Diagnostic accuracy of nitroglycerine as a 'test of treatment' for cardiac chest pain: a systematic review

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ABSTRACT

To determine the accuracy of using nitroglycerine as a 'test of treatment' in the diagnosis of cardiac chest pain we undertook a systematic review of studies of diagnostic accuracy. Databases searched included PubMed, Cochrane Database, Google Scholar, Science Citation Index, EMBASE and manual searching of bibliographies of known primary and review articles. Studies were included if sublingual nitroglycerine was the index test, its effect on the patient's pain score was recorded and the reference test was performed on at least 80% of patients. The data from the five papers were used to form 2×2 contingency tables. Five eligible studies were found, all in the acute setting (although one paper collected its data in the follow-up setting, all patients had acute presentations). The sensitivity ranged from 35% to 92% and the specificity from 12% to 63%. However, in all but one paper the Youden indices were close to zero suggesting that the response to nitroglycerine is not useful as a diagnostic test. The combined sensitivity was 0.52 (95% CI 0.48 to 0.56) and combined specificity was 0.49 (95% CI 0.46 to 0.52). The diagnostic OR from the combined studies was 1.2 (95% CI 0.97 to 1.5), which is not significantly different from 1. In the acute setting, nitroglycerine is not a reliable test of treatment for use in the diagnosis of coronary artery disease. However, further studies are needed to determine the diagnostic accuracy of nitroglycerine for recurrent exertional chest pain.

INTRODUCTION

Coronary artery disease is a huge economic burden to a stretched healthcare system and is the leading cause of death in the UK.[1] The incidence of angina pectoris is 0.83 per thousand population aged 31–70 years. New cases of angina pectoris can be crudely estimated at 22 600 patients per annum.[2] It is in the interests of both the patient and NHS resources to effectively identify patients who require further investigation for chest pain of a cardiac aetiology. It is crucial to prevent missed diagnoses and deaths in patients with coronary artery disease, occurrences that can lead to an increased mortality in this patient group.[3]

Nitroglycerine is thought to induce venous dilation and enhance pooling, thereby relieving the load on the stressed ischaemic heart. Administration of nitroglycerine has been shown to be safe, and effective in significantly reducing chest pain, although often patients will not experience complete relief of symptoms.[4] Some patients presenting with oesophageal spasm find nitroglycerine relieves the acute symptom of chest pain.[5] Consequently, if nitroglycerine is effective in relieving chest pains of different aetiologies, then it will not be effective as a diagnostic tool. Recent NICE guidance[6] warns: 'Do not use people's response to glyceryl trinitrate (GTN) to make a diagnosis', although response to GTN is included as one of the three features of typical angina.

Chest pain is a diagnostic dilemma in both the emergency department and the general practice setting, with several protocols and clinical recommendations being designed to aid the accuracy of this process.[7 8] None of these systems are perfectly accurate in diagnosing coronary artery disease, with 1–4% of patients with acute coronary syndrome being sent home from accident and emergency departments.[9] It is commonly believed that if a patient's chest pain is relieved following the administration of nitroglycerine, then this chest pain is likely to be of a cardiac aetiology. Hence, response to nitroglycerine has been used as a test in the diagnosis of coronary heart disease[10] and is frequently used in the emergency department when assessing patients presenting with chest pain.

This review aims to assess the usefulness of nitroglycerine as a diagnostic tool for the presence of coronary artery disease, by examining whether its effectiveness in relieving chest pain corresponds to a diagnosis made by a reference standard.

METHODS

Search strategy

Studies were identified by searching PubMed, EMBASE and Google Scholar from the beginning of each database until February 2010. A Science Citation Index forward search looked for further articles eligible for inclusion. The bibliographies of primary studies identified and of relevant review articles found through initial searches were checked for additional relevant studies.

The PubMed search strategy included terms for the index test, reference tests, the patient problem and a diagnostic filter: (1) chest pain OR angina OR myocardial infarction OR acute coronary syndrome OR myocardial ischaemia; (2) acute OR recurrent; (3) nitroglycerin OR glyceryl tri-nitrate OR GTN; (4) coronary artery disease/diagnosis; (5) angio*; (6) cardio* exam*; (7) stress echo* OR ECG; (8) #1 AND #2 AND #3 AND (#4 OR #5 OR #6 OR #7).

