Chest Pain Relief by Nitroglycerin Does Not Predict Active Coronary Artery Disease

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Background: **The belief that chest pain relief with nitroglycerin indicates the presence of active coronary artery disease is common. However, this hypothesis has not been tested.**

Objective: **To define the diagnostic and prognostic value of chest pain relief with nitroglycerin.**

Design: **Prospective observational cohort study.**

Setting: **Urban community teaching hospital.**

Patients: **459 consecutive patients with chest pain admitted through the emergency department who received nitroglycerin from emergency services personnel or an emergency department nurse. Follow-up was obtained by telephone contact at 4 months.**

Measurements: **Chest pain relief was defined as a decrease of at least 50% in patients' self-reported pain within 5 minutes of the initial dose of sublingual or spray nitroglycerin. Active coronary artery disease was defined as any elevated serum enzyme levels, coronary angiography demonstrating a 70% or greater stenosis, or a positive exercise test result.**

Results: **Nitroglycerin relieved chest pain in 39% of patients (181 of 459). In patients with active coronary artery disease as the likely cause of their chest pain, 35% (49 of 141) had chest pain relief with nitroglycerin. In contrast, in patients without active coronary artery disease, 41% (113 of 275) had chest pain relief ($P > 0.2$). Four-month clinical outcomes were similar in patients with or without chest pain relief with nitroglycerin ($P > 0.2$).**

Conclusions: **These data suggest that, in a general population admitted for chest pain, relief of pain after nitroglycerin treatment does not predict active coronary artery disease and should not be used to guide diagnosis.**

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In the United States, "chest pain" accounts for up to 20% of emergency department visits and hospitalizations and uses valuable hospital resources (1). The major concern in most patients presenting with chest pain is that it represents active coronary artery disease (CAD). However, the causes of chest pain in patients presenting to the emergency department vary, and only a small percentage of such patients are actually having angina or an acute coronary syndrome as the manifestation of their CAD (2).

Nitrates are an accepted mainstay in treating both acute and chronic coronary disease; however, the diagnostic and prognostic value of chest pain relief with nitroglycerin has been poorly studied. The Coronary Artery Surgery Study (CASS) (3) used prompt relief of chest pain by rest or nitroglycerin as 1 of the criteria for "definite angina," and Diamond and colleagues (4, 5) listed prompt relief of chest pain by rest or nitroglycerin as 1 of 3 diagnostic criteria for angina. In addition, Sox and colleagues (6) gave chest pain relief by nitroglycerin the greatest weight in their chest pain decision rule. In contrast, in developing their chest pain protocol, Goldman and colleagues (7) gathered information on chest pain response to nitroglycerin but did not use it in their decision-making algorithm. Its absence implies that it may not have substantial prognostic information. Recent research reports (8), handbooks (9), and current publications by the American Heart Association and American College of Cardiology (10–12) list chest pain relief by nitroglycerin as a poor prognostic sign in materials meant for physicians and describe it as a defining characteristic of angina in materials meant for physicians and patients. In addition, current emergency department literature refers to chest pain relief with rest or nitroglycerin as conferring an intermediate risk (13), although other emergency department literature implies that chest pain relief by nitroglycerin does not predict acute myocardial infarction (14).

Nitroglycerin is also useful in treating noncardiac conditions, such as esophageal spasm (15), thus questioning its diagnostic ability in ischemic heart disease. Recently, Shry and colleagues (16) conducted a retrospective evaluation of 223 patients presenting to the emergency department with chest pain and found equal rates of pain relief in patients with cardiac ischemia and those with noncardiac causes of their pain. We designed this prospective study to better assess the diagnostic and prognostic value of response to nitroglycerin as a predictor of an ischemic cause of chest pain.

METHODS

Patients

All patients evaluated in the emergency department between February and June 2001 and subsequently admitted to the cardiac intensive care unit, progressive care unit, medicine housestaff service, nurse practitioner service, or emergency department extended-stay unit with the admission diagnosis of "rule out myocardial infarction" or "chest pain" were study candidates. To be enrolled in the study, patients had to have documented chest pain while under medical supervision and be given sublingual nitroglycerin or spray nitroglycerin by a medical professional. To ensure that all eligible patients admitted with chest pain were enrolled, patient study lists were checked against hospital ad-

Context

Many people think that relief of chest pain by nitroglycerin helps diagnose coronary artery disease.

