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An Electrocardiographic and Acoustic Cardiographic Study of Acute Coronary Occlusion During Percutaneou Coronary Intervention

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An Electrocardiographic and Acoustic cardiographic Study of Acute Coronary Occlusion During Percutaneous Coronary Intervention

by

Eunyoung Lee

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

NURSING

in the

GRADUATE DIVISION

of the

To my husband, Mintai Kim

for your support, patience, and love

To my daughter, Suzie Kim

The fear of the Lord is the beginning of knowledge,

but fools despise wisdom and discipline

Proverbs 1: 7

A skillful doctor can hurt patients without good intention.

However, even a good doctor can hurt patients without skill and knowledge.

- *from the words of Dae-Jang-Geum,*

the first female doctor In Korean History

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This dissertation contains multiple papers in review for publication. The papers are the product of my work while a doctoral student at UCSF and represent research comparable in scope and contribution to the portion of the dissertation it replaces. Paper 1 is currently in review by the Journal of Electrocardiology. Paper 2 is in review by the American Journal of Cardiology. The abstract for this paper was presented as Jos Willems Young Investigator poster presentation at the conference of The International Society for Computerized Electrocardiology on May 2, 2008 (Riverside, CA). Paper 3 is currently in review by Annals of Noninvasive Electrocardiology. The co-authors listed in each paper directed and supervised the overall integrity of the research study that forms the basis for the dissertation.

An Electrocardiographic and Acoustic Cardiographic Study of Acute Coronary Occlusion During Percutaneous Coronary Intervention

Eunyoung Lee
Doctor of Philosophy
University of California, San Francisco, 2008

Ventricular dysfunction, as measured by a rise in ventricular filling pressure or abnormal wall motion on echocardiogram, has often been observed without or prior to ST changes during ischemia. However, these conventional measurement methods for ventricular function are either invasive or not readily available at the bedside.

The overall aim of this dissertation has been to investigate whether, using acoustic cardiography, the appearance or increased intensity of diastolic heart sounds, a non-invasive measurement of ventricular function, may (a) augment the detection of ischemia when combined with ST changes and (b) occur earlier than ST changes or angina during ischemia induced by coronary occlusion during PCI.

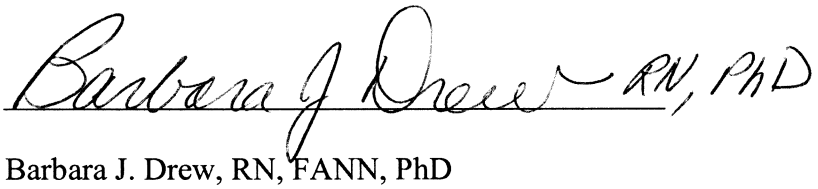
A prospective observational study was performed with a convenience sample of 80 patients referred for non-urgent cardiac catheterization with possible PCI. Acoustic and ECG data were gathered simultaneously and continuously before and during cardiac catheterization and PCI.

Among the 80 patients, 24 patients received PCI and developed ST changes > 2 SD in ≥ 2 contiguous leads during coronary occlusion. Diastolic heart sounds occurred in all patients who met the standard ST-T wave criteria for ischemia; in two-third of patients without ST changes; and in about 90% of patients without angina during coronary occlusion. All patients who did not have diastolic heart sounds during coronary occlusion

in PCI did not have ST changes that met the standard ST-T wave criteria. Our study showed that the combined use of diastolic heart sounds and ST-T wave criteria improved the sensitivity to predict myocardial ischemia by 31.6% but reduced the specificity by 22.2%. The absence of diastolic heart sounds was shown to be helpful to rule out the presence of myocardial ischemia.

Electrocardiographic ST-T changes were the earliest sign of ischemia during coronary occlusion and they were also the first to resolve after balloon deflation. Anginal symptoms were either the last event in the ischemic cascade or, in 90% of patients, did not occur during coronary occlusion. The monitoring of changes in diastolic heart sounds along with ECG monitoring at the bedside may improve the early detection of myocardial ischemia.

