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Clinical Investigations

Improved Risk Stratification in Unstable Angina: Identification of Patients at Low Risk for in-Hospital Cardiac Events by Admission Echocardiography

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Summary

Background: Current protocols for risk stratification of patients with acute chest pain syndromes rely on clinical parameters and are oriented toward identification of patients at high risk for adverse cardiac events; however, this paradigm for risk stratification does not adequately address the observation that adverse cardiac events are relatively uncommon in this population. In an era of cost containment, consideration also should be given to identification of patients at low risk for adverse cardiac events, who may be safely discharged without expensive inpatient hospitalization.

Hypothesis: The purpose of this study was to develop echocardiographic predictors that identify unstable angina patients at low risk for adverse cardiac events and that discriminate between low- and high-risk patients.

Methods: The predictive accuracy of retrospectively determined echocardiographic predictors were compared in a population-based sample of 66 consecutive unstable angina patients undergoing echocardiography within 24 h of admission.

Results: Echocardiographic predictors of adverse events included wall motion score index ≥ 0.2, ejection fraction $\leq 40\%$, and mitral regurgitation severity > 2. One or more echocardiographic predictors of adverse events were present in 32 patients (48%). A composite echocardiographic predictor of adverse events was specific, had a high positive predictive value for the identification of high-risk patients, and discriminated between unstable angina patients at high and low risk for adverse cardiac events.

Conclusion: Echocardiographic predictors of adverse events are specific and discriminate between unstable angina patients at high and low risk for adverse cardiac events.

Key words: unstable angina, chest pain, risk stratification, echocardiography

Introduction

The clinical diagnosis of unstable angina accounts for more than 570,000 hospital admissions and 3 million patient-days in the United States each year.[1,2] Current protocols for risk stratification among patients presenting with acute chest pain syndromes are oriented toward identification of patients at high risk for adverse cardiac events and rely on conventional clinical parameters that are assessed by history, physical examination, and electrocardiography.[1–8] However, the current clinically based paradigm for risk stratification does not adequately address the observation that adverse cardiac events are relatively uncommon in this population.[4,9,10] Furthermore, clinical parameters associated with high risk have low specificities and positive predictive values, that is, many patients classified as high risk do not experience adverse cardiac events.[4,10]

In an era of cost containment, consideration also should be given to identification of patients at low risk for adverse cardiac events, who may be safely discharged without expensive in-patient hospitalization. This requires definition of diagnostic parameters with high specificity for the detection of low-risk patients, who are unlikely to experience adverse cardiac events, that is, parameters with high negative predictive

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values. In this context, admission echocardiography is more sensitive and specific than clinical parameters for the diagnosis of myocardial ischemia.[11–16] Echocardiography can be performed and interpreted rapidly, provides prognostic information regarding left ventricular function and valvular integrity, and may identify alternate etiologies for acute chest pain syndromes.[15,16]

In this study, admission echocardiographic parameters were identified and evaluated for their ability (1) to identify patients at low risk for in-hospital adverse cardiac events, and (2) to discriminate between low-risk and high-risk patients.

Materials and Methods

Patient Population

The study sample was derived from a previously reported population of 393 patients with unstable angina consecutively admitted to our medical center over 18 months.[3] Unstable angina was defined as new onset angina, accelerated angina, angina at rest, or postinfarction angina. Myocardial infarction was excluded by measurement of serum creatine kinase levels. In all, 71 patients who underwent transthoracic echocardiography within 24 h of admission were identified; 66 videotapes of echocardiographic studies were available for review. No patient underwent coronary revascularization prior to echocardiography.

Outcomes

Adverse cardiac events, documented for the duration of hospitalization, included death, myocardial infarction occurring ≥ 24 h following admission, congestive heart failure, and ventricular tachyarrhythmias. The diagnosis of congestive heart failure required the demonstration of new pulmonary crackles associated with either jugular venous distention or an S_3 gallop. Ventricular tachyarrhythmias included ventricular fibrillation or ventricular tachycardia of more than 30 s duration or that required pharmacologic therapy.