Contribution

In this prospective study, 459 patients who received nitroglycerin for chest pain in the emergency department were admitted for further evaluation and then followed for 4 months. Nitroglycerin relieved pain in 39% of all patients, in 35% of the 141 patients with subsequent evidence of active coronary disease, and in 41% of the 275 patients with no subsequent evidence of active coronary disease.

Implications

In emergency department settings, relief of chest pain with nitroglycerin does not help diagnose active coronary artery disease.

–The Editors

mission logs. Clinical care in the emergency department was not protocolized but was at the discretion of the emergency department physicians. In the study emergency department, similar to many others, patients presenting with chest pain and CAD risk factors are generally admitted to rule out myocardial infarction. For patients with chest pain but a less serious risk profile, short-stay hospitalization is common. Trained study investigators completed study forms for each patient. To verify the accuracy of data collection, a designated study investigator randomly audited 20% of charts. Only patients presenting to the Johns Hopkins Bayview Emergency Department, Baltimore, Maryland, were enrolled in this study.

The Johns Hopkins Bayview Medical Center Institutional Review Board approved the study before its initiation. This study received a waiver of informed consent, because it was observational, did not affect routine clinical care, and posed minimal risk to participants. The clinical nurse or physician caring for the patient gave a standard explanation of why nitroglycerin was being used (to treat chest pain), instructions on its use, and a brief statement that it may cause a transient headache or lightheadedness.

Data Collection

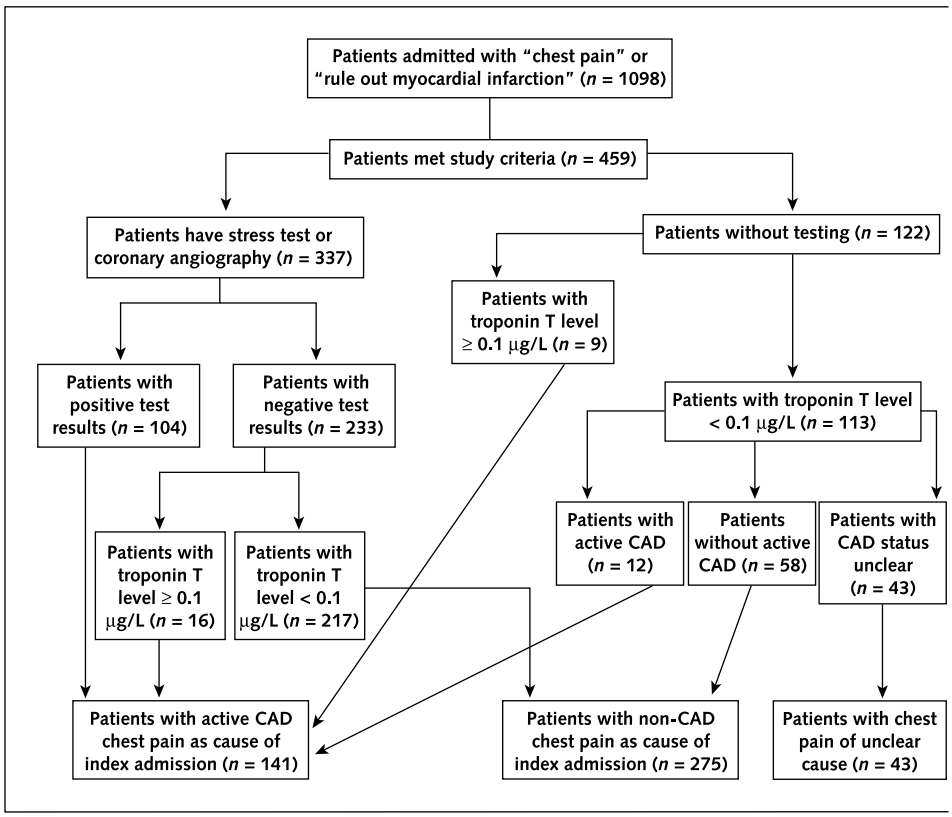
A standardized form was used to record demographic characteristics, CAD risk factors, history of CAD, electrocardiography findings, and basic laboratory values. History of CAD was defined as a history of myocardial infarction, coronary revascularization, cardiac catheterization with flow-limiting stenoses (≥70% lesions), or a positive stress test result with or without imaging. The standardized data collection form was also used to record the patient's initial rating of severity of chest pain on a scale of 1 to 10 (1 = mild; 10 = severe), nitroglycerin preparation used (sublingual or spray), repeated assessment of chest pain intensity within 5 minutes, and other medications given at the time of nitroglycerin administration (17). Nitroglycerin was given by emergency medical services personnel (if given before arrival in the emergency department) or the emergency department nurse. The person administering the medication assessed level of pain immediately before and approximately 5 minutes after administration and recorded the values in the chart. The standard protocol used by emergency medical services and in the emergency department consists of administering 1 dose of nitroglycerin every 5 minutes for chest pain. Thus, the 5-minute assessment of pain level was done before administering any additional nitroglycerin. The first 12-lead electrocardiogram, which was generally obtained while the patient was having pain, was used for assessing electrocardiographic findings.

