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Prognostic Value of Symptoms during a Normal or Nonspecific Electrocardiogram in Emergency Department Patients with Potential Acute Coronary Syndrome

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Abstract

Objectives: Emergency department (ED) patients with symptoms concerning for acute coronary syndrome (ACS) and a normal electrocardiogram (ECG) are at risk for adverse cardiovascular events. The authors hypothesized that patients with a normal or nonspecific ECG during symptoms have a lower risk for ACS than do those who are asymptomatic.

Methods: This was a prospective cohort study of ED patients with potential ACS. Outcomes were acute myocardial infarction (AMI), ACS, and 30-day cardiovascular events (death, AMI, revascularization). Fisher's exact test, t-tests, and logistic regression were used for data analysis.

Results: Of 2,593 patient visits, 2,007 patients had normal or nonspecific ECG findings. There were 1,196 who had symptoms during ECG, whereas 811 did not. Patients with symptoms at ECG acquisition were younger (49.9 vs. 55.2 years; $p < 0.001$) and were more likely to be black (70% vs. 64%; $p = 0.002$), female (63% vs. 58%; $p = 0.03$), and to have used cocaine (5% vs. 2%; $p = 0.004$). They were less likely to have hypertension (49% vs. 58%; $p < 0.001$), and diabetes (22% vs. 17%; $p = 0.002$). Patients with and without symptoms were equally likely to have AMI (both 2.8%; $p > 0.99$), ACS (10.1% vs. 11.5%; $p = 0.34$), and 30-day adverse outcomes (both 5.3%; $p > 0.99$). After adjustment for baseline cardiovascular-risk factors, odds ratios for patients with symptoms at the time of ECG acquisition were not significantly different for any of the outcomes: AMI (1.1; 95% confidence interval [CI] = 0.6 to 1.9); ACS (1.1; 95% CI = 0.8 to 1.4); or 30-day events (1.2; 95% CI = 0.8 to 1.9).

Conclusions: Patients who are symptomatic during acquisition of a normal or nonspecific ECG have rates of adverse cardiovascular events similar to those of patients without symptoms. Clinicians should not rely on the absence of ECG abnormalities during symptoms to help exclude ACS.

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Much research has been dedicated to studying patients with potential acute coronary syndromes (ACS) to more accurately identify those at risk for adverse cardiovascular events. As a consequence, several methods for risk stratification have evolved. Many of these risk stratification schemes, including the Thrombolysis In Myocardial Infarction (TIMI) Risk Score,[1] the Goldman risk criteria,[2–4] Acute Cardiac Ischemia Time-Insensitive Predictive Instrument (ACI-TIPI),[5] and others[6–12] have incorporated electrocardiogram (ECG) findings that are suggestive or diagnostic of myocardial ischemia. Unfortunately, it is estimated that only one third of patients with acute myocardial infarction (AMI) demonstrate the classic ST-segment elevation that is associated with myocardial ischemia.[13] Patients with classic ECG findings of ischemia are more

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likely to present with chest pain,[13] to be diagnosed with an AMI, to die, and to have other life-threatening complications[9,14–19] than are their counterparts who lack diagnostic ECG findings.

However, a normal or nonspecific ECG does not signify exemption from risk for current or future cardiovascular events. Although patients with normal and nonspecific ECGs at the time of ED presentation are less likely to be hospitalized and emergently evaluated for ACS than are those with diagnostic ECGs,[20,21] some of these patients will later evolve ECG changes that are consistent with myocardial ischemia.[22–25] In one large series, patients with an initially normal or nonspecific ECG were found to have 5.7% and 8.7% in-hospital mortality rates, respectively.[13]

Although there are dynamic ECG changes observed with the evolution of ACS,[24–26] patients frequently present to the ED after resolution of chest pain (or other symptoms) concerning for ACS. Symptom resolution may result in a missed window of opportunity to detect electrocardiographic evidence of ischemia. To date, no algorithm has reliably predicted which patients with potential ACS ultimately will have an adverse cardiovascular outcome on the basis of the absence of ECG findings consistent with ischemia[16,27,28] alone, or in combination with cardiac markers[29] or with duration[30] and nature[31,32] of chest-pain symptoms. Although a patient with a nondiagnostic ECG in the setting of symptoms may be less likely to be suspected of having an ischemia-related cause for those symptoms, to our knowledge, no study has yet to evaluate the predictive value of a normal or nonspecific ECG acquired during the concerning symptoms.

