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Utility Contrast Echocardiography in the Emergency Department

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The diagnosis and risk stratification of patients presenting with suspected cardiac chest pain to the emergency department (ED) is difficult, inefficient, and costly. Echocardiography can be used to directly detect myocardial ischemia through the identification of a new wall thickening (WT) abnormality. Contrast echocardiography provides further incremental benefit both for assessment of WT, as well as from the evaluation of myocardial perfusion. This review will discuss how echocardiography can be used to diagnose, risk stratify, and potentially reduce costs in patients with suspected acute coronary syndromes in the ED. (J Am Coll Cardiol Img 2010;3:197–203) © 2010 by the American College of Cardiology Foundation

The diagnosis of an acute coronary syndrome (ACS) has relied on the history, the presenting electrocardiogram (ECG) and serial cardiac serum biomarkers for decades. This practice has not changed even though a patient's description of their symptoms can be highly variable, and up to a quarter of patients with acute myocardial infarction (AMI) have no chest pain (CP) or a main complaint other than CP (such as dyspnea, fatigue, or abdominal discomfort) (1). Women are much more likely to present with atypical symptoms such as jaw rather than chest pain, or with nausea or vomiting (2). Of the estimated 5.6 million annual emergency department (ED) visits for CP, <10% present with ST-segment elevation (3). In a study of 3,814 patients presenting with CP to the ED, 93% of the presenting ECGs were called normal or nondiagnostic (4). The sensitivity of serum cardiac markers for an AMI is very poor until many hours after the onset of symptoms (5), and patients with unstable angina (UA) have no elevations of serum cardiac markers by definition (3). Single determinations of creatine kinase at the time of patient presentation have a sensitivity of only 36% for detecting AMI. The sensitivity increases to 69% at 4 h, and to 95% to 99% by 15 h (1). Likewise, cardiac troponins and myoglobin also have limited sensitivity early after the onset of ischemia.

Cardiac ischemia is the most common "life-threatening" cause of CP in patients presenting to an ED. However, only 10% to 30% of patients who present with CP are eventually diagnosed with an ACS (6–8). In the ACI-TIPI (Acute Cardiac Ischemia Time-Insensitive Predictive Instrument) study (9) that included 10,689 patients at least 30 years of age, presenting with chest, left arm, jaw, or epigastric pain or discomfort, dyspnea, or other symptoms suggestive of acute ischemia, an ACS was diagnosed in only 17% of patients (AMI in 8% and UA in 9%), whereas nonischemic cardiac conditions were diagnosed in 21% and noncardiac problems in 55%.

Although most patients end up having minor causes of CP, prolonged observation and extensive workups are currently required prior to discharge. The cost of excluding ACS is 8 to 10 billion dollars annually in the U.S. alone, and time consuming for both physicians and patients. On the other end of the spectrum, up to 11% of

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patients are inadvertently discharged from the ED with a missed AMI (average 2.1%), and UA is missed in up to 4% (5,10–12). This misdiagnosis and inappropriate discharge leads to increased mortality for those patients who have an AMI outside the hospital (12).

Thus, in patients with CP but without suggestive evidence of ACS at the time of presentation (such as the presence of ST-segment elevation, tall "peaked" T waves, ST-segment depression, or deep T inversions on the initial ECG, or elevated cardiac serum markers), a tool that could improve our diagnostic acumen for ACS, and help exclude cardiac CP in all other patients would be invaluable. Such a tool would need to detect either anatomically significant coronary artery disease, reduced perfusion to myocytes, or the consequences of abnormal perfusion (e.g., abnormal cardiac function). Ideally, such a tool would also be rapid, noninvasive, highly accurate, safe, and portable. In recent years, a variety of cardiac imaging modalities that can assess left ventricular systolic function, myocardial perfusion, or coronary anatomy have been evaluated for this purpose, including echocardiography, single-photon emission computed tomography (SPECT), cardiac magnetic resonance, and electron beam or multi-detector computed tomography. Among them, echocardiography is the only technology that can be performed rapidly at the patient's bedside, without having to discontinue monitoring or move the patient out of an acute care setting, even when the patient is still symptomatic and receiving ongoing treatment.