Echocardiography

All transthoracic echocardiographic examinations were performed within 24 hours of admission using Sonos 500 or 1000 (Hewlett-Packard Company, Andover, Mass.) or CFM 750 (VingMed Sound, Santa Clara, Calif.) ultrasound units. Data were stored on super-VHS videotapes. Three echocardiographic parameters were evaluated: regional wall motion, left ventricular ejection fraction (LVEF), and mitral regurgitation (MR) severity.

Regional wall motion: Regional wall motion was analyzed by two independent readers and scoring was performed using a model that divided the left ventricular myocardium into 12 segments, each representing approximately equal myocardial mass.[17] The wall motion of each segment was scored semiquantitatively (0 = normal, 1 = hypokinetic, 2 = akinetic, 3 = dyskinetic) relative to the segment with the best systolic thickening. The resulting wall motion score index (WMSI), calculated as the sum of the individual segment wall motion scores divided by the number of scored segments, was a measure of regional heterogeneity in systolic function.

Left ventricular ejection fraction: Left ventricular ejection fraction (LVEF) was estimated visually by two investigators[18,19] and calculated independently by a third investigator using the apical biplane method of disks.[19]

Mitral regurgitation: The severity of MR was determined by visual inspection of the diameter of the color Doppler MR signal at the mitral orifice in at least two views and was scored semiquantitatively (0 = none, 1 = trivial, 2 = mild, 3 = moderate, 4 = severe).

Risk Stratification

Echocardiographic predictors of adverse outcomes: For each echocardiographic parameter, a threshold analysis was performed to determine the parameter value that most powerfully discriminated between patients with and without adverse outcomes (the threshold value). Serial chi-square tests were performed across the range of parameter values, and the parameter value with the highest chi-square p value was considered the threshold value.

This analysis identified the following echocardiographic predictors of adverse outcome: (1) WMSI ≥ 0.2, (2) LVEF < 40%, and (3) MR severity ≥ 2. Patients in whom one or more of the echocardiographic predictors were present were categorized EchoPos.

Statistical Analysis

The study sample and parent population were compared with regard to demographic characteristics and the occurrence of adverse outcomes, using independent *t*-tests and chi-square tests when appropriate. Interobserver variability for echocardiographic parameters (LVEF, WMSI) was described by means and standard deviations of the differences between parameter values obtained by the two observers. Correlations between echocardiographic parameters (LVEF, WMSI, MR severity) were determined by Spearman's rho. Visual estimates of LVEF were compared with calculated values using the Pearson r, paired *t*-tests, and the method of Bland and Altman.[20]

Results

Population

The study included 66 patients, (37 men, 29 women) with a mean age of 67 ± 16 (± standard deviation) years. The study group was similar to the parent population with respect to age (mean age 64 ± 15 years, p = 0.569), gender (57% men, X^2 = 0.131, p = 0.936), and previously identified clinical predictors of in-hospital cardiac events, such as admission ST-segment

TABLE I Clinical characteristics of subjects

	% (n = 66)
Age ≥ 70 years	51
Male	56
Diabetes mellitus	35
Previous MI	23
MI within previous 14 days	5
IV nitroglycerin required	36
ST-segment depression on ECG	24

Abbreviations: MI = myocardial infarction, IV = intravenous, ECG = electrocardiogram.

TABLE II Echocardiographic predictors of adverse cardiac events

	No. of patients	SENS	SPEC	PPV	NPV	p Value
WMSI ≥ 0.2	23	75	73	39	93	0.002
LVEF ≤ 0.40	16	67	86	53	92	<0.001
MR ≥ 2	26	69	70	37	90	0.009
EchoPos	32	100	59	38	100	<0.001

Abbreviations: SENS = sensitivity, SPEC = specificity, PPV = positive predictive value, NPV = negative predictive value, WMSI = wall motion score index, LVEF = left ventricular ejection fraction, MR = mitral regurgitation, EchoPos = presence of one or more echocardiographic predictors.

changes, recent myocardial infarction, use of beta blockers, need for intravenous nitroglycerin, and incidence of diabetes mellitus (Table I).[3]

Outcomes

One or more adverse cardiac events occurred in 13 patients (20%); the incidence of adverse events in the parent population was 18%. In this study, three patients died before hospital discharge, five suffered delayed myocardial infarction, six experienced ventricular tachyarrhythmias, and seven developed congestive heart failure.