We hypothesized that patients presenting to the ED with symptoms suggestive of ACS and a normal or nonspecific ECG during symptoms would have lower rates of AMI, ACS, and 30-day adverse cardiovascular events than would those patients who have a normal or nonspecific ECG while asymptomatic.

METHODS

Study Design

We conducted a prospective observational study on ED patients with symptoms concerning for ACS and a normal or nonspecific ECG to determine whether there are differences in cardiovascular outcomes depending on whether the patient was symptomatic at the time of ECG acquisition. Data collection was approved by the Institutional Committee on Research Involving Human Subjects at our institution. Informed consent was obtained from all study participants.

Study Setting and Population

This study was conducted at the Hospital of the University of Pennsylvania. The ED serves an urban population with approximately 55,000 adult patient visits per year. Trained research assistants were available to enroll study participants 16 hours a day, 7 days a week.

Study Protocol

Patients 24 years of age or older who presented to the ED with symptoms concerning for ACS and who received an ECG were enrolled. Eligible patients were identified by an initial ECG that was interpreted by the treating physician as normal or nonspecific according to the Standardized Reporting Guidelines[33] (Table 1, category 1 or 2). All management and disposition decisions were at the discretion of the treating physician and were independent of study enrollment.

The following clinical information was recorded by treating physicians prospectively on all study participants: presence of chest pain at ED presentation, characteristics of chest pain or anginal equivalent (neck, jaw, arm, or back pain; dyspnea; syncope; palpitations; nausea and/or vomiting), medical history, presenting TIMI Risk Score,[1] cardiac-related components of the physical exam, ECG and chest radiograph findings, and preliminary ED diagnosis. Research assistants recorded cardiac-marker results, medications administered during the ED stay, and patient disposition.

Investigators followed the hospital course for admitted patients daily. Data recorded on hospitalized patients included any cardiovascular complications, serial cardiac marker results, cardiac diagnostic testing, and final diagnosis. Primary outcomes were AMI, ACS, and 30-day cardiovascular events (AMI, revascularization, or death). ACS included a diagnosis of AMI or unstable angina. The

Table 1
Electrocardiographic Classification Criteria

ECG Classification	Criteria
Normal*	No evidence of ischemia
Nonspecific*	Abnormal T-wave axis in lead III, atrial fibrillation or flutter, nonspecific ST or T-wave changes
Early repolarization	Early repolarization without any other abnormalities
Abnormal but not diagnostic of ischemia	Prolonged PR, QRS, QTc intervals; bundle branch blocks; left ventricular hypertrophy with strain; nonspecific intraventricular conduction deficits; nonspecific ST- or T-wave changes not meeting the definition for ischemia
Ischemia known to be old	ST depression more than 0.1 mV, measured 80 ms from the J point; inverted T waves more than 0.3 mV; or Q waves at least 30 ms in duration without change from prior ECG
Ischemia not known to be old	Same as above but with no prior ECG for comparison or changed from prior ECG
Suggestive of myocardial infarction	ST elevation greater than 0.1 mV, measured 80 ms from the J point in ≥ 2 contiguous leads; $\pm$ reciprocal ST depression

* Patients included in study.

diagnosis of AMI was determined by using the European Society of Cardiology–American College of Cardiology criteria.[34] A diagnosis of unstable angina was assigned if there was documented reversible ischemia on a stress test, at least 70% coronary artery stenosis in at least one vessel on cardiac catheterization, or creatine kinase and its myocardial band isoenzyme (CK-MB), or troponin I elevation above normal but less than the level diagnostic of an AMI (troponin I of $\geq$0.4 ng/mL but <2 ng/mL; CK-MB of $\geq$5 ng/mL but <10 ng/mL). Cardiac troponin I and CK-MB were measured by an enzyme-linked immunoassay with an Abbott AxSYM automated analyzer (Abbott Laboratories, Mountain View, CA). The lower limit of detection for troponin I was 0.3 ng/mL (range, 0 to 50.0 ng/mL). The lower limit of detection for CK-MB was 0.7 ng/mL (range, 0 to 300 ng/mL).