Definitions

Nitroglycerin-responsive chest pain was defined as a 50% or greater reduction in the intensity of chest pain within approximately 5 minutes of administering 0.4 mg of sublingual or 0.4 mg of spray nitroglycerin. There has been little previous quantitative work on chest pain. We used a 50% or greater reduction in chest pain as a marker of pain relief for several reasons. Because pain is highly subjective, we felt that a relative reduction in reported pain, rather than an absolute reduction, would be more valuable in assessing the effectiveness of nitroglycerin therapy. From preliminary observations, we found that few patients have complete relief of chest pain with a single nitroglycerin dose. Many patients received additional doses at 5-minute intervals. They also generally received other interventions with the additional doses, especially if pain relief was not substantial. Such therapies would potentially obscure the effect of the nitroglycerin alone. We therefore chose to evaluate the effect of nitroglycerin alone by assessing the response to the first dose. However, to better assess the diagnostic significance of other degrees of chest pain relief, we completed receiver-operating characteristic (ROC) curves for percentage and absolute reductions in chest pain intensity, as described in the Statistical Analysis section.

Active CAD was defined as appropriate symptoms with at least 1 of the following during the index hospitalization or during the follow-up period: any measurement of elevated serum troponin T level (≥0.1 μg/L [normal level < 0.1 μg/L in the study laboratory]) (18), coronary angiography demonstrating a 70% or greater stenosis, a positive exercise test result with or without imaging, or the diagnosis of active CAD without testing (defined as the primary diagnosis for admission being active CAD as noted by the clinical attending physician, with concurrence by a study cardiologist who was blinded to nitroglycerin response, on the basis of standard clinical criteria). For patients who had both stress testing and cardiac catheterization during hospitalization or follow-up, the results of coronary angiography were considered to be the gold standard in determining the presence (or absence) of active CAD. If no other

Figure 1. **Patient enrollment and study flowchart.**



CAD = coronary artery disease.

cardiac testing was performed, results of testing performed up to 6 months before the index hospitalization were used to determine active CAD.

No active CAD was defined as no troponin T level elevation during the index hospitalization or the follow-up period and at least 1 of the following: coronary angiography without flow-limiting stenoses or a negative exercise test result with or without imaging. In addition, if patients had no history of CAD, did not have cardiovascular testing during the index hospitalization or the follow-up period, and had no other cardiac events, active CAD was not considered the cause of their index hospitalization. Patients with a known history of CAD but with atypical symptoms, no events during follow-up, and other clinical explanations for their chest pain (neoplasm or obstructive lung disease) were also considered not to have active CAD.

Follow-up

Trained study investigators conducted telephone interviews with patients approximately 4 months after the index hospitalization. Four months was chosen as the follow-up interval on the basis of previous major unstable angina trials, which have shown only a modest increase in clinical end points at 1 year compared with 3 months (19–22). This follow-up was used to determine clinical status, health care–seeking behavior, interval cardiac events, hospitalizations, testing, and medication use. Hospital records were reviewed to confirm patient-reported hospitalization and testing, and the Social Security death index was used to confirm all patient deaths and to determine the vital status of all patients who were lost to follow-up (23).