Approved:



Barbara J. Drew, RN, FANN, PhD

Dissertation Chairperson

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Introduction

Ischemic heart disease is the single leading cause of death in the United States, with 451,326 deaths estimated in 2004 alone (Centers for Disease Control and Prevention, 2007). Among those deaths, about one third are caused by acute myocardial infarction. Approximately, 7.5 million people in the United States have suffered myocardial infarction and about 1.25 million people are newly diagnosed with myocardial infarction (i.e. heart attack) every year with 650,000 new events and 450,000 recurrences, as reported by the National Heart Lung and Blood Institute (NHLBI), (Statistics about heart attack, 2008). However, as many as 3 to 4 million Americans experience myocardial ischemia without chest pain (American Heart Association, 2008). They may have a heart attack without prior warning.

Early detection of myocardial ischemia is important to prevent cell damage from myocardial infarction and to provide timely treatment. Although the 12- lead ECG is the "gold standard" for the diagnosis of myocardial ischemia, about 45-55% of ECGs in patients who present to the emergency room with chest pain do not meet the clinical ST criteria for ischemia and the patients are diagnosed with acute myocardial infarction later by a positive serum marker (Brady *et al*, 1999; Rouan *et al*, 1989; Storrow *et al*, 2000).

Independent of electrical changes, ventricular dysfunction has been documented during myocardial ischemia or infarction, by increased ventricular filling pressure as measured by a directly inserted catheter (Barry *et al*, 1974; Iskandrian *et al*, 1986; Levy & Fox, 1987) or by abnormal wall motion in the ischemic area of the echocardiogram (Alam *et al*, 1986; Hauser *et al,* 1985). Ventricular dysfunction, as measured by a rise in ventricular filling pressure or abnormal wall motion on echocardiogram has been shown to occur without or prior to ECG changes or angina during ischemia induced by

percutaneous coronary intervention (PCI) (Alam *et al*, 1986; Hauser *et al*, 1985; Serruys *et al*, 1984; Sigwart *et al*, 1984; Visser *et al*, 1986) or exercise (Heller *et al*, 1991; Sugishita *et al*, 1983). Angina has been reported to be the final event during ischemia (Alam *et al*, 1986; Hauser *et al*, 1985; Serruys *et al*, 1984; Sigwart *et al*, 1984; Visser *et al*, 1986). In addition, animal studies have suggested that ventricular function may be impaired without ST changes during repeated ischemia and that ischemia may be detected only later with ST changes and severe ventricular dysfunction (Braunwald *et al*, 1982; Geft *et al*, 1982; Scheuer *et al*, 1966). However, these conventional measurement methods for ventricular function either require invasive procedures with a risk of complications or are not readily available at the bedside when a patient is experiencing angina.

Diastolic heart sounds, the third and fourth heart sounds, occur when ventricular compliance is decreased. An S3 occurs during early diastole when transmitral flow decelerates rapidly with resistance of the left ventricle due to decreased left ventricular compliance or structural changes (Lindroos et al, 1994; Manson et al, 1995). An S4 occurs during late diastole when atrial contraction requires extra strength to fill the ventricle due to increased ventricular filling pressure caused by noncompliance of the ventricle (Lindroos *et al*, 1994; McGuire *et al*, 1997). The third and fourth heart sounds have been shown to correlate with left ventricular dysfunction such as a rise in ventricular filling pressure (Cohn *et al*, 1971; Marcus *et al*, 2005) and abnormal wall motion in an ischemic zone (Narain *et al*, 2005; Tavel, 1996;).

The S3 or S4 has often been observed in patients with myocardial infarction (Cohn *et al*, 1973; Gould *et al*, 1972; Hill *et al*, 1969; Master & Friedman, 1942; Stock,

1966; Taylor & Nixon, 1972) or exercise-induced ischemia (Aronow *et al*, 1971; McNair, 1967). The occurrence of diastolic heart sounds during ischemia has also been explained by the impairment of ventricular compliance in the ischemic area. However, in previous studies, the association between diastolic heart sounds and ischemia has not been systematically studied. Also, the frequency and significance of diastolic heart sounds as shown in those previous studies are questionable because these studies did not consider the presence of, and changes in, pre-existing diastolic heart sounds. Also, in those studies, the diastolic heart sounds were measured by auscultation or cumbersome phonocardiography, which are either inaccurate or impractical.