Even if a diagnosis of ACS is made expediently, risk stratification is still required to determine whether the patient should be referred for early invasive evaluation, or whether conservative management alone is adequate. High-risk clinical features such as recurrent angina at rest, elevated cardiac biomarkers, dynamic ST-segment depression, congestive heart failure, hemodynamic instability, high-grade ventricular arrhythmias, or a history of recent revascularization can help to identify patients most likely to benefit from early cardiac catheterization (3). Most patients with an ACS, however, do not present with these features, so ancillary imaging that can risk stratify patients quickly would also be invaluable.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome
AMI = acute myocardial infarction
CP = chest pain
ECG = electrocardiogram
ED = emergency department
MBF = myocardial blood flow
MCE = myocardial contrast echocardiography
MP = microvascular perfusion
mTIMI = modified Thrombolysis In Myocardial Infarction
NSTEMI = non–ST-segment elevation myocardial infarction
SPECT = single-photon emission computed tomography
UA = unstable angina
WT = wall thickening

Pathophysiology of ACS

Due to the autoregulatory capacity of the coronary microcirculation, resting myocardial blood flow (MBF) remains constant over a wide range of coronary driving pressures (13). Consequently, MBF does not fall below normal resting levels until a coronary obstruction exceeds 85% to 90% of the luminal area of an epicardial coronary artery (14). With such critical stenoses, supply/demand mismatch can result in angina occurring at rest, which is one of the 3 principal presentations of UA (3). The coronary lesion most commonly associated with the development of an ACS is characterized by erosion or disruption of an atherosclerotic plaque, with resultant nonocclusive thrombus formation which reduces resting MBF and leads to an ACS. UA and non–ST-segment elevation myocardial infarction (NSTEMI) share the same pathophysiology, with NSTEMI being a more serious manifestation of the process. An NSTEMI is associated with myocardial injury and detectable quantities of biomarkers. If there is no biomarker evidence of necrosis, the patient is determined to have UA (3).

Echocardiography in Suspected ACS

The use of 2D echocardiography to detect ACS is based on a close relationship between resting MBF and regional wall thickening (WT). Because myocardial contractility is a major determinant of myocardial oxygen consumption, reductions in resting MBF are followed within seconds by the development of hypokinesis (Fig. 1) (15). Normal resting MBF (1 $ml \cdot kg^{-1} \cdot min^{-1}$) is associated with WT of approximately 30%. With acute reductions in resting MBF, WT abnormalities develop within seconds. Thus, the assessment of WT provides a direct measure of the presence of myocardial ischemia. Even a brief coronary occlusion (5 to 15 min) results in severely reduced regional systolic function (15). Depending on the duration and severity of the ischemic insult, and the adequacy of reperfusion, these functional changes are evident for hours despite reperfusion, and may take up to 48 h to normalize (16–18).

The use of echocardiography to evaluate for WT abnormalities is a class I indication in patients with suspected myocardial ischemia but nondiagnostic ECG and negative cardiac serum markers (19).

Early studies evaluating echocardiography in patients presenting to the ED with CP found that WT had a high sensitivity for detecting AMI (92% to 93%) and cardiac ischemia (88%); however, the specificity was limited to 53% to 57%, and 78%, respectively (20,21). WT abnormalities can be detected even if patients present many hours after their index event (22). In patients who suffer an NSTEMI with subendocardial or even patchy myocellular necrosis, WT

abnormalities are persistent since WT is derived mainly from the inner 20% to 30% of the myocardium (23). Although wall motion abnormalities are present in patients with remote myocardial infarction, old scarred segments are often thinned, whereas wall thickness may be preserved in the setting of an ACS.

Incremental Benefits of Contrast Agents for Echocardiographic Detection of ACS

It is critical to evaluate WT of all segments accurately, so microbubble contrast agents must be considered to enhance delineation of left ventricular endocardial borders (24–26). It has recently been shown in a study where technically difficult patients received contrast agents that the percentage of visualized segments increased from 68% to 99%, and the proportion of segments with an identified WT abnormality increased from 16% to 23%. The detection of these abnormalities resulted in a direct impact on patient management (27). False negative studies, however, have also been reported in up to 1% of patients with a small AMI detected only by serum cardiac markers (19,20).