Study selection and data extraction

Cohort and cross-sectional studies were reviewed, initially by screening the title and abstract (by both authors) and then by reviewing the full documents. To be included in the review the studies had to be cohort studies in patients with chest pain in whom the index test—administration of sublingual nitroglycerine—was performed, and a reference test of clinical diagnosis was performed on more than 80%

Table 1 Characteristics of participants, interventions and diagnostic outcome of patients receiving nitroglycerine for chest pain

Criterion	Diercks *et al*[11]	Steele *et al*[12]	Henrikson *et al*[13]	Shry *et al*[14]	Wu *et al*[18]
Population					
Number of patients	664 (52% male)	270	459	223 (47% female)	405 (66% male)
Mean age	54±12 years	Not stated	Not stated	60±14 years	61 years
Presenting complaint	Active chest pain during medical evaluation	Active chest pain, admitted with an uncertain diagnosis	Documented chest pain during medical evaluation; admitted with a diagnosis of ' rule out MI' or 'chest pain'	Presented with ongoing chest pain	Presented with chest pain >1 month; no history of MI, coronary angiography/ angioplasty or CABG.
Setting	Emergency department in a urban tertiary care centre	Emergency department of an academic tertiary care centre	Emergency department of an urban community teaching hospital	Emergency department of an academic teaching hospital	Outpatients department of an academic tertiary care centre
Intervention					
Index test (nitroglycerine)	Sublingual nitroglycerine Dose not stated	Sublingual nitroglycerine 400 μg given every 5 min up to three doses	0.4 μg sublingual nitroglycerine or 0.4 μg spray nitroglycerine	Nitroglycerine administered within 10 min of presentation Dose and type not controlled	Sublingual nitroglycerine. Dose and type not stated in paper. Index test forms part of a wider chest pain questionnaire.
Evaluation of pain	11-point numeric scale within 10 min of nitroglycerine	10-point numeric scale; time frame between nitroglycerine and record not stated	Patient self-reported pain within 5 min of first dose of nitroglycerine Scale not stated	Patients reported pain on a numeric scale of 1–10, before and within 10 min of nitroglycerine	Patients reported relief by nitroglycerine as part of a chest pain questionnaire.
Categorisation of response	No, minimal, moderate or significant/complete reduction	Positive if reduction ≥3 points or/complete resolution	Positive if ≥50% in chest pain	Positive if reduction in pain ≥2 units, no reduction in pain	Relief—yes or no
Outcome					
Presence of cardiac chest pain	MI Unstable angina MI	MI, ACS, cardiac catheterisation showing >70% stenosis or positive provocation test	MI, ACS, CAD on angiogram with >70% stenosis, positive exercise tolerance test (diagnosis by attending physician)	MI, ACS, abnormal stress test, CAD on angiogram >50% stenosis in left main coronary artery or >70% in other coronary arteries, (diagnosis by staff cardiologist)	CAD on angiogram (by cardiologist) Stenosis >50% of the luminal diameter in >1 major branch.
Prevalence of cardiac chest pain	122 (18%)	83 (31%)	141 (34%)	74 (33%)	244 (60%)
Reference standard for AMI	Elevation of the cardiac injury marker troponin I above diagnostic threshold (>2.0 ng/ml)	Troponin level	Not distinguished from active CAD	Raised cardiac enzymes	Not distinguished from cardiac chest pain
AMI of CHD (%)	68/122 (56%)	35/83 (42%)	91/141 (65%)	32/74 (43%)	0/244 (0%)

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHD, coronary heart disease; MI, myocardial infarction.

of patients within the study. The sensitivity and specificity of the index test needed to be reported or calculable from the data provided.

The patient cohort within each paper was reviewed, with a view to dividing these patients into two groups—those with acute chest pain and those with recurrent chest pain; the diagnostic accuracy of nitroglycerine as a test of treatment was assessed separately for each group.

Data from the papers were extracted by both authors on study characteristics, study quality and the accuracy of results obtained. Study characteristics consisted of the patients presenting complaint, administration of nitroglycerine, method of recording pain response, presence of other confounding pain relief medications and method of conducting the reference test.

The outcome measure of interest is the accuracy of nitroglycerine as a diagnostic test of treatment for cardiac chest pain, as reflected by its sensitivity and specificity.

For all studies, a 2×2 table was constructed and then used to calculate sensitivity and specificity, and plotted on a receiver operating characteristic curve. The quality of the papers was assessed for the method of recruitment to the study (whether it was consecutive or random), whether the index test and reference test were objective and standard across all patients, whether assessors were blinded to the outcomes and whether there was at least 80% verification with the reference test.