Audicor System (Inovise, Portland, OR), an acoustic cardiography, is a new noninvasive measure of ventricular function that incorporates the principles of phonocardiography to detect diastolic heart sounds. It allows recording and interpretation of ECG and acoustic data simultaneously and continuously using two heart sensors located at the leads V3 or V4. The Audicor system is compatible with and applied to a conventional 12-lead ECG machine.

Given the limitations of previous studies and the current understanding of the mechanism of diastolic heart sounds during ischemia, this dissertation explores a novel approach to measuring ventricular function using acoustic cardiography, which provides an adjunctive tool to the 12-lead ECG for the diagnosis of myocardial ischemia. This dissertation consists of three papers. These three papers are based on the findings of a prospective observational study in patients who were referred for diagnostic cardiac catheterization and possible PCI at the University of California, San Francisco.

Paper 1 explores, in 24 patients, the frequency and significance of diastolic heart sounds before and after ischemia induced by balloon inflations of approximate 30-seconds in duration during PCI. Paper 2 compares an ischemia group (n=19) and a non-ischemia group (n=18) to investigate whether diastolic heart sounds may detect ischemia independent of ECG changes and augment the diagnosis of ischemia as an adjunct to ECG changes. Paper 3 reports the sequence of the onset and normalization of ischemic events including ST changes, changes in diastolic heart sounds, and angina.

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Paper 1

Frequency of Diastolic Third and Fourth Heart Sounds with Myocardial Ischemia Induced During Percutaneous Coronary Intervention

Lee, E., Michaels, A.D., Selvester, R.H., & Drew, B.J. Frequency of diastolic third and fourth heart sounds with myocardial ischemia induced during percutaneous coronary intervention.

Introduction

In patients with acute coronary syndrome, early detection of myocardial ischemia is crucial in preventing myocardial cell death because it enables patients to receive early revascularization therapy or percutaneous coronary intervention (PCI). The standard 12-lead electrocardiogram (ECG) is the cornerstone for the early detection of myocardial ischemia that is likely to develop into acute myocardial infarction (MI). However, the standard ECG is non-diagnostic in about one-half of acute MIs that are later confirmed with positive biomarkers [1-3].

Ventricular dysfunction during myocardial ischemia and infarction has been frequently observed. Investigators have demonstrated abnormal wall motion in the ischemic myocardial zone on echocardiography [4-5] and a rise in left ventricular end-diastolic pressure (LVEDP) as measured by pulmonary artery catheter monitoring [6-8] or direct measurement of ventricular pressure [9-10], reflecting reduced contractility and/or compliance of the myocardium. Also, a few animal study results [11-13] suggest that, without ST segment changes, ventricular function may be impaired during repeated ischemia, inducing "stunning of the myocardium." However, traditional measurements of ventricular function are impractical in clinical settings because they require an invasive procedure or are not available when a patient experiences transient ischemia. Moreover, they do not provide continuous monitoring of the dynamic process of ischemia that develops into infarction.

Acoustic cardiography is a new noninvasive measure of ventricular function that incorporates the principles of phonocardiography to detect diastolic heart sounds [14-18]. Diastolic third and fourth heart sounds (S3, S4) have been shown to be strongly

associated with elevated LVEDP and abnormal wall motion in myocardial ischemia [19-21] as well as in other heart diseases [14-18]. The prevalence of diastolic heart sounds during acute MI [20-26] and myocardial ischemia [19, 29-30] was investigated in the 1960's and 1970's using cumbersome phonocardiographic instruments of that era or human auscultation, which has proven to be unreliable and impractical [31-32]. A noninvasive measure of abnormal ventricular function that could be readily applied and continuously monitored for real-time clinical decision-making may provide diagnostic information about ischemia/infarction that is independent of the heart's electrical activity.