Follow-up was conducted at 30 days from initial presentation for each patient via direct telephone contact with patients or their family members. Patients were queried about any cardiac testing or rehospitalization. All post-admission hospital events and 30-day outcomes were recorded on a separate data collection instrument. Patients were excluded from analysis if 30-day follow-up was incomplete.

Data Analysis

All analyses were performed by using SAS statistical software (Version 9.1, SAS Institute, Cary NC). Data are presented as means ($\pm$SD) for age and as frequency and percentage for categorical variables. Chest-pain onset and duration are reported as medians with interquartile ranges. To determine whether symptomatic and asymptomatic patients differed by baseline characteristics and outcomes (AMI, ACS, or 30 day events), Student's t-test and Fisher's exact test were used for continuous and categorical data, respectively. To adjust for possible confounders when examining the two groups with regard to final outcome, a forced-entry logistic regression model was used for the following factors: age, male gender, black race, cocaine use, TIMI Risk Score, and total number of cardiac risk factors. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each outcome with respect to presence or absence of symptoms.

RESULTS

During the study period there were 2,593 ED patient visits with symptoms suggestive of ACS. Of these patients, 2,078 had normal or nonspecific ECG findings, and 2,007 (97%) had complete 30 day follow-up and comprised the study cohort. The cohort was 67% black, 29% white, and 61% female. There were 1,196 patients who had symptoms concerning for ACS at the time the initial ECG was obtained, whereas 811 patients were asymptomatic. There were equal proportions of patients in each group with normal and nonspecific ECGs. Characteristics of these two groups at time of ED presentation are listed in Table 2.

Patients with symptoms during ECG were younger (49.9 vs. 55.2 years; $p < 0.001$) and more likely to be black (70% vs. 64%; $p = 0.002$), female (63% vs. 58%; $p = 0.03$), have prolonged symptoms (300 vs. 10 minutes; $p < 0.001$), and use cocaine (55% vs. 2%; $p = 0.004$). Patients who were asymptomatic during their normal or nonspecific ECG were more likely to have high cholesterol (27% vs. 23%; $p = 0.04$), hypertension (58% vs. 49%; $p < 0.001$), and diabetes (22% vs. 17%; $p = 0.002$).

Patients with and without symptoms were not different with regard to having multiple episodes of chest pain before ED arrival (48% vs. 44%), a history of coronary artery disease (15% vs. 17%), or myocardial infarction (11% vs. 9%), and were not more likely to be admitted to the hospital (67% vs. 70%).

With regard to the main outcomes, there were no significant differences between patients with and without symptoms during acquisition of a normal or nonspecific ECG. There were 23 asymptomatic and 34 symptomatic patients who sustained an AMI during initial hospitalization (2.8% for both; $p > 0.99$). There were 93 and 121 patients in the symptomatic and asymptomatic groups, respectively, who were diagnosed with ACS during index hospitalization (11.5% vs. 10.1%; $p = 0.34$). Forty-three patients in the asymptomatic group, as compared with 63 patients with symptoms, had an adverse event at 30-day follow-up (5.3% for both; $p > 0.99$).

No significant difference was observed between those with and without symptoms with regard to the three outcomes: AMI (OR, 1.0; 95% CI = 0.6 to 1.7), ACS (OR, 0.88; 95% CI = 0.7 to 1.1), and 30-day adverse events (OR, 0.99; 95% CI = 0.7 to 1.4). Moreover, after adjusting for the prespecified confounders, the ORs for all outcomes still demonstrated no significant difference between the two groups: AMI (OR, 1.1; 95% CI = 0.6 to 1.9), ACS (OR, 1.1; 95% CI = 0.8 to 1.4), or 30-day adverse events (OR, 1.2; 95% CI = 0.8 to 1.9; Table 3).

