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Screening Patients With Chest Pain in the Emergency Department Using Electron Beam Tomography: A Follow-up Study

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OBJECTIVES The high sensitivity of electron beam tomography (EBT) in the detection of coronary artery calcium (CAC) and obstructive coronary artery disease prompted us to investigate the association between CAC detection and future cardiac events in patients with acute chest pain syndromes requiring hospitalization.

BACKGROUND Three studies have documented that EBT is a rapid and efficient screening tool for patients admitted to the emergency department (ED) with chest pain, but there is a paucity of long-term follow-up data on these chest pain patients.

METHODS We conducted a prospective observational study of 192 patients admitted to the ED of a large tertiary care hospital for chest pain syndromes. Upon admission, patients underwent EBT scanning in addition to the usual care for chest pain syndromes. During the 17-month enrollment period, 221 patients were scanned (54% men with a mean age of 53 ± 9 years). Average follow-up was 50 ± 10 months using chart review.

RESULTS Fifty-eight patients had coronary events confirmed by a blinded medical record review. The presence of CAC (a total calcium score >0) and increasing score quartiles were strongly related to the occurrence of hard cardiac events including myocardial infarction and death ($p < 0.001$) and all cardiovascular events ($p < 0.001$). Stratification by age- and gender-matching further increased the prognostic ability of EBT (for scores above vs. below the age- and gender-matched CAC scores; odds ratio: 13.1, 95% confidence intervals: 5.62, 35.9).

CONCLUSIONS These data support previous reports demonstrating that the presence of CAC in a symptomatic cohort is a strong predictor of future cardiac events. This study supports the use of EBT in a symptomatic cohort with prompt discharge of those patients with negative scans. Furthermore, the absence of CAC is associated with a very low risk of future cardiac risk events in this population over the subsequent seven years (annual event rate <1%). (J Am Coll Cardiol 2001;38:105–10) © 2001 by the American College of Cardiology

Electron beam tomography (EBT) is a sensitive, accurate, quantitative and reproducible method to detect coronary artery calcium (CAC), a marker of plaque burden (1–4). Studies have demonstrated that the absence of CAC is associated with a very low event rate in symptomatic (5,6) and asymptomatic cohorts (7–10).

Every year over 1.5 million patients are admitted to the hospital after presenting to the emergency department (ED) with chest pain (11). Only a small percentage of these admitted persons have acute coronary syndromes, and the vast majority of patients are discharged with noncardiac diagnoses. Patients who present to the ED with equivocal or indeterminate findings on initial evaluation are commonly admitted to the hospital. Three studies have documented that EBT is a rapid and efficient screening tool for patients admitted to the ED with chest pain and nonspecific electrocardiograms (ECG) (12–14). The reluctance to accept this modality in the ED setting has been due to a paucity of long-term follow-up data on these chest pain patients (15). Thus, we sought to follow patients originally scanned in an ED upon presentation with chest pain and follow this group for seven years for subsequent cardiac events.

METHODS

Patient population. Harbor-UCLA Medical Center is an urban county teaching hospital. The annual ED census is 90,000 patients. The study was conducted between April 1, 1992 and August 30, 1993. Patients were eligible for the study if they were 30 years of age or older, presented to the ED with chest discomfort lasting 20 min or more within the past 12 h, had a nondiagnostic ECG and were believed to require admission to exclude myocardial infarction (MI).

Unstable patients exhibiting systolic blood pressure of <90 mm Hg or >180 mm Hg, heart rate <50 beats/min or >120 beats/min, pulmonary rales of at least two-thirds of the way up to the posterior thorax, chest X-ray diagnostic of

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Abbreviations and Acronyms

CAC = coronary artery calcium
CI = confidence interval
CS = calcium score
EBT = electron beam tomography
ECG = electrocardiogram
ED = emergency department
Hu = Hounsfield unit
MI = myocardial infarction
OR = odds ratio

significant congestive heart failure, ventricular tachycardia >10 beats/min, ventricular fibrillation, rapid atrial fibrillation (>120 beats/min) unresponsive to treatment, complete heart block, symptomatic Mobitz type I second-degree atrioventricular block and Mobitz type II block unresponsive to treatment were excluded from the study. Patients with ECG evidence of prior MI, coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty or chest pain unresponsive to treatment were excluded. Patients with known or suspected pregnancy were excluded. Patients with ST segment elevation >1 mm in two consecutive leads or evidence of significant ischemic T wave inversion of ≥5 mm were also excluded from the study.

Stable patients meeting entrance criteria underwent informed consent and were scanned. The EBT scanner was available from 7 AM to 11 PM, five days a week. This study was approved by the Institutional Review Board at Harbor-UCLA Research and Education Institute.