Previous studies of diastolic heart sounds have limitations as following: (a) most frequency studies have been conducted with acute MI [20-26] and not ischemia, (b) the presence of and changes in pre-existing diastolic heart sounds were not considered and thus the findings of frequency and significance of diastolic heart sounds during ischemia/infarction in these previous studies are questionable, and (c) the prevalence of diastolic heart sounds in myocardial ischemia has only been reported during exercise [19, 29-30], which reflects the model of oxygen-demand ischemia. The PCI-induced ischemia model used in this study may provide more accurate information as to the frequency and significance of diastolic heart sounds during ischemia due to coronary occlusion, which may require timely treatment to prevent more profound damage to myocardial cells.

The purpose of this study was to determine whether new or increased intensity diastolic heart sounds, as measured by computerized acoustic cardiography, occur more frequently during myocardial ischemia induced by PCI than at baseline prior to the procedure.

Methods

Research Design, Sample and Setting

A prospective, observational study was conducted in the adult cardiac catheterization laboratory at the University of California, San Francisco. A convenience sample of patients undergoing non-urgent diagnostic coronary angiography with possible PCI was enrolled. Excluded from the study were patients with acute ST elevation MI receiving primary PCI or with other hemodynamically unstable situations requiring urgent cardiac catheterization. Also excluded were patients without an ability to develop an S4 (atrial fibrillation or flutter), patients likely to have diastolic heart sounds due to non-ischemic conditions (i.e., severe valvular heart disease, anemia, pregnancy, thyrotoxicosis, atrioventricular shunt, or tachycardia >120 bpm), and patients with paced rhythm, as well as non-English speaking patients. However, patients with ECG confounders for ischemia (e.g., bundle branch block, left ventricular hypertrophy) were not excluded from the study. The study was approved by the institution's Committee on Human Research and written informed consent was obtained prior to cardiac catheterization.

Instruments

Computerized acoustic cardiography. The Audicor system (Inovise Medical Inc., Portland, OR) can be applied to standard 12-lead electrocardiographs to record and interpret ECG and heart sound data using dual-purpose electrode sensors that detect both ECG and acoustic data (Figure 1). A Hewlett Packard XLi cardiograph (Philips, Andover, MA) was used to record 12-lead ECGs at a sampling rate of 1000 Hz. Acoustic

and ECG data were recorded continuously before and during the cardiac catheterization and PCI procedures and stored for off-line analysis.

The Audicor system's computer algorithm identifies normal and extra heart sounds by the timing of heart sounds relative to ECG waveforms and by the characteristics (i.e. frequency, amplitude) of the sounds. Sounds with the appropriate characteristics that consistently occur at the proper time for an S3 or S4 are rated from 0-10, with 10 as the loudest value. The algorithm diagnoses the presence of an S3 or S4 when the intensity exceeds a value of 5. The Audicor algorithm for detecting diastolic heart sounds has been validated in prior studies comparing the detection of S3 and S4 to hemodynamic parameters obtained during cardiac catheterization [16]. Also, its validity has been reported in a study correlating diastolic heart sounds with tissue Doppler imaging, echocardiography and B-type natriuretic peptide levels [17].

Procedure

A research nurse dedicated solely to the study gathered all data before and during cardiac catheterization and PCI. The 12-lead ECG and Audicor system were attached with torso-positioned limb leads in the standard Mason-Likar configuration [33]. A small device was attached to the Audicor system that produced a temporary flat line segment on the V3 or V4 ECG lead when a switch was depressed. This allowed the research nurse to mark precise timing of balloon inflations and deflations. The following events were recorded: coronary angiography, balloon inflation, balloon deflation, medication administration, and insertion of other intracoronary devices, such as intravascular

ultrasound. The research nurse also noted any chest pain or anginal equivalent symptoms during PCI balloon inflation.

Selection of ischemic events for analysis

A software program, FIAT Tools (Inovise Medical, Portland, OR), was used for off-line analysis for ECG wave data and acoustic data obtained from the Audicor system. Automated continuous median 10-second data was provided for both ECG and acoustic data recorded before and during cardiac catheterization and PCI in each patient.