Statistical Analysis

To calculate sample size, we used previous work by others and pilot data suggesting that the frequency of nitroglycerin-responsive chest pain would be 50% and that approximately 50% of nitroglycerin-responsive and nitroglycerin-unresponsive groups would have CAD (24). To detect a 15–percentage point difference in the prevalence of active CAD between the groups with a type I error of 5% and a power of 80% in a 2-sided test, 170 patients would be required in each group or a total of 340 patients would need to be enrolled in the study.

To address concerns about the validity of the results in specific populations that might be expected to respond differently to nitroglycerin, 3 subgroup analyses were prespecified: all patients who had troponin T levels less than 0.10 μg/L (that is, patients in whom myocardial infarction was ruled out), all patients with a known history of CAD, and all patients with no history of CAD.

Means are presented as means (±SD). Chi-square and unpaired *t*-tests with a significance level of 0.05 were used for simple comparisons of baseline characteristics and outcomes. Sensitivity and specificity were determined by usual

Table 1. **Patient Demographic Characteristics by Response to Nitroglycerin***

Characteristic	Pain Relief ($n = 181$)	No Pain Relief ($n = 278$)	*P* Value
Presentation			
Mean age ± SD, *y*	59.1 ± 16.1	58.3 ± 15.9	>0.2
Women, *n (%)*	96 (53)	153 (55)	>0.2
Race, *n (%)*			
African-American	33 (18)	50 (18)	>0.2
White	147 (81)	223 (80)	>0.2
Other	1 (1)	5 (2)	>0.2
Known previous CAD, *n (%)*	57 (31)	114 (41)	0.04
Hypertension, *n (%)*	112 (62)	163 (59)	>0.2
Diabetes mellitus, *n (%)*	43 (24)	68 (24)	>0.2
Hypercholesterolemia, *n (%)*	71 (39)	119 (43)	>0.2
Current tobacco use, *n (%)*	76 (42)	124 (45)	>0.2
Family history of CAD, *n (%)*	60 (33)	109 (39)	0.19
Long-term nitrate use at admission, *n (%)*	28 (15)	58 (21)	0.15
Medication administered concurrently with nitroglycerin, *n (%)*			
Oxygen	102 (56)	180 (65)	0.07
Aspirin	57 (31)	97 (35)	>0.2
Morphine	8 (4)	13 (5)	>0.2
β-Blocker	5 (3)	9 (3)	>0.2
Diuretic	1 (1)	3 (1)	>0.2
Electrocardiographic findings, *n (%)*			>0.2
ST-segment elevation	7 (4)	16 (6)	>0.2
ST-segment depression	8 (4)	16 (6)	>0.2
Left bundle branch block	6 (3)	5 (2)	>0.2
Any of the preceding abnormalities	21 (12)	37 (13)	>0.2

* CAD = coronary artery disease.

methods, and 95% CIs were determined by using the methods of Newcombe (25). Likelihood ratios with 95% CIs were determined by the log method of Simel and colleagues (26). Two ROC curves were calculated: one by varying the percentage of pain relief defined as a "positive response" to nitroglycerin and the other by varying the number of units of pain relief defined as a positive response.

Role of the Funding Source

This study was conducted without any outside funding. The conception and design of the study; the collection, analyses, and interpretation of the data; and the drafting and revision of the manuscript, along with the decision to submit for publication, were done solely by the investigators without any external input.

RESULTS

Patient Sample

Figure 1 outlines the clinical recruitment process and outcomes of specific groups of study participants. During the 5-month enrollment period for the study, 1098 patients were screened and 459 patients met inclusion and exclusion criteria and were enrolled in the study. The predominant reasons for exclusion were chest pain before medical supervision and a lack of chest pain as an admission symptom for patients with a preliminary diagnosis of "rule out myocardial infarction." In addition, patients who could not quantify their chest pain were excluded. Of the total study sample ($n = 459$), 181 patients (39%) had at least 50% relief of their chest pain with nitroglycerin (nitroglycerin responsive), while 278 patients (61%) did not.