EBT protocol. EBT CORONARY SCAN PROTOCOL. The EBT studies were performed with the Imatron C-150XL Ultrafast computed tomographic scanner (Imatron, San Francisco, California) in the high-resolution volume mode using a 100-ms exposure time. Electrocardiographic triggering was employed at 80% of the R-R interval, so that each image was obtained at the same point in diastole. Proximal coronary artery visualization was obtained without contrast medium injection, and at least 30 consecutive images were obtained at 3-mm intervals beginning 1 cm below the carina and progressing caudally to include the proximal coronary arteries. Total radiation exposure using this technique was <1 rad per patient.

The lesion score was calculated by multiplying the lesion area by a density factor derived from the maximal Hounsfield unit (Hu) within this area, as previously described (1). The density factor was assigned in the following manner: 1 for lesions whose maximal density was 130 to 199 Hu, 2 for lesions 200 to 299 Hu, 3 for lesions 300 to 399 Hu and 4 for lesions >400 Hu. A total calcium score (CS) was determined by adding individual lesion scores from each of four anatomic sites (left main, left anterior descending, circumflex and right coronary arteries). Neither patients nor treating physicians were aware of the results of the coronary scan.

Determination of end points. Follow-up was done by hospital record review by an investigator blinded to EBT data. Standard coronary disease risk factors (e.g., hypercholesterolemia, hypertension, diabetes, smoking and family history of premature coronary disease) were obtained from direct measurements from the hospital chart. Patients were determined to have hypercholesterolemia if they had a total fasting cholesterol of >240 mg/dl or increased low-density cholesterol (>160 mg/dl) or decreased high-density cholesterol (<35 mg/dl) or were on cholesterol-lowering medication. Subjects were identified with hypertension if they had repeated elevated measures of blood pressure (>140/90) or were on antihypertensive therapy. Participants currently using insulin or oral hypoglycemic agents were classified as diabetic, as well as patients having fasting blood sugar ≥126 mg/dl or random blood sugar ≥200 mg/dl. Cigarette smoking was defined as current use of >10 cigarettes per day. Follow-up time was determined as the period between patient enrollment (scan date) and last contact (inpatient or outpatient) in the medical record. All end points were determined by consensus of three reviewers blinded to the EBT results and previous hospitalizations. Patients with acute MI had two of three criteria: chest pain lasting >30 min, rise and fall of creatine kinase with MB fraction >4% and new pathologic Q waves of >0.04 s duration (16). Coronary revascularization procedures, ischemic stroke (by standard neurological and computed tomographic criteria) and subsequent hospitalization for angina were included. Only cardiac death, either sudden death associated with a chest pain syndrome or assessed by autopsy, was included. Noncardiac deaths (n = 5) were excluded from analysis. Only one event was counted for each patient, in the following order of importance: coronary death, MI, revascularization procedure, stroke and hospitalization for angina.

Statistical analysis. Means were expressed ± SD. To examine the relation of incident MI, cardiac death, revascularization and hospitalization for angina and stroke, the Student *t* test was used. Multivariate logistic regression analyses were performed using models with the occurrence of hard events and any cardiovascular events as the dependent variable. Independent variables were selected for inclusion in the models from those variables that were significantly correlated with outcome on univariate regression analysis. The analyses were performed using traditional risk factors (derived from the initial admission to the ED), including age, race, gender, elevated total cholesterol, hypertension, current cigarette smoking, diabetes mellitus and family history of premature heart disease. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated from the multivariate logistic regression variable estimates.

RESULTS

Of the 221 patients originally scanned, 13 were excluded from follow-up due to acute cardiac event upon initial

Table 1. Baseline Clinical Characteristics

	No Events	Events	All Patients
Number of patients (n)	134	58	192
Age (mean ± SD)	52 ± 10	56 ± 10	53 ± 10
Men (%)	53	56	54
Race (%)			
Caucasian	32	45	36
African American	23	29	25
Asian American	15	10	14
Hispanic	30	14*	26
Hypertension (%)	55	74*	61
Diabetes (%)	22	27	24
Dyslipidemia (%)	32	48*	37
Premature family history (%)	21	36*	26
Smoking (%) current	32	46*	36

*$p < 0.05$ prevalence in no events versus events.

presentation. Follow-up was obtained in 192 patients of the remaining 208 (92%), mean age of 53 ± 9 years. Average follow-up was 50 ± 10 months (1 to 84 months). Eighty-eight (46%) were women (mean age: 55 years ± 10 years), 104 were men (mean age: 52 years ± 12 years).