Echocardiographic Predictors

Wall motion score: Poor image quality precluded regional wall motion analysis in three patients (4%). Of the remaining 63 patients, 31 had discrete regional wall motion abnormalities. The WMSI ranged from 0 to 1.33, with a mean value of 0.25 ± 0.39. The mean difference between values reported by each observer was 0.01 ± 0.05. Threshold analysis identified a WMSI ≥ 0.2 to be the threshold value, that is, the WMSI value that best discriminated between patients with and without adverse cardiac events. Twenty-three patients (35%) had a WMSI ≥ 0.2.

Left ventricular ejection fraction: LVEF was visually estimated in 62 patients with adequate images (94%). The mean value was 54.8 ± 17.1% (range 18–80%) with an average interobserver difference of 1.0 ± 3.5%. Visual estimates of LVEF correlated well with values calculated using the apical biplane method of disks (55.2 ± 17.5%, r = 0.94). The mean difference (bias) between values obtained by these methods was small and not significant (2.7 ± 6.2%). An LVEF value of 40% was the threshold value that best discriminated between patients with and without adverse cardiac events. Sixteen patients (24%) had an LVEF < 40%.

Mitral regurgitation: Of 63 patients (96%) in whom color Doppler interrogation of the mitral valve was adequate, 44 had MR; it was trivial in 18 patients, mild in 25 patients, and moderate in 1 patient. No patient had severe MR. In all but one patient, the two observers agreed on the assessment of MR severity. Mild or more MR (MR ≥ 2), present in 39% of patients, was identified as the threshold value that best discriminated between patients with and without adverse cardiac events.

Composite echocardiographic predictor (EchoPos): One or more echocardiographic predictors of adverse cardiac events were present in 32 patients (48%), designated EchoPos. In 34 patients (52%), none of the echocardiographic predictors were present.

In addition, admission echocardiography identified clinically relevant pathology in nine patients (14%) including severe aortic stenosis (aortic valve area < 1.0 cm^2) in four patients, significant pericardial effusion in two patients, severe pulmonary hypertension in two patients, and probable pulmonary embolism in one patient.

Left ventricular ejection fraction correlated inversely with both WMSI and MR severity (−0.78, p < 0.0001 and −0.52, p < 0.0001, respectively). The direct correlation between WMSI and MR severity was also significant (0.54, p < 0.0001).

Freedom from Adverse Cardiac Events

Each individual echocardiographic predictor discriminated between patients with and without adverse cardiac events (p = 0.036, Table II). Only EchoPos had 100% sensitivity for the occurrence of adverse cardiac events. The positive predictive value of EchoPos was 38% (p < 0.01) (Fig. 1). EchoPos had a negative predictive value of 100% (i.e., absolute freedom from adverse cardiac events was predicted only by the absence of all echocardiographic predictors). Because of its high specificity (59%), EchoPos discriminated between patients with and without adverse cardiac events (Table II, Fig. 2).

Discussion

The findings of this study suggest that information obtained from transthoracic echocardiography performed within 24 h of hospital admission can be used for accurate and safe triage of patients with unstable angina. Three easily measured echocardiographic variables (WMSI ≥ 0.2, LVEF ≤ 40%, and MR ≥ 2) discriminated between unstable angina patients at high risk and low risk for in-hospital adverse cardiac events. A