Table 1 shows the demographic characteristics and comorbid conditions of the study patients. The rates of administration of other medications did not vary significantly ($P > 0.2$) between nitroglycerin-responsive and nitroglycerin-unresponsive groups (**Table 1**). Few patients received additional analgesics (such as morphine). If these patients were excluded, the relationship between chest pain relief by nitroglycerin and active CAD remained unchanged. In addition, there were no significant differences ($P > 0.2$) in the rates of electrocardiographic findings between nitroglycerin-responsive and nitroglycerin-unresponsive groups (**Table 1**). The random chart audit confirmed a greater than 99% accuracy of study data as recorded.

Follow-up and Outcomes

Of 459 patients enrolled, 4-month follow-up data were obtained for 389 patients (85%) by telephone contact ($n = 313$), review of medical records that confirmed a repeated hospitalization to the index or affiliated hospital during the follow-up interval ($n = 59$), or review of death certificates ($n = 17$). Mean follow-up interval was 173 ± 56 days. **Table 2** details the outcomes over the study period. Of note, there was no statistically significant difference in the incidence of death, subsequent myocardial infarction, or coronary revascularization either individually or as a combined end point between the nitroglycerin-responsive and nitroglycerin-unresponsive groups.

Accuracy of Chest Pain Relief for Diagnosing Active CAD

A total of 141 patients (31%) were determined to have active CAD as the cause of their index chest pain (**Figure**

1), and 275 patients (60%) were determined not to have active CAD as the cause of their index hospitalization. A total of 58 patients without testing were classified as not having active CAD because they had no history of CAD and no events during follow-up ($n = 53$) or had an obvious and persuasive alternative explanation for their chest pain ($n = 5$).

The cause of chest pain could not be determined from the available data in only 43 of 459 patients (9%), all of whom were omitted from the sensitivity and specificity analysis. None of these patients had any testing, and most (31 of 43 patients) could not be located on follow-up. The remaining 12 patients had no events during follow-up but had a known history of CAD and a nondiagnostic index hospitalization.

Relationship of Chest Pain Relief to Active CAD: Sensitivity and Specificity

In **Figure 2** (*top*), sensitivity and specificity for nitroglycerin-responsive chest pain and active CAD are displayed for patients in whom the cause of index chest pain could be determined, using 50% or greater reduction in pain as the definition of response. In patients in whom active CAD was the likely cause of their pain, 35% (49 of 141) had pain relief with nitroglycerin. In contrast, nitroglycerin relieved pain in 41% of patients without active CAD (113 of 275) ($P > 0.2$). **Figure 2** also presents the sensitivities and specificities for the prespecified subgroup analyses; the bottom panel shows the positive and negative likelihood ratios for chest pain relief by nitroglycerin and active CAD. Of note, the CIs for all likelihood ratios include 1.0, indicating that in the overall sample and in the subgroups, chest pain relief with nitroglycerin had no positive or negative value as a predictor of active CAD.

Alternate Definitions of Chest Pain Relief

To better study the relationship of lesser and greater degrees of chest pain relief by nitroglycerin and active CAD, we constructed ROC curves. The ROC curve is a plot of the sensitivity (or true-positive rate) against 1 − specificity (or false-positive rate), which can also be described as a plot of likelihood ratios at a series of different diagnostic cutoffs. The closer an ROC curve is to the upper left corner of the graph, the more accurate it is; the closer the ROC curve is to $y = x$, the less value it has as a test. In **Figure 3**, ROC curves for chest pain relief by nitroglycerin and active CAD are presented. To obtain the curve in the top panel of **Figure 3**, various percentages of reduction in pain intensity were studied, while in the bottom panel, various absolute changes in pain intensity were studied. For both ROC curves, the plotted points closely approximated a likelihood ratio of 1.0, indicating that regardless of which definition is used (that is, percentage chest pain reduction or absolute chest pain reduction), the test of chest pain relief with nitroglycerin has no value in determining the presence or absence of active CAD.