Of the 192 patients, 69 (36%) were Caucasian, 48 (25%) were African American, 26 (14%) were Asian American and 49 (26%) were Hispanic. There were no significant differences in the prevalence of CAC (score >0) in different racial groups, except Hispanics (white 72%, African American 52%, Asian American 69%, Hispanic 47%). Prevalence of coronary calcium was significantly lower among Hispanics as compared with Caucasians (47% vs. 73%, $p = 0.004$). Hypertension, hypercholesterolemia, premature family history and tobacco use were all significantly more prevalent among those who suffered cardiac events as compared with those patients in the no event group ($p < 0.05$ for all measures).

During the follow-up period, 58 subjects (30%) had cardiac events. There were 30 (15.6%) hard events confirmed by medical records (11 cardiac deaths, 19 nonfatal MIs) and 28 (14.6%) other cardiovascular events (9 bypass surgeries, 4 angioplasties, 11 hospitalizations for angina and 4 ischemic strokes). Racial differences with regard to coronary events were evaluated. Clinical characteristics are presented in Table 1. Hispanics had a significantly lower coronary event rate when compared with Caucasians. These differences persisted after controlling for age, standard cardiac risk factors and gender using logistic regression. However, these differences were not significant once the presence of coronary calcium was added to the model. No other racial differences were noted in this study.

For the entire study group, scores ranged from 0 to 4,607. The 25th, 50th and 75th percentile scores were 0, 4 and 332, respectively. For hard events (MI and cardiac death), there were no events in the first quartile, 1 in the second quartile, 10 in the third quartile and 19 in the fourth quartile. For total cardiovascular events (n = 58), there were 2 in the first quartile, 1 in the second quartile, 27 in the third quartile and 27 in the fourth quartile. The mean CS for those who did not suffer a cardiac event was 240 ± 698 as compared with 595 ± 636 for those who suffered a hard event ($p = 0.009$ as compared with those in the no event group) and 446 ± 550 for those with any cardiovascular events ($p = 0.03$ as compared with those in the no event group).

Table 2. Electron Beam Tomography for Hard and All Coronary Events at Various Calcium Score Thresholds

Threshold	Sensitivity	Specificity	PPV	NPV	Overall Accuracy
Hard Events					
>0	1.00	0.47	0.26	1.00	0.55
>4 (median)	0.97	0.51	0.27	0.99	0.58
>332	0.63	0.81	0.39	0.92	0.79
All Events					
>0	0.97	0.55	0.48	0.97	0.68
>4 (median)	0.93	0.59	0.55	0.95	0.69
>332	0.47	0.83	0.55	0.78	0.72
≥50%	0.88	0.60	0.49	0.92	0.69
≥75%	0.64	0.72	0.49	0.82	0.69

NPV = negative predictive value; PPV = positive predictive value.

The sensitivity, specificity, positive and negative predictive values and overall accuracy are listed in Table 2 for different scoring thresholds and age- and gender-adjusted thresholds. The annualized event rate (all cardiovascular events) was 0.6% for the 76 subjects with a CAC score of 0 compared with 13.9% per year for the 38 subjects with a CAC score >400 ($p < 0.001$). There was a graded relation between the CAC score category and the incidence of cardiovascular event (Fig. 1). Twenty-two of 38 patients with scores >400 had cardiac events during the follow-up (positive predictive value 58%). Cox proportional-hazards regression showed CAC to be associated with a greater risk for having a new cardiovascular event independent of age, gender, race and other risk factors. Those with any CAC had an increased risk of new cardiovascular events (OR: 27.8, 95% CI: 1.88, 815, $p = 0.02$).

Adjustment for age and gender further risk stratified patients, those with CAC in the third and fourth quartiles had an RR of 13.1 (95% CI: 5.6, 36, $p < 0.001$) for new cardiovascular events as compared with those in the lower two quartiles (Fig. 2). Twenty-eight of 30 hard cardiac events occurred in patients with above average age- and gender-adjusted scores (51% to 99%). A majority of patients who suffered a hard event (MI or death) had a CAC score in the upper range of normal (88% >50th percentile, 64% >75th percentile). The positive predictive value over a short follow-up period was 49% for both groups. Fifty-one of 58 (88%) total cardiovascular events occurred in the top two quartiles of age- and gender-adjusted scores. Multivariate logistic regression analysis demonstrated CAC score and age- and gender-matched calcium percentiles to be the strongest predictors of future events. Age, male gender and hypertension were the only other independent predictors of future cardiovascular events in the model.