Myocardial contrast echocardiography (MCE) can also be used to assess microvascular perfusion (MP). Thus, MCE can directly detect reduced resting MBF as well as its consequences on WT. Microbubbles remain entirely intravascular, are hemodynamically inert, and have a microvascular rheology identical to that of red blood cells (28,29). These properties make microbubbles excellent tracers for assessing MBF.

Microbubbles reside exclusively within the vascular space, so they act as blood pool agents, and their concentration in the myocardium reflects the myocardial blood volume (MBV), 90% of which is in capillaries. Thus, steady-state contrast enhancement provides an assessment of capillary blood volume (30). At steady state during a continuous intravenous infusion of microbubbles, the number of microbubbles entering or leaving any microcirculatory unit is constant, and will depend on the flow rate. By destroying microbubbles with an ultrasound pulse, and then determining the rate of replenishment of microbubbles into tissue, microbubble (or red blood cell) velocity can be determined (MBF velocity) (31). In an ACS, reduced MBF of the ischemic segments will be manifested by both reduced MBF velocity as well as MBV, which will appear as slow contrast enhancement and a subendocardial perfusion defect.

Figure 2 shows echocardiographic images from a woman with no prior cardiac history presenting with dyspnea to the ED and a nondiagnostic ECG, demonstrating akinesis of the mid to distal septum, anterior wall, and apex in the apical 4-chamber view (Fig. 2A, end-diastole; Fig. 2B, end-systole, with akinetic

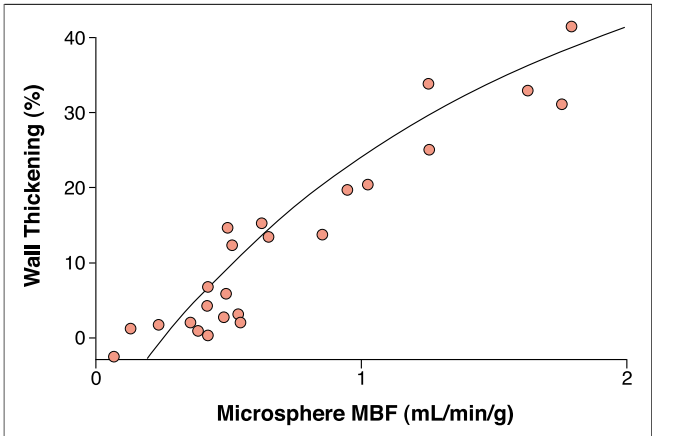

Figure 1. Relation Between MBF and WT

The echocardiographic detection of myocardial ischemia is based on the pathophysiologic relation illustrated in this figure. Normal resting myocardial blood flow (MBF) of 1 ml/min/g of tissue is associated with wall thickening (WT) of 20% in this experimental animal model. Reductions in resting MBF with a screw occluder are followed within seconds by the development of hypokinesis. Modified, with permission, from Leong-Poi et al. (15).

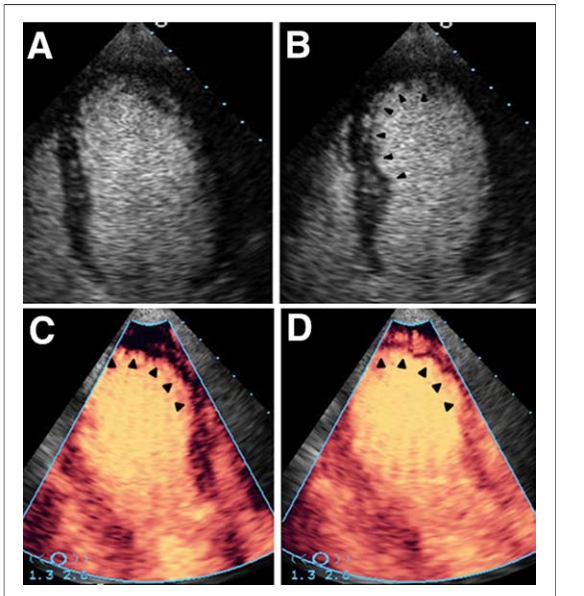

Figure 2. Echocardiographic Images of a Patient With CP

(A) End-diastolic apical 4-chamber view of the left ventricle. **(B)** End-systolic apical 4-chamber view of the left ventricle. Akinetic septum and apex delineated by **arrowheads**. **(C)** Apical 3-chamber view demonstrating a perfusion defect in the anterior septum **(arrowheads)**. **(D)** Apical 3-chamber view demonstrating a persistent subendocardial defect, with replenishment of microbubbles into the mid- and subepicardium of the septum **(arrowheads)**. CP = chest pain.