Statistical calculations and analysis were done using Excel and the diagnostic test procedures were performed using MetaAnalyst (http://tuftscaes.org/meta_analyst/).

RESULTS

The literature search identified 183 potential studies from which five eligible primary papers[11–14 15] were found: three were prospective observational cohort studies, one was a retrospective review and one was a retrospective observational cohort study. One further primary retrospective study was found through a forward citation search.[16] However, this study did not report or collect data on response to nitroglycerine except as part of an item defining 'typical angina' (Hermann, personal communication). The remaining five studies met the inclusion criteria, and in total included 1978 patients, all adults, all presenting to the emergency department of large hospitals with a complaint of chest pain and admitted with an uncertain diagnosis. None of the studies examined the use of nitroglycerine in recurrent exertional chest pain.

All studies used a similar recruitment process, looking solely at patients with an uncertain diagnosis of chest pain. All three prospective studies used similar methods of administration for the index test, although with different methods of elimination of other potentially confounding variables. Neither retrospective review standardised their index test due to the nature of the studies (table 1).

There is some variability in the methodological quality of the studies (table 2). The retrospective review has the poorest methodological quality, due to a lack of reported follow-up, dosing and administration of the index test and objectivity in the reference standard. The three prospective studies demonstrate better methodological quality, as there are minimal important elements not reported. The study by Henrikson *et al* has the strongest methodological quality due to the standardisation of the index test, use of consecutive patients and increase in the length of follow-up. The paper by Wu *et al* also demonstrates poor methodological quality when the data relating to administration of nitroglycerine were extracted—no

Table 2 Design, methods and results of the five eligible studies

	Diercks *et al*[11]	Steele *et al*[12]	Henrikson *et al*[13]	Shry *et al*[14]	Wu *et al*[18]
Study design	Prospective observational cohort	Prospective observational cohort	Prospective observational cohort	Retrospective case note review	Retrospective observational cohort
Recruitment	Index test applied to all patients regardless of initial pain score	The index test was not applied to those with an obvious diagnosis of myocardial ischaemia or those who could not quantify their pain	Patient recruitment was consecutive, helping to minimise bias Patients whose chest pain had resolved before admission were excluded	Paper does not state whether patients were consecutive admissions Enrolment to study dependent upon medical notes	Consecutive admissions to outpatients' department/day case coronary angiography Excluded if pathological Q waves on ECG or regional wall abnormality on echo
Maintenance	The reference standard was assessed in all patients during their admission 30-day follow-up was obtained in 591/664 patients; reasons for loss to follow-up not stated	12 subjects were lost to 4-week follow-up due to loss of contact Analysis of results was based upon all 270 patients	Follow-up was longer, so the endpoint of the reference standard was more accurate; 4-month follow-up data was obtained for 389 patients	The number of patients lost to follow-up not stated	405 patients recruited at point of follow-up—therefore no patients lost
Measurement					
Blinding	Subjects: not blinded Assessors: not stated	Subjects: not blinded Assessors: not blinded	Subjects: not blinded Assessors: not stated	Subjects: not blinded Assessors: not blinded	Subjects: not blinded Assessors: not blinded
Results					
Response criterion	Complete or moderate relief	3-unit reduction in pain	>50% reduction in pain	2-unit reduction in pain	Response of 'yes' to relief by nitroglycerine
Sensitivity	0.51 (62/122)	0.72 (60/83)	0.35 (49/141)	0.92 (68/74)	0.51 (124/244)
Specificity	0.50 (271/542)	0.37 (70/187)	0.59 (162/254)	0.12 (18/149)	0.63 (102/161)
Youden index	0.01	0.097	−0.063	0.040	0.14
LR+/LR−* OR (95% CI)	1.02/0.98=1.03 (0.70 to 1.53)	1.16/0.74=1.6 (0.89 to 2.7)	0.85/1.1=0.76 (0.50 to 1.2)	1.05/0.67=1.6 (0.59 to 4.1)	1.39/0.78=1.8 (1.2 to 2.7)

*Likelihood ratio positive/likelihood ratio negative, diagnostic OR.