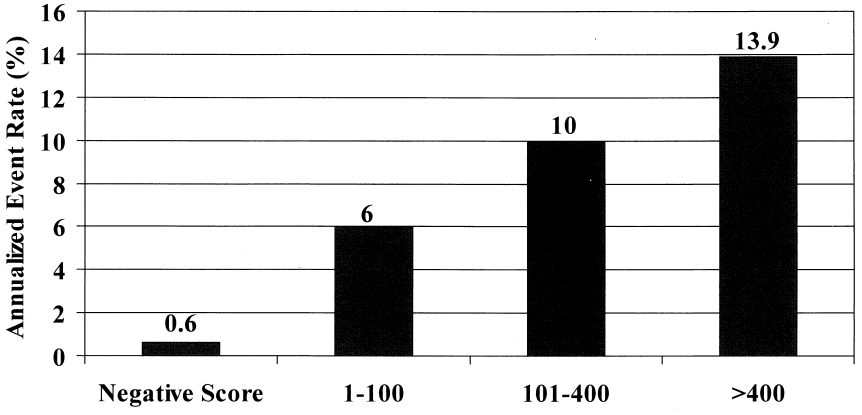

Figure 1. Annualized rates for future cardiovascular events by Cox proportional-hazards regression. Patients with scores >400 had an event rate of 58% over the entire study, with an annualized event rate of 13.9%. This was significantly greater than the 0.6% annual event rate of those with scores of zero ($p < 0.001$).

These results are summarized in Table 3, along with corresponding OR and CI.

DISCUSSION

Coronary artery calcification is highly predictive of future cardiac events. Every prognostic study of EBT demonstrates that CAC burdens predict future cardiac events (5–10). This study, representing a long follow-up of symptomatic persons presenting to the ED with chest pain, is consistent with other studies, demonstrating a graded relation between the extent of CAC and the incidence of future cardiovascular events. This study demonstrates that CS percentiles, based on patient age and gender, are better predictors than absolute CS and categorical risk factors. Detrano et al. (6) examined the prognostic value of EBT CS for predicting cardiovascular events in 491 patients undergoing cardiac angiography and found a 10-fold event rate increase in patients with CS over the 75th percentile as compared with those below the 25th percentile (OR: 10.8, 95% CI: 1.4 to 85.6). Logistic regression including gender, age, CS and angiographically diseased vessels showed that only EBT CS predicted events. This study, also in symptomatic patients, demonstrates a similar increase in predictive power. Similarly, studies of asymptomatic persons all demonstrate highly significant event prediction using CAC scores (7–10).

Calcium detection and events. All cases of cardiac death and MI occurred in patients with CAC. One case of percutaneous revascularization and one ischemic stroke occurred in the absence of CAC. Both the treating physician and patient were blinded to the result of the EBT led to the relatively low rate of revascularization and significant rate of fatal and nonfatal MI. This blinding increases the likelihood that this study was free of treatment bias (where patients with positive scores have increased utilization of pharmacologic therapy that can prevent future events), which most likely leads to an underestimation of the power of CAC to predict future events (7–10). Persons with coronary calcium have been reported to be more likely to

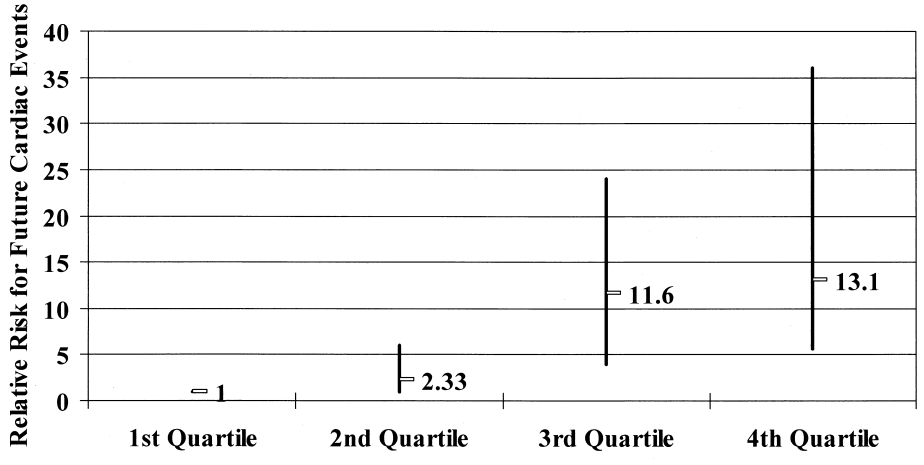

Figure 2. Relative risks for total cardiovascular events, using age- and gender-adjusted quartiles by multivariate logistic regression. The relative risk of those patients with high age- and gender-adjusted scores (>75th percentile) was 12-fold higher than those with no or little coronary calcium (0 to 25th percentile). Confidence intervals (95%) are displayed for each quartile.