To ensure that selected balloon occlusions were most likely to represent acute ischemia, only subjects who received PCI and had ST amplitude changes (delta ST) at the J point >2 SD in ≥ 2 contiguous ECG leads were included in the analysis. The use of the 2 SD criterion guaranteed that ST amplitude during balloon inflation was significantly different from that prior to balloon inflation with a 95% confidence interval and alpha of 0.05. In subjects who had more than one PCI balloon occlusion reaching the >2 SD delta ST amplitude criteria, the single inflation with the maximal delta ST was selected for analysis. Therefore, only one PCI-induced ischemic episode was analyzed per subject.

The differences in ST amplitude and intensity of diastolic heart sounds were obtained from the values of ST amplitude and intensity of diastolic heart sounds at baseline and during balloon inflation. To minimize baseline variation due to noise, the baseline ST amplitude was calculated from an average of 30 consecutive automated 10-second 12-lead ECGs over a 3-5 minute period before catheters were inserted.

To determine the frequency of ECG changes during balloon occlusion that reached the threshold for the clinical diagnosis of acute myocardial ischemia, we used the

criterion of a delta ST at J point ≥100 μV in ≥2 contiguous leads with the sequence of leads aVL, I, minus aVR, II, aVF, III and V_{1-6} (i.e. leads II, III, and aVF for inferior wall ischemia, leads V1-V4 for anterior/septal wall ischemia, and leads I, avL ,V5, and V6 for apical or lateral wall ischemia). A positive finding for diastolic heart sounds developing during PCI balloon occlusion was defined as either: (a) the new onset of an S3 or S4 (i.e. intensity value ≥5) in a patient without diastolic heart sounds at baseline prior to PCI, or (b) an increase in intensity greater than 2 SD in patients with diastolic heart sounds at baseline.

Statistical Analysis

Frequency lists and proportions were used to describe the prevalence of new or intensified S3 and S4 and ST changes during the selected balloon occlusion. To determine whether observed diastolic heart sound differences between baseline and balloon occlusion were statistically significant, the McNemar test for correlated proportions was used. In addition, observed changes in the intensity value (0-10) of diastolic heart sounds were compared at baseline and during PCI using the paired t-test. For all statistical analyses, a two-tailed p value < 0.05 was considered statistically significant. SPSS 15.0 was used for statistical analysis. Using the difference of proportion and proportions of discordant pairs of diastolic heart sounds between baseline and coronary occlusion from 2x2 tables used for McNemar test, power analysis also was performed, with a given sample size and an alpha of 0.05, to investigate that the magnitude of difference of proportion between baseline and balloon occlusion measured by McNemar test has an enough power.

Results

A total of 80 patients undergoing non-urgent coronary angiography consented to participate in the study and were attached to the Audicor system. Of these 80 patients, 56 were excluded from this analysis for the following reasons: no PCI performed (n=45); Audicor leads taken off due to hemodynamic instability (n=2) or the leads obscured the fluoroscopic imaging of the coronary artery (n=3); lack of data storage (n=1); cancellation of the procedure (n=3); missing data regarding timing of balloon inflation and deflation (n=1); and PCI without ST change >2 SD (n=1). In this one patient who did not develop a delta ST >2 SD during a 22-second balloon inflation, no new or increased intensity diastolic heart sounds or chest pain occurred. Thus, a total of 24 subjects who underwent PCI and had ST changes >2 SD during balloon inflation were selected for the final analysis.

Consistent with standard clinical practice, antiplatelet agents (e.g., aspirin and plavix), antithrombotic agents (e,g., GP IIb-IIIa. angiomax), anticoagulants (e.g., heparin), and nitroglycerin were given during cardiac catheterization to patients in our study who underwent PCI. All 24 patients received oral aspirin and plavix, intravenous heparin drip, and an intracoronary nitroglycerin bolus. In addition, some patients received integrillin (n=12), angiomax (n=2), and reopro (n=7) during cardiac catheterization.