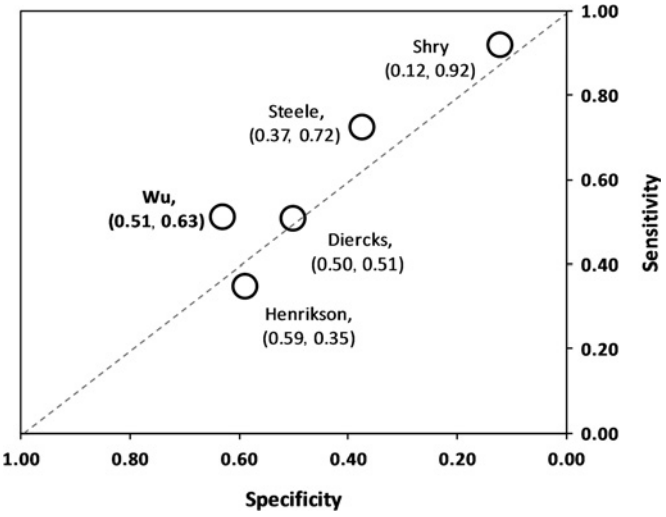

Figure 1 Receiver operating plot for the five studies with first author names (sensitivity/specificity) shown. Uninformative tests will fall on the dashed diagonal.

mention is made of the dose or timeframe in which the test is administered, or the exact nature of the response; neither does it discuss confounding variables such as other analgesia—which may explain the increased diagnostic OR in this study.

The receiver operating plot (figure 1) shows that the 'test' was uninformative in five studies, with all studies near the 'no information' diagonal: three just above and two on the line or below. The combined sensitivity was 0.52 (95% CI 0.48 to 0.56) and combined specificity was 0.49 (95% CI 0.46 to 0.52). The diagnostic ORs (table 2) ranged from 0.76 to 1.8 with the CIs of all studies except the Wu *et al* study crossing the null value of 1.0. The overall diagnostic OR from the combined studies was 1.2 (95% CI 0.97 to 1.5), which is not significantly different from 1. However, there was moderate heterogeneity (χ^2=9.7, p=0.045), which appeared mostly due to the Wu *et al* study.

DISCUSSION

This systematic review of nitroglycerine as a diagnostic tool has demonstrated that the accuracy of this 'test of treatment'[17] for diagnosis is poor. Four studies showed a poor ability of GTN to accurately discriminate between those with cardiac chest pain and those with non-cardiac pain; with the paper by Wu *et al* reporting a slightly higher ability but in an outpatient setting. This review confirms that nitroglycerine is an unreliable diagnostic tool for patients presenting with chest pain of uncertain aetiology. The likelihood ratio for nitroglycerine as a diagnostic test is close to 1 in four of the papers, indicating that the post-test probability of a diagnosis of coronary artery disease is almost equivalent to the pre-test probability. It was increased in the paper by Wu *et al*, but this can be accounted for by the less accurate nature of administration and recording of response to nitroglycerine. The result was consistent across the remaining four papers, irrespective of which pain score was used. Consequently, nitroglycerine is not useful as a triage tool in the emergency room. If it is administered for pain relief, the response should not be taken as an indicator of a coronary cause.

All five studies have some flaws. First, workup bias—patients with 'positive results' are more likely to be fully assessed—is present in all studies. In a follow-up letter to Henrikson *et al*'s study, Evans and Reilly[18] attempted to correct for the workup bias and suggested that sensitivity should have been 0.33 (rather than 0.35) and specificity 0.84 (rather than 0.59). However, these corrected results would still suggest the 'test' is very weak. Second, the 'gold standard' for coronary artery disease is imperfect and the misclassification will tend to underestimate the true accuracy. Finally, these studies were all in the acute care setting, but even then, some degree of selection occurred, and hence there is still the possibility that there are subgroups of patients in the emergency setting where this 'test' may be useful. However, none of these flaws is likely to substantially change the conclusions.

These results are limited to the acute care setting, and further research in this setting is unlikely to be fruitful. The one (excluded) study which looked at history of response to nitroglycerine as part of the definition of 'typical angina' found inducible ischaemia on stress testing in 14% of patients with typical angina, 11% with atypical angina and 16% with no chest pain.[15] However, we found no studies relevant to the ambulatory care setting of patients presenting with recurrent exertional chest pain. Hence, research is still needed on the usefulness of sublingual nitroglycerine in recurrent chest pain. Meanwhile, practitioners and guidelines should warn against the use of nitroglycerine as a test.

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