Discussion

Our data demonstrate that chest pain relief with nitroglycerin does not accurately predict active CAD in a general population presenting to an emergency department and should therefore not be used as a triage tool. The sensitivity and specificity of this therapeutic response were low both in the overall study sample and in the prespecified subgroup analyses, including patients with known CAD (**Figure 2**, *top*). Both the positive and negative likelihood ratios were close to 1.0, indicating that chest pain relief by nitroglycerin is not useful as a diagnostic test (**Figure 2**, *bottom*). In addition, the ROC curves demonstrated that alternative definitions of chest pain relief do not improve the diagnostic performance of nitroglycerin.

Several studies have found that nitroglycerin can relieve chest pain due to esophageal or other smooth-muscle spasm, and thus the chest pain relief noted in some noncardiac patients is not unexpected (15). On the other hand, true acute coronary occlusions are not expected to be relieved by nitroglycerin, and thus such patients may have limited pain relief despite having CAD (2, 27). However, in subgroup analysis, when we excluded patients in whom myocardial infarction was ruled in and who presumably had a fixed coronary obstruction, nitroglycerin relieved pain in only 40% of patients who later had a positive result on a stress test or angiography (**Figure 2**, *top*).

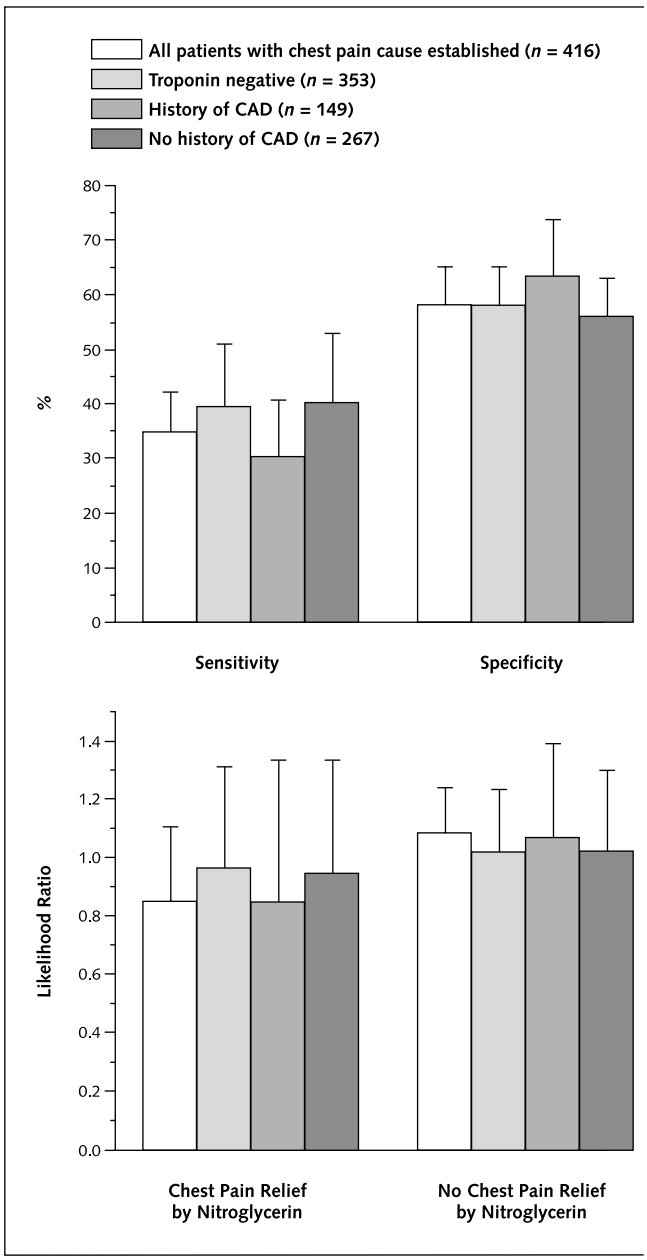
We defined *chest pain relief* as a reduction of at least 50% in intensity of chest pain. As stated in the Methods section, this was deemed to be a clinically meaningful value