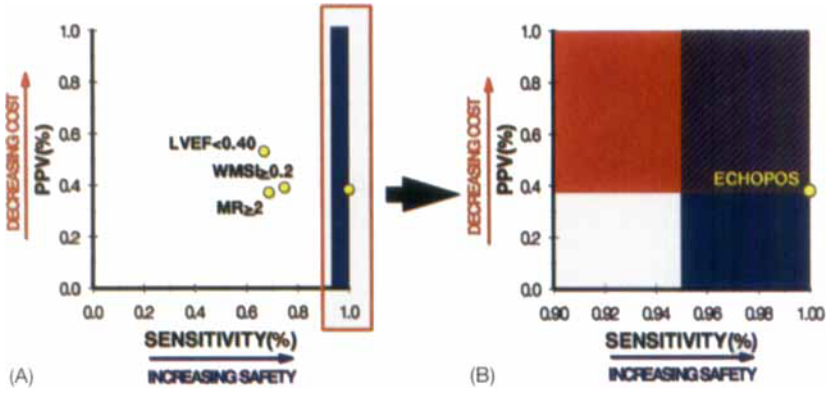

FIG. 1 Sensitivities and positive predictive values of echocardiographic predictors. In this figure, sensitivities are displayed on the horizontal axis and positive predictive values (PPV) are displayed on the vertical axis. As sensitivity increases, the false negative rate decreases, resulting in increasing certainty that patients at risk for adverse events are not missed (increasing safety). As PPV increases, the false positive rate decreases and unnecessary admissions are avoided (decreasing cost). (A) Only EchoPos had a sensitivity of 100%. (B) The area within the rectangle has been magnified. LVEF = left ventricular ejection fraction, WMSI = wall motion score index, MR = mitral regurgitation, ECHOPOS = presence of one or more echocardiographic predictors.

composite echocardiographic parameter, EchoPos, not only identified the small group of patients with in-hospital adverse cardiac events, but also identified the large cohort of patients with benign outcomes.

Risk Stratification in Unstable Angina—the Current Paradigm

Several clinical parameters have been identified previously as independent and sensitive predictors of in-hospital adverse cardiac events in patients with unstable angina.[1–8] Accordingly, the Agency for Health Care Policy and Research (AHCPR) has recommended the implementation of clinical practice guidelines based on these clinical parameters.[2,10]

The current paradigm is exclusively oriented toward patient safety, that is, identification of high-risk patients. Thus, a pre-requisite to any alteration of this paradigm is maintenance of status quo, that is, 100% sensitivity for the identification of patients with adverse cardiac events. Clinically, this 100% sensitivity is obtained at the expense of a low positive predictive value, such that few patients identified clinically as high risk actually experience adverse cardiac events, resulting in unnecessary costs.[4,9,10]

Identification of Unstable Angina Patients at Low Risk—a Paradigm Nudge

In an era of cost containment, it may be appropriate to broaden this paradigm to identify patients at low risk for adverse cardiac events, who might be managed more cost effectively. A prerequisite for safe application of the broadened paradigm is the identification of predictors with 100% nega-

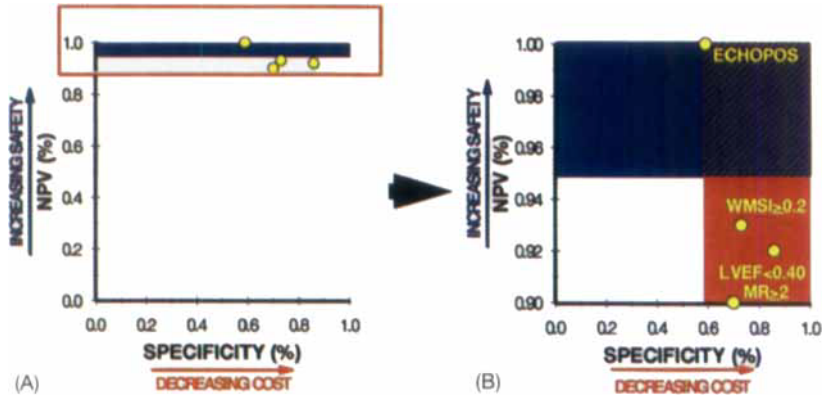

FIG. 2 Specificities and negative predictive values of echocardiographic predictors. In this figure, specificities are displayed on the horizontal axis and negative predictive values (NPV) are displayed on the vertical axis. As NPV increases, the false negative rate decreases, resulting in increasing certainty that all patients at risk for adverse events are identified (increasing safety). As specificity increases, the false positive rate decreases and unnecessary admissions are avoided (decreasing cost). (A) All of the echocardiographic predictors had NPVs >90%. (B) The area within the rectangle has been magnified. EchoPos was the only echocardiographic predictor with an NPV of 100%. Abbreviations as in Figure 1.

tive predictive value, that is, predictors whose absence assures freedom from adverse cardiac events. Admission echocardiography may provide a solution to this problem. The only echocardiographic predictor with 100% sensitivity for identification of high-risk patients was EchoPos, a composite predictor that incorporated each echocardiographic predictor (Fig. 1). Because of its high positive predictive value (38%), EchoPos achieved the prerequisite level of safety (100% sensitivity) at a potentially lower cost (i.e., higher positive predictive value, Fig. 1). EchoPos was the only echocardiographic predictor with 100% negative predictive value, that is, the only echocardiographic predictor that identified all patients who were ultimately discharged without experiencing an adverse cardiac event (Fig. 2). Because of its high specificity (59%), EchoPos reliably discriminated between patients at high risk and low risk (Table II, Fig. 2), and has the potential to facilitate the cost-effective triage of low-risk patients.