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territory delineated by arrowheads). Perfusion imaging using harmonic power Doppler was performed to evaluate resting MBF. This demonstrated a slow rate of replenishment of microbubbles into the anterior septum in the apical 3-chamber view (denoting either very slow antegrade flow in the left anterior descending coronary artery due to a critical stenosis, or a completely occluded left anterior descending coronary artery with slow collateral flow) (Fig. 2C). At a long pulsing interval of 8 cardiac cycles, however, nearly complete contrast enhancement of the entire akinetic territory except for a subendocardial perfusion defect (Fig. 2D), denoting extensive microvascular integrity and viability despite prolonged ischemia.

Diagnostic and Prognostic Utility of MCE in Suspected Cardiac CP

The accuracy, clinical utility, diagnostic, and prognostic value of MCE have been evaluated in the ED setting (32–34). In a multicenter study comparing MCE with SPECT, it was found that the 2 imaging modalities were equal in their ability to diagnose AMI. In terms of predicting future cardiac events, MCE provided a 17% increase in incremental information for predicting future events which was comparable with the 23% increase in information with SPECT (32). More recently, WT assessed with MCE was shown in a large single-center study to increase significantly the diagnostic information over demographic variables, clinical risk factors, and ECG data (Bonferroni-corrected $p < 0.0001$) for predicting cardiac-related death, AMI, UA, congestive heart failure, and revascularization within 48 h of ED presentation (33). When MP was added, significant additional diagnostic information was obtained (Bonferroni-corrected $p = 0.0002$) (33).

As previously discussed, apart from the identification of ischemia, accurate risk stratification of CP patients is also important. Those who are intermediate or high risk for an adverse outcome may require admission to a cardiac care unit or telemetry unit, treatment with potent antiplatelet agents (35–37), or early referral for cardiac catheterization (38). MCE can be used to provide earlier and more accurate triage of these patients than clinical evaluation with the Thrombolysis In Myocardial Infarction (TIMI) risk score (39), which is derived from multiple clinical variables including cardiac troponin-I (cTNI). Because cTNI may not be elevated or immediately available at the time of patient presentation, complete risk stratification and initiation of therapy may be unnecessarily delayed.

The prognostic utility of a score derived only from variables that are available immediately at the time of a patient's presentation to the ED was evaluated (34). Because laboratory results may not be received for many hours after the initial presentation, a modified TIMI risk score (mTIMI) that excluded cTNI was derived (maximum score of 6). Based on their mTIMI scores, patients were categorized as either low (score ≤ 2), intermediate (score of 3 or 4), or high (score ≥ 5) risk. Although patients with a low mTIMI score had the lowest incidence of primary events, 4.1% of patients still had an early AMI within 24 h of enrollment. Patients with an intermediate score had a similar event rate as those with a high-risk score (11% versus 8.9%, $p = 0.71$). Thus, the mTIMI score was unable to discriminate between these groups (34).

With MCE, on the other hand, the incidence of a primary (nonfatal AMI or total mortality) event within 24 h of enrollment was only 0.4% in patients with normal WT and MP. In comparison, a 2.3% AMI rate has been reported for patients with CP discharged from the ED based on routine evaluation (9). The negative predictive value of MCE is therefore excellent. Even in patients with a low mTIMI score, MCE provides further risk stratification. Those patients with abnormal WT and MP had a significantly worse cardiac outcome than patients with normal MCE (34). The ability of MCE to provide incremental intermediate (30 day) and late (2 year) prognostic information was also shown in these studies (33,34).

Since MCE data can potentially be obtained immediately at the bedside when a patient with CP presents to an ED, we hypothesized that a risk score incorporating clinical, ECG, and MCE variables would accurately predict adverse events occurring within 48 h of presentation. We developed a logistic risk model in an initial cohort of 1,166 patients, and subsequently validated the model in a subsequent cohort of 720 patients. Significant multivariate predictors of nonfatal myocardial infarction or cardiac death within 48 h of presentation were found to be nonspecific ST-T changes on the ECG, any abnormality on the ECG, abnormal WT, or abnormal MP; each predictor was assigned a value of 1, with the risk score for each patient being the sum total. Patients with a risk score of 0 were found to have an early event rate of 0.3%, which increased significantly to an event rate of 58% for those with a maximum risk score of 4 in cohort 1. Likewise, in cohort 2, the risk score-stratified patients into 5 distinct risk groups with event rates ranging from 0.5% to 50% (40).