Table 2. **Outcomes by Response of Chest Pain to Nitroglycerin***

Outcome	Pain Relief ($n = 158$)		No Pain Relief ($n = 240$)		*P* Value
	Patients, *n*	Rate (95% CI), %	Patients, *n*	Rate (95% CI), %	
Death	4	3 (1–6)	14	6 (3–10)	0.12
Coronary artery bypass grafting	9	6 (3–11)	9	4 (2–7)	>0.2
Percutaneous transluminal coronary angioplasty	14	9 (5–14)	31	13 (9–18)	0.2
MI during index admission	18	11 (7–17)	44	18 (14–24)	0.06
MI during follow-up	12	8 (4–13)	17	7 (4–11)	>0.2
Combined end point of death, revascularization, or MI	37	23 (17–31)	71	30 (24–36)	0.18

* MI = myocardial infarction.

Figure 2. **Predictive value and likelihood ratios of chest pain relief by nitroglycerin for active coronary artery disease (*CAD*).**

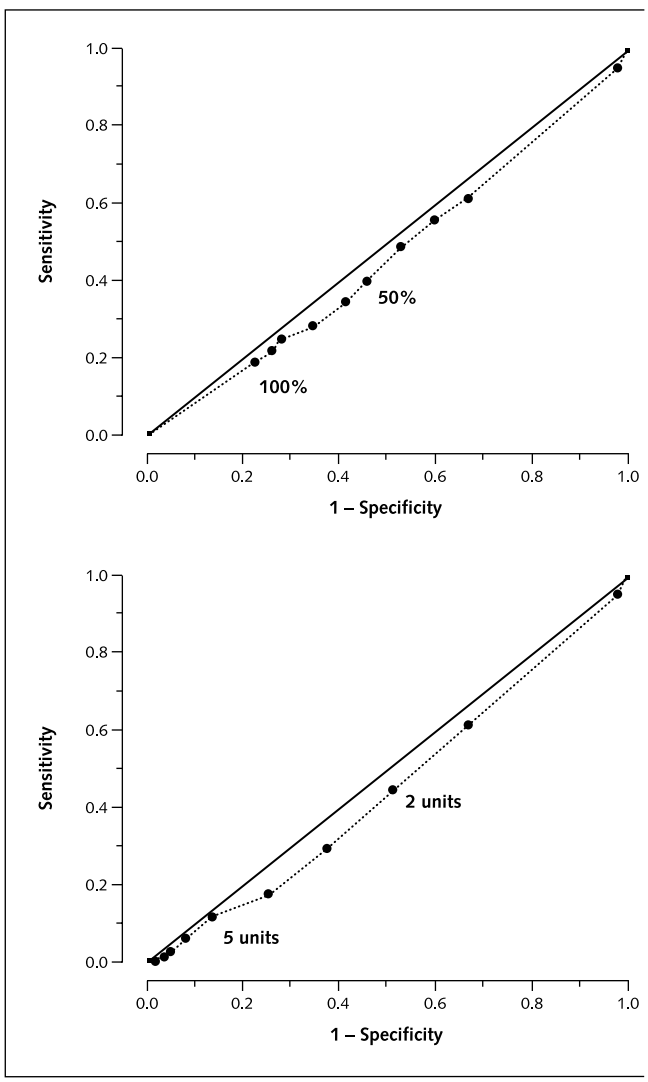


Top. The sensitivity and specificity of chest pain relief by nitroglycerin for the presence of active CAD are low both in the overall study sample and in the prespecified subgroup analyses. **Bottom.** The 95% CIs for both the positive (*left*) and the negative (*right*) likelihood ratios for the response of chest pain to nitroglycerin include 1.0, indicating that this test has no statistically significant diagnostic value in both the overall study sample and in the prespecified subgroup analyses.

to assess pain reduction. We also considered other definitions of pain relief. As demonstrated in **Figure 3**, after we varied the definition of pain relief as a function of percentage of pain reduction after nitroglycerin therapy or of the absolute pain reduction, the ROC curves showed that the likelihood ratio closely approximated 1.0 at all definitions tested, that is, with all of these definitions of pain relief, the results remained unchanged. Given the wide variation in self-reported pain and the limitations of various pain scales, we prefer using a percentage reduction in pain intensity to reporting an absolute reduction. However, no matter which technique was used, the ROC curves demonstrated that the results were unchanged.