Patients in both groups had a similar distribution of normal and nonspecific ECG findings across outcomes; evaluation of only patients with a normal ECG yielded the same results as that of patients with a normal or nonspecific ECG. Symptom duration for patients with adverse outcomes was not significantly different from symptom duration for the entire group of symptomatic (300 vs. 195 minutes) and asymptomatic (10 vs. 15 minutes) patients.

DISCUSSION

Individually, a nondiagnostic ECG and chest-pain symptoms have limited prognostic value for identifying patients free from risk for adverse cardiovascular outcomes. In this study, we evaluated the likelihood of adverse outcomes given these factors in combination. Specifically, we hypothesized that patients with a normal or nonspecific ECG in the setting of symptoms would be less likely to have an ischemia-related cause for their symptoms and, therefore, be less likely to have adverse cardiac events. The results of this study do not, in fact, support that hypothesis. We found no significant difference in outcome rates between patients with and without symptoms during acquisition of a normal or nonspecific ECG. Our groups varied at baseline with regard to a number of risk factors known to contribute to increased risk for cardiovascular events, but even after adjusting for these factors, there was no difference in outcomes between

Table 2
Presenting Characteristics of Patients with and without Symptoms during Acquisition of a Normal or Nonspecific ECG

Characteristic	Symptomatic (n = 1,196)	Asymptomatic (n = 811)	p-value
Age in yr	49.9 ± 13	55.2 ± 15	<0.001
Gender			0.03
Female	756 (63)	473 (58)	
Male	440 (37)	338 (42)	
Race			0.002
African American	838 (70)	515 (64)	
White	307 (26)	264 (33)	
Other	46 (4)	31 (4)	
Chest pain onset (min)*	360 (120–1,440)	154 (30–600)	<0.001
Chest pain duration (min)*	300 (60–1,440)	10 (1–90)	<0.001
Multiple episodes of chest pain	580 (48)	357 (44)	NS
Cardiac risk factors			
Hypertension	591 (49)	473 (58)	<0.001
Diabetes	202 (17)	182 (22)	0.002
Hypercholesterolemia	270 (23)	216 (27)	0.04
Family history of CAD	198 (17)	109 (13)	NS
Tobacco use	495 (41)	302 (37)	NS
Cocaine use in prior 7 d	60 (5)	20 (2)	0.004
Cardiac history			
Coronary artery disease	180 (15)	138 (17)	NS
Myocardial infarction	131 (11)	77 (9)	NS
Prior stress test	323 (27)	213 (26)	NS
Abnormal results	44 (14)	25 (12)	NS
Prior catheterization	191 (16)	133 (16)	NS
Abnormal results	84 (44)	60 (46)	NS
Prior CABG	21 (2)	38 (5)	<0.001
Congestive heart failure	99 (8)	92 (11)	0.02
TIMI Risk Score			0.001
0	477 (40)	285 (35)	
1	356 (30)	225 (28)	
2	192 (16)	146 (18)	
3	104 (9)	93 (11)	
4	55 (5)	50 (6)	
5	10 (1)	12 (1)	
6	2 (0.2)	0	
ECG classification			NS
Normal	772 (65)	523 (64)	
Nonspecific	424 (35)	288 (36)	
Initial ED diagnosis			NS
Acute myocardial infarction	18 (2)	4 (0.5)	
Angina	257 (22)	156 (19)	
Atypical chest pain	434 (37)	290 (36)	
Nonischemic	484 (41)	359 (44)	
ED disposition			NS
Admitted	803 (67)	565 (70)	
Discharged	390 (33)	245 (30)	

CABG = coronary artery bypass graft; CAD = coronary artery disease; TIMI = Thrombolysis In Myocardial Infarction.
* Medians with interquartile ranges.

patients with and without symptoms during a normal or nonspecific ECG.