Cost Effectiveness of MCE

The addition of contrast-enhanced echocardiography to the evaluation of all CP patients could dramatically increase the already high cost associated with these ED visits. It has been shown, though, that MCE can be cost efficient in such patients by detecting those whose CP is noncardiac in nature and reducing unnecessary admissions or other downstream cardiac testing. A cost-efficiency analysis was performed in 957 patients presenting to the ED with suspected cardiac CP, but no ST-segment elevation on the ECG, who underwent MCE. On the basis of routine clinical criteria without knowledge of MCE findings, 641 (67%) patients were admitted to the hospital, whereas 316 (33%) were discharged directly from the ED. The average cost per patient using routine evaluation was $5,000. Since patients with normal MCE have a very low early primary cardiac event rate of 0.6%, such patients could have been discharged directly from the ED. Hence, if MCE had been used for decision making, 55% of patients would have been discharged directly from the ED. Preventing unnecessary admissions and tests would have saved an average of $900 per patient, in addition to reducing their ED stay (41).

Safety of MCE in ACS

The black box warning initially imposed by the Federal Drug Administration in October 2007 was revised in May 2008 and no longer restricts the use of echocardiographic contrast agents in patients with suspected ACS. The safety of echocardiographic contrast agents has been documented in many large retrospective registries. The risk of an anaphylactoid reaction is 1:15,000, which is much lower than the risk of an allergic reaction to iodinated radiographic contrast agents used for computed tomography coronary angiography or cardiac catheterization, which would be alternatives to MCE in the ACS population (42). Another retrospective analysis of >58,000 doses of ultrasound contrast agents administered to >4.2 million hospitalized patients showed no difference in 24-h mortality between those who received contrast versus those who did not, despite those receiving contrast agents having a significantly higher frequency of unstable cardiopulmonary conditions (43). The safety of Sonovue (Bracco Imaging SpA, Milan, Italy), which is currently available in Europe, has been prospectively evaluated in 500 patients undergoing stress MCE 2 to 5 days after presenting with CP to the ED. The authors reported no deaths, AMI, significant arrhythmias, or any other life-threatening events. Adverse events were not significantly different between the MCE group and the control group (44). The Federal Drug Administration has recommended 30 min of monitoring in patients with known or suspected ACS who receive ultrasound contrast agents, which should be easily accommodated in the ED.

Implementation of MCE in the ED

Although performance of MCE may be feasible during the day in most medical centers, the logistics of nighttime performance and interpretation of images will have to be individualized for each site. At our center, cardiology fellows are trained in the performance of contrast-enhanced studies for left ventricular opacification, and we also have sonographers on call. Sites could consider adding evening shifts for sonographers to increase the hours of coverage or use other creative solutions. As ultrasound technology becomes more incorporated into the management of acutely ill patients in future, appropriately trained ED physicians may themselves perform focused cardiac ultrasound studies on patients with suspected ACS, similar to the incorporation of ultrasound in the Focused Assessment with Sonography in Trauma (FAST) exam.

The evaluation of WT abnormalities on echocardiography is one of the most subjective and difficult skills to master. Interpreters should therefore be experienced, well-trained echocardiographers. Most image review software now offers secure on-line access of digitally acquired MCE images to allow rapid interpretation of WT and/or MP at night or on weekends.

Summary

MCE meets most of the requirements of an ideal tool for the assessment of suspected cardiac CP: it can directly assess the degree and adequacy of MP as well as the presence of WT abnormalities. It is rapid, noninvasive, highly accurate, safe, and portable. The assessment of WT and MP provides incremental diagnostic and prognostic information over other clinical variables that are routinely used today. Furthermore, by accurately excluding cardiac CP and preventing unnecessary hospitalizations or cardiac testing, MCE can even reduce the cost of managing these challenging patients.

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