:1210-21.
7. Decker WW, Prina LD, Smars PA, et al. Continuous 12-lead electrocardiographic monitoring in an emergency department chest pain unit: an assessment of potential clinical effect. *Ann Emerg Med* 2003;41:342-51.
8. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee on the management of patients with unstable angina) [published erratum appears in *Circulation* 2000;102(14):1739]. *Circulation* 2000;102(10):1193-209.
9. McCarthy BD, Beshansky JR, D'Agostino RB, et al. Missed diagnosis of acute myocardial infarction in the emergency department: results from a multicenter study. *Ann Emerg Med* 1993;22:579-82.
10. Pope JH, Aufderheide TP, Ruthazer R, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med* 2000;342:1163-70.
11. Selker HP, Beshansky JR, Griffith JL, et al. Use of the acute cardiac ischemia time-insensitive predictive instrument (ACI-TIPI) to assist with the triage of patients with chest pain or other symptoms suggestive of acute cardiac ischemia. *Ann Intern Med* 1998;129:845-55.
12. Selker HP, Zalenski RJ, Antman EM, et al. An evaluation of technologies for identifying acute cardiac ischemia in the emergency department: executive summary of the National Heart Attack Alert Program Working Group Report. *Ann Emerg Med* 1997;29:1-12.
13. Zalenski RJ, McCarren M, Roberts R, et al. An evaluation of a chest pain diagnostic protocol to exclude cardiac ischemia in the emergency department. *Arch Intern Med* 1997;157:1085-91.
14. Gisolf J, Westerhof BE, van Dijk N, et al. Sublingual nitroglycerin used in routine tilt testing provokes a cardiac output-mediated vasovagal response. *J Am Coll Cardiol* 2004;44:588-93.
15. Shry EA, Dacus J, Van De Graaff E, et al. Usefulness of the response to sublingual nitroglycerin as a predictor of ischemic chest pain in the emergency department. *Am J Cardiol* 2002;90:1264-6.
16. Henrikson C, Howell E, Bush D, et al. Chest pain relief does not predict active coronary artery disease. *Ann Intern Med* 2003;139:979-86.
17. Diercks D, Boghos E, Guzman H, et al. Changes in the numeric descriptive scale for pain after sublingual nitroglycerin do not predict cardiac etiology of chest pain. *Ann Emerg Med* 2005;45:581-5.
18. Antman EM, Cohen M, Bernink P, et al. The TIMI risk score for unstable angina/non-ST elevation MI. A method for prognostication and therapeutic decision-making. *JAMA* 2000;284:835-42.
19. Mackinnon A. A spreadsheet for the calculation of comprehensive statistics for the assessment of diagnostic tests and inter-rater agreement. *Comput Biol Med* 2000;30:127-34.

Correspondence to: Dr. Robert Steele, Emergency Department, Loma Linda University Medical Center, 11234 Anderson St, Loma Linda CA 92354