Admission Echocardiography—Significance of Individual Echocardiographic Predictors

As expected, resting left ventricular systolic function was a predictor for cardiac events. Several investigators have identified LVEF as an important prognostic indicator in patients with acute myocardial ischemia/infarction.[21–23] Since regional wall motion was scored relative to the segment with maximal systolic thickening, the WMSI reported in this study was an index of regional systolic heterogeneity, rather than merely a surrogate for global LVEF. Indeed, the correlation between WMSI and LVEF in this study would suggest that no more than 60% of the variation in global performance could be explained on the basis of regional variations in systolic function.

Severity of MR also was a powerful predictor of cardiac risk. Previous studies of acute myocardial infarction have demonstrated a worse prognosis for patients with MR.[15, 24, 25] A highly significant negative correlation was found between MR severity and LVEF; however, the exact cause of the MR observed in our patients could not be determined from the data in this study.

Finally, other pathologic conditions that may have accounted for the clinical presentation and that may have altered management strategies, such as severe aortic valve stenosis, significant pericardial effusion, possible pulmonary embolism, and pulmonary hypertension, were diagnosed by echocardiography in 14% of patients.

Limitations

The clinical data for this study were collected prospectively, whereas the echocardiographic data for this relatively small patient sample were analyzed in a retrospective fashion. This raises the possibility of selection bias involving the patients in whom early echocardiography was performed, since echocardiograms were ordered for clinical reasons by the treating physician. This may also explain the high frequency at which abnormalities such as MR and aortic stenosis were detected in this study and the low percentage of studies with poor image quality. Although this is a theoretical concern, the comparisons presented above indicate that the study population was not different from the original population in regard to demographic characteristics, frequency of adverse cardiac events, or incidence of any of the clinical variables previously shown to predict in-hospital adverse cardiac events.[3]

Statistically significant correlations were found between the various echocardiographic parameters; however, a multivariate analysis that would address the relative predictive power of the individual parameters was prohibited by the small number of patients and events in the study. Although the correlation between the echocardiographic parameters was statistically significant, evidence for their individual predictive power is provided by the observation that an echocardiographic parameter with 100% negative predictive power for the identification of patients without adverse cardiac events (EchoPos) could be discerned only by inclusion of the predictive information inherent in each of the echocardiographic predictors.

The lag time of up to 24 h between patient presentation and echocardiography could potentially have confounded the findings of this analysis, since ischemia might have resolved either spontaneously or due to anti-ischemic medication before patients were imaged. Improvement of regional systolic function with medical therapy had been described and may predict a good long-term outcome.[13] In addition, patients might have received medications that favorably altered left ventricular loading and inotropic conditions by the time the echocardiograms were performed, so that the severity of MR and left ventricular dysfunction might have been underestimated in this study. Despite this potential limitation, the echocardiographic predictors discriminated low-risk from high-risk patients. This speaks to the discriminatory power of the echocardiographic predictors identified in this study.

Conclusions

Echocardiography is a relatively inexpensive, noninvasive test that is widely available and can be performed and interpreted rapidly, especially in the era of digital image transmission.[26] Admission echocardiography can discriminate between patients with unstable angina at high risk and low risk for in-hospital cardiac events. Utilization of a composite echocardiographic predictor with a high negative predictive value for adverse cardiac events, that incorporates LVEF, WMSI, and MR severity, may be a cost-effective strategy that facilitates rational triage of patients with unstable angina. Implementation of a chest pain triage algorithm based on the expanded paradigm that includes echocardiographic identification of patients at "low risk" for adverse cardiac events requires validation in a prospective study. The safest and most cost-effective strategy for integrating clinical, echocardiographic, and stress testing data remains an open question and a fertile area for research.

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