Table 3. Multivariate Analyses of the Association of Coronary Artery Calcium Scores and Traditional Risk Factors With All Events

Variable	Odds Ratio	95% CI
Units of age (per 10 years)	3.29	1.41, 8.27
Family history	1.81	0.86, 3.77
Tobacco use	1.38	0.69, 2.77
Hypertension	2.27	1.09, 4.90
High cholesterol	1.82	0.93, 3.59
Diabetes	1.14	0.51, 2.52
Male gender	2.19	1.14, 4.27
CS (above zero)	27.8	1.88, 815.6
CS percentile >50%	11.6	3.94, 37.6
CS percentile >75%	13.1	5.62, 36

CI = confidence interval; CS = Calcium score based on age- and gender-matching.

undertake preventive health measures, including beginning cholesterol- or blood pressure-lowering medications, starting aspirin, beginning an exercise program, following a low-fat diet or quitting smoking (17).

The lower incidence of coronary events in Hispanics as compared with Caucasians in this study is significant ($p = 0.01$). The difference in event rates was at least partially explained by the lower prevalence of coronary calcium among Hispanics in this study (47%). This lower atherosclerotic burden among Hispanics might explain the lower overall mortality rates from coronary disease (as compared with Caucasians) reported in large studies (18).

Calcium scanning in the ED. The use of EBT in an ED setting has been previously reported (12,14). These studies demonstrate that patients presenting to the ED with angina-like chest pain and normal or indeterminate ECG findings may be effectively triaged based upon results of the EBT scan. These studies demonstrate sensitivities of 98% to 100% for identifying patients with acute MI. The high sensitivity and negative predictive value may allow early discharge of those patients with nondiagnostic ECG and negative EBT scans (scores = 0). Four month follow-up demonstrated no cardiac events in the study by Laudon et al. (12), concluding that EBT is a rapid and efficient screening tool for such patients in the ED setting. The reluctance to utilize the test more widely for patients with chest pain stems from the limited follow-up in these studies (15). The results of this observational clinical study extend follow-up to seven years, supporting the use of EBT in a symptomatic cohort, with prompt discharge of those patients with negative scans. The risk of immediate MI is negligible, and the annual event rate is well below <1%.

The use of EBT as a risk assessment tool should improve the physician's ability to stratify individuals at high risk of events, to whom aggressive treatment of risk factors for coronary artery disease can be more appropriately directed, and help direct the admission or discharge of emergency room patients. Almost half of all symptomatic patients with age- and gender-adjusted scores >50th percentile had a cardiovascular event in the next 50 months (positive predictive value 49%).

Study limitations. The number of patients enrolled was small. While the scanner was open 50% of the time, many patients who fit the entry criteria were not enrolled from the ED. While there was no obvious enrollment bias, it is important to note that this study of symptomatic patients was not inclusive of all types of patients presenting to the ED. Patients with prior MI or revascularization or ECG or enzyme changes consistent with an acute MI were felt to need admission regardless of coronary calcium and were, thus, not included. The racial diversity was fair; however, the small number of patients precludes any assessment of racial differences.

The event rate of this study group was very high, even during the relatively short follow-up period. Thirty percent of patients had a cardiovascular event during the subsequent 50 months. This was a symptomatic cohort, with a high incidence of cardiovascular risk factors, especially hypertension and diabetes. Neither patients nor treating physicians were aware of the results of the coronary scan. While this allowed an unbiased approach to the patient with regard to the treatment for chest pain, the utilization of cholesterol-reducing medications, aspirin and other antiatherosclerotic medications was subsequently low. The follow-up (mean 50 months, maximum up to eight years) was incomplete, and many patients, as this study was performed at a county facility, were lost to follow-up after only several months.

Our results imply that EBT may be a sufficiently powerful tool to be used in the ED to decide the need for admission in patients presenting with chest pain and nondiagnostic ECGs. To fully assess the potential of this tool, long-term prognostic power must be demonstrated in larger studies.

Conclusions. This study demonstrated that EBT is an efficient and safe test to use in patients presenting to the ED with acute chest pain, allowing rapid discharge with a negative scan. Furthermore, the absence of calcium implies a very low (0.6% annual) incidence of coronary events, whereas the presence of coronary calcium is an independent predictor of future cardiac events. These data support previous reports showing CAC, especially in age- and gender-matched cohorts, to be a very strong predictor of future cardiovascular events.

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