From a total of 147 coronary balloon occlusions in the 24 subjects, the occlusions with a maximal ST change > 2 SD over the baseline in each subject were selected. The average duration of the 24 balloon occlusions selected for analysis was 28.0 ± 7.8 seconds, ranging from 11 to 40 seconds. The 24 balloon occlusions were performed in the following coronary arteries: left main (1), left anterior descending (12), left circumflex

(4), right coronary artery (5), obtuse marginal (1), and saphenous vein graft to ramus intermediate artery (1). The mean change in the ST segment from baseline to balloon inflation on the lead with the maximal ST change in the 24 cases was 184.6 ± 186.4 μV (range: 22.5 - 841.7μV). The ST changes in 24 subjects include ST elevation (epicardial ischemia) in 17 and ST depression (endocardial ischemia) in 5 subjects.

Clinical and angiographic characteristics

The clinical and angiographic characteristics of the study population were typical for patients undergoing non-urgent PCI (Table 1). Five of the 24 patients had ECG confounders for ischemia, including 4 with left ventricular hypertrophy (LVH) and secondary repolarization abnormalities and 1 with left bundle branch block (LBBB).

Frequency of diastolic heart sounds before and during PCI-induced ischemia

An example of the Audicor recordings in a subject without diastolic heart sounds at baseline who developed both an S3 and S4 during balloon occlusion is shown in Figure 2. The frequency and proportion of diastolic heart sounds before and during balloon occlusion are summarized in Table 2. A new S3 developed in 9 of the 24 subjects (37.5%) during PCI-induced ischemia ($p=0.021$). A new or increased intensity S4 developed in 13 (54.2%, $p> 0.05$); however, in 2 subjects, a pre-existing S4 disappeared. In total, a new or increased intensity S3 or S4 occurred in 16 of 24 subjects (66.7%) during PCI. If subjects with ECG confounders of LVH or LBBB were excluded, the frequency of a new or increased intensity S3 or S4 during PCI was greater (15 of 19 subjects, 78.9%).

Among the 24 subjects, power analysis showed that a significant increase in the frequency of S3 during balloon inflation compared with the frequency at baseline had a power of 80%, and a significant increase in the frequency of S4 had a power of 51%. In total, the increase in the significance of the frequency of S3 or S4 during PCI, compared with the frequency at baseline, had a power of 89% with an alpha of 0.05. Also, when we performed a power analysis for the 19 subjects who did not have ECG confounders, the power of the significance of the difference between baseline and coronary occlusion was greater: 70% for S3, 83% for S4, and 98% for S3 or S4.

Among the 24 subjects, a baseline S3 was present in one subject and an S4 in 5 subjects. The subject with a pre-existing S3 had increased intensity from 5.4 to 6.8 during balloon inflation; however, this increase was not >2 SD from baseline. This same subject also had a pre-existing S4 at baseline that did increase in intensity >2 SD from 7.7 to 10.0 during balloon inflation. Of the 5 subjects with a pre-existing S4 at baseline, one subject developed an increased intensity of S4 > 2 SD above the baseline. The remaining 4 subjects with a pre-existing S4 did not develop a significant increase in S4 intensity during balloon inflation; however, 2 subjects developed a new or increased intensity S3.

The Audicor-measured intensity of diastolic heart sounds (0-10) was compared at baseline and during balloon inflation. A significant increase occurred in the intensity of the S3 from a mean of 3.3 ± 0.8 (baseline) to 5.1 ± 2.0 (balloon inflation, $p<0.0001$). Likewise, a significant increase in the intensity of the S4 occurred from a mean of 4.8 ± 1.4 (baseline) to 6.1 ± 2.5 (balloon inflation, $p=0.016$).

Diastolic heart sounds in subjects with ECG confounders

Five balloon occlusions involved ECG confounders of ischemia at baseline (1-LBBB, 4- LVH with secondary repolarization abnormalities). The average delta ST between baseline and balloon inflation was 281.5 ± 317.9 μV (range: 83.0 – 841.7 μV). Among the 5 patients with ECG confounders, the intensity of the S3 increased during balloon inflation (mean: 3.0 ± 0.8 versus 4.2 ± 1.2, p=0.026). However, the intensity of the S4 at baseline and during balloon inflation was not significantly different (mean: 5.8 ± 2.4 versus 4.6 ± 2.7, p=0.199).