We did not collect data on the development of ischemic changes on subsequent ECG tracings for our patient population. Several studies now have demonstrated that serial ECGs increase sensitivity for detecting ischemia.[25,28,35] By using the National Registry of Myocardial Infarction database, Welch et al.[13] demonstrated that

Table 3
Risk of Cardiovascular Outcomes in Patients with a Normal or Nonspecific ECG in the Presence or Absence of Symptoms

Outcome	Symptomatic, n (%)	Asymptomatic, n (%)	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Acute myocardial infarction	34 (3)	23 (3)	1.0 (0.6, 1.7)	1.1 (0.6, 1.9)
Acute coronary syndrome	121 (10)	93 (11)	0.88 (0.7, 1.1)	1.1 (0.8, 1.4)
30-d outcomes	63 (5)	43 (5)	0.99 (0.7, 1.4)	1.2 (0.8, 1.9)

20.1% and 18.4% of patients with initially normal and nonspecific ECGs, respectively, later developed ECG changes consistent with ischemia. Mortality for patients with initially normal ECGs approached 9.2%, and for those with initially nonspecific ECGs exceeded (12.3%) that for patients with initially diagnostic ECGs (11.5%). That study did not specifically address whether these patients were symptomatic during ECG acquisition but found that patients with diagnostic ECGs were more likely to present sooner after symptom onset in comparison to patients with normal and nonspecific ECGs (47.4% and 44.4%, respectively).

Unlike the Welch et al.[13] report, in which patients with documented myocardial infarctions were studied, our investigation involved a cohort of general ED chest-pain patients. In a similar ED population, Singer et al.[30] found that the negative predictive value of a normal or nonspecific ECG did not improve with a longer time from onset of symptoms, at least up to 12 hours. Our study further addressed the utility of the ECG by focusing on the presence or absence of symptoms during a single ECG acquired at ED presentation. In our study, patients who were symptomatic had a more prolonged time from symptom onset and duration of symptoms than did those who were asymptomatic at ED presentation. Patients with adverse outcomes were representative of the overall groups in that they had similarly disparate duration of chest-pain symptoms. Although the presence of symptoms did not appear to increase the utility of the ECG in our study cohort, further investigation may be warranted to determine whether there is a relationship between duration of symptoms and outcomes for patients with ACS.

In addition, although we report similar proportions of patients in each group with multiple episodes of chest pain, we do not know which patients experienced a more stuttering pattern to their chest-pain symptoms that may be more indicative of ACS. Further studies are needed to address ECG findings on patients with intermittent chest-pain symptoms and to address serial ECG changes in patients both in the presence and absence of chest-pain symptoms. Normal and nonspecific ECG findings in asymptomatic patients may in fact reflect resolution of an ischemic event, with pseudonormalization of the ECG.

LIMITATIONS

This study has several limitations that warrant discussion. Consistent with our overall ED population, our study cohort was comprised of a majority of black and female patients. This may limit the generalizability of our findings to other patient populations. Although we did not assess interrater reliability for ECG interpretation, studies published elsewhere have demonstrated that the classification system used in this study is reliable.[36,37] We collected information regarding whether symptoms were present at the time of ED arrival, not specifically during ECG acquisition. Because we strive to meet the guideline goal of ECG provided within 10 minutes of arrival, to obtain the ECG before treatment, and to have the treating physician complete the clinical data form immediately after patient evaluation, we assumed that the presence of symptoms on arrival equated with the presence of symptoms at the time of ECG acquisition. Last, we do not report here on outcomes for patients with abnormal ECG findings. As such, we cannot report the sensitivity, specificity, and positive and negative predictive values for the normal and nonspecific ECG classifications studied.

CONCLUSIONS

Our findings build upon the existing knowledge that normal or nonspecific ECG findings do not exclude adverse cardiovascular events. Emergency physicians striving to identify patients at low risk for ACS should neither be reassured nor make disposition decisions on the basis of a single normal or nonspecific ECG, irrespective of patient symptoms. This study demonstrates that the presence or absence of symptoms during a single normal or nonspecific ECG did not help to risk stratify a broad group of ED patients with potential ACS.

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