Chest pain relief with nitroglycerin also did not predict subsequent outcomes (**Table 2**). The 2 groups did not significantly differ ($P > 0.2$) in terms of rates of death, myocardial infarction, or revascularization, either as individual or combined end points. Of interest, in all groups

Figure 3. **Receiver-operating characteristic curves for chest pain relief by nitroglycerin and active coronary artery disease.**



Two series of sensitivities and specificities were calculated by varying the decrease in pain intensity defined as *pain relief*: Pain relief is considered as a percentage reduction in pain intensity (*top*) and as an absolute reduction in pain intensity (*bottom*). Both curves closely approximate a likelihood ratio of 1.0, indicating that, independent of cutoff, chest pain relief by nitroglycerin has no statistically significant diagnostic value. Representative points are labeled on the receiver-operating characteristic curves, including 50% and 100% pain reduction (*top*) and 2.0-unit and 5.0-unit reduction (*bottom*).

there was a trend toward worse outcomes in the group without pain relief. When we excluded patients in whom myocardial infarction was ruled in, a group in which a single dose of nitroglycerin would probably not relieve chest pain, the rate of the combined end point of death, myocardial infarction, or coronary revascularization was 14% in the nitroglycerin-responsive group as well as 14% in the nitroglycerin-unresponsive group ($P > 0.2$).

Our study has some limitations. The findings depend on self-reported pain, a highly subjective experience, and the pain rating scale of 0 to 10 has many difficulties in interpretation and recall (17, 28). However, using the self-reported change in pain intensity rather than the absolute value of pain intensity within a short interval (approximately 5 minutes) probably provided a more accurate assessment of the efficacy of the specific therapy used (nitroglycerin). The physicians caring for the patients were aware of the response of the patients' chest pain to nitroglycerin. This may have influenced the decision to pursue further testing and work-up, and thus patients with pain relief may have been more vigorously evaluated than patients without pain relief. This work-up bias should have led to the discovery of more disease in patients with pain relief, but the disease burden uncovered was similar regardless of whether pain was relieved. In addition, although the study investigators had access to the information on response to nitroglycerin, the assignment to diagnostic category (that is, active CAD vs. no active CAD) was based chiefly on hard criteria in the medical record and was thus insulated from assignment bias.

This study, although prospective, is observational. For patients who had further testing ($n = 336$), the testing method was at the discretion of the physicians directing the patients' care. Therefore, not all patients had the same test. This does, however, reflect common clinical practice. To be enrolled, patients had to be hospitalized after presenting to the emergency department, introducing the concern for a selection bias. However, in patients with chest pain at rest (such as all of the participants in this study), relief of chest pain with nitroglycerin commonly results in hospitalization (24). Also, as noted earlier, in patients with chest pain that may not be typical of angina or that is relieved with other additional agents, such as antacids, a short-stay hospitalization is prompted more by the patient profile than by the character of the pain. This is especially true in our present era of rapid "rule out myocardial infarction" protocols, where the cost and time involved in a "quick rule out" are trivial compared with the possible costs of a missed myocardial infarction (29). Patients sent home from the emergency department (none of whom were included in our study) are substantially less likely to have active CAD than patients who are hospitalized (30, 31). This may only modestly affect our study's specificity. However, one can argue that our study probably was biased in favor of patients with CAD but still did not show any diagnostic value for nitroglycerin-responsive chest pain.

This study was performed entirely in the emergency department setting in patients who had active chest pain while under medical supervision. Our findings of the lack of diagnostic and prognostic value of chest pain relief by nitroglycerin for active CAD, however, could possibly be extrapolated to an outpatient (clinic) population. The sources of chest pain in the outpatient setting, whether attributable to CAD or to some other process, probably overlap substantially with the causes of chest pain in the emergency department. Further investigation is needed to define the value of chest pain relief by nitroglycerin in the outpatient setting.

Our data refute common beliefs about the relationship between active CAD and the diagnostic value of nitroglycerin-responsive chest pain and strongly suggest that the response of chest pain to nitroglycerin, although therapeutically beneficial, has little diagnostic or prognostic value.

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