Of the 4 subjects with LVH, none had an S3 at baseline but a new S3 developed in 1 subject during balloon inflation. In these 4 subjects with LVH, the mean intensity of the S3 increased from 3.1 at baseline to 4.4 during balloon inflation; however, this was not statistically significant. Two of the 4 patients with LVH had an S4 at baseline; in one, the pre-existing S4 disappeared and in the other, there was not an increased intensity >2 SD during balloon inflation. Overall in the patients with LVH, the intensity value (0-10) for detection of an S4 decreased in 3 of the 4. In the one subject with LBBB, a balloon inflation of 27 seconds in a saphenous vein graft to the ramus intermediate artery resulted in a delta ST of 83 μV. Diastolic heart sounds were not present in this subject at baseline nor did new or increased intensity S3 or S4 develop during balloon inflation.

Diastolic heart sounds in subjects without clinical criteria for ischemia

Fifteen of the 24 subjects (62.5%) had a delta ST amplitude >2 SD during balloon inflation, but did not have clinical ST criteria sufficient for ischemia (delta ST ≥ 100μV in ≥2 contiguous ECG leads). Of these 15 subjects, a new or increased intensity S3 or S4

developed in 10 (66.7%; Table 3). Nine of the 24 subjects (37.5%) developed clinical ST criteria (delta ST ≥ 100μV in ≥2 contiguous ECG leads) during balloon inflation. A new or increased intensity S3 or S4 was detected in 6 of these 9 subjects (66.7%).

Diastolic heart sounds in subjects with and without chest pain during PCI

Chest pain was reported during balloon inflation in 3 of the 24 subjects (12.5%). The duration of balloon inflation in subjects with chest pain was averaged as 32 ±1.0 seconds compared to 27.4 ± 8.2 seconds in those without chest pain (p=0.347). The mean delta ST was 238.2 ± 179.6 μV in patients with chest pain compared to 176.9 ± 190.4 μV in those without chest pain (p=0.022). None of the 3 subjects who reported chest pain during balloon inflation had diastolic heart sounds at baseline but all 3 subjects developed a new or increased S3 or S4 during balloon inflation. In detail, an S3 developed in 1 (33.3%), and an S4 developed in all 3 (100%) during balloon inflation. One subject who had chest pain during PCI developed a new S4 without a clinical ST change ≥100μV in ≥ 2 contiguous leads. In that case, the intensity of the S4 increased from 4.6 to 10.0 during balloon inflation.

Of the 21 subjects without chest pain during balloon inflation, a new or increased intensity S3 developed in 8 (38.1%) and a new or increased intensity S4 developed in 10 (47.6%). In total, thirteen of the 21 subjects without chest pain (61.9%) developed a new or increased intensity S3 or S4 during balloon inflations.

Discussion

This is the first study to investigate the frequency of S3 and S4 diastolic heart sounds during PCI-induced myocardial ischemia. In this study, we used a novel computerized acoustic cardiographic technology as a non-invasive measurement of ventricular function. Of our 24 subjects who underwent balloon occlusion during PCI with an average 28 seconds of duration, two-thirds of subjects developed a new or increased intensity S3 or S4 during ischemia. Most of these patients with diastolic heart sound findings did not have associated chest pain symptoms or standard ECG criteria for ischemia. Also, our study showed that new or increased intensity S4 (54%) occurred more frequently than S3 (38%) or standard ST changes (38%). In addition, two-thirds of patients without clinical ECG criteria for ischemia and two-thirds of patients without chest pain during balloon occlusion developed new or increased intensity diastolic heart sounds. Among the 24 subjects, three reported chest pain during balloon inflation. All three patients developed a new or increased S3 or S4 during ischemia but one patient did not develop ST changes $\geq 100\ \mu V$ in ≥ 2 contiguous leads.

Similar to our study, previous studies of patients with acute MI [22-28] and myocardial ischemia induced by exercise testing [19, 29-30] showed that an S3 or S4 occurred more frequently during exercise than at rest. Aronow and colleagues [30] observed that an S3 occurred more frequently during and after exercise than at rest (15% at baseline, 60% during exercise). In addition, they found that an S4 was even more likely to develop (43% at baseline, 94% during exercise). Similarly, in a study of Cohn and colleagues [19], an S3 and/or S4 were found during exercise testing in 22 of 41 (54%) patients.

Several investigators [19, 29-30] reported the occurrence of diastolic heart sounds when ECG changes were nonspecific for myocardial ischemia. McNair [29] observed that an S3 was present in 46% of 39 patients with angina who had non-specific ECG changes. Similarly, Aronow and colleagues [30] reported that among 49 patients who developed angina during exercise, 17% developed an S4 without significant ST changes. In that study, an S4 was found in all 49 patients who developed angina. Our study results confirmed these findings. In our study, 15 of the 24 subjects (62.5%) did not develop standard ECG criteria for ischemia; however, two-thirds of them (10/15) developed new or intensified diastolic heart sounds. Diastolic heart sounds reflect left ventricular mechanical dysfunction whereas ECG changes reflect electrical abnormalities. Our study showed that patients with a new or increased S3 or S4, especially S3, during balloon inflation are likely to have a more elevated left ventricular end-diastolic pressure (22.0 ± 5.3mmHg vs. 14.3 ± 7.3 mmHg in S3) and lower ejection fraction (54.3 ± 9.7% vs.564 ± 13.1% in S3) than those who did not, although no statistical significance was found due to small sample size. Therefore, the combined use of diastolic heart sounds with ECG changes is likely to augment each other in the detection of ischemia that is likely to develop into infarction and may help to prevent more profound ventricular dysfunction due to ischemia.

A drawback of using diastolic heart sounds to detect myocardial ischemia/infarction is that patients who present with chest pain may have pre-existing diastolic heart sounds due to aging, LVH, or other heart diseases. A major limitation of previous heart sounds studies in patients with acute MI has been the failure to measure the prevalence of diastolic heart sounds at baseline. An advantage of computerized

acoustic cardiography over human auscultation is the ability to quantitatively assess changes in the intensity of diastolic heart sounds over time. Our study shows that the intensity of S3 or S4 increases significantly with PCI-induced ischemia even when there are pre-existing diastolic heart sounds. Of the 5 patients with pre-existing S3 and/or S4 heart sounds in the present study, 3 (60%) developed an increased intensity S3 or S4. Our results are consistent with those of Sawayama and colleagues [34] who observed that the amplitude of the S3 and S4 were larger in patients with angina than in normal subjects. Our study suggests that quantification of the intensity of diastolic heart sounds may improve the detection of myocardial ischemia in patients with pre-existing diastolic heart sounds.

Many patients with possible acute coronary syndrome have LVH or LBBB, which results in ST deviation at the baseline. Thus, the diagnosis of myocardial ischemia and infarction in this population using ECG changes alone is limited. Future studies of patients with ECG confounders are warranted to determine whether acoustic cardiography could help identify acute ischemia in this population.

Our study also demonstrates that new or intensified diastolic heart sounds occur during silent ischemia. All patients in our study who developed chest pain during balloon inflation had positive diastolic heart sound findings. Moreover, nearly two-thirds (62%) without chest pain also had positive diastolic heart sound findings. The patients in our study who experienced chest pain during balloon inflation had a greater change in their ST amplitude than those without chest pain. This suggests that chest pain may be a later sign of ischemia compared to new or intensified diastolic heart sounds. The timing of these electrical and mechanical events is a subject for future research.

Clinical implications

The major problem in detecting myocardial ischemia is its transient nature. Our study shows that new or intensified diastolic heart sounds, indicating the impairment of ventricular function, occur with and without electrical changes or angina during myocardial ischemia. Different from echocardiography, acoustic cardiography provides both acoustic and electrocardiographic data simultaneously and continuously. These benefits may help to detect myocardial ischemia, either transient or evolving to infarction, and to enable health care providers to make "real-time decisions" for the timely treatment of patients who present with chest pain in the emergency room, who are being transported to the emergency room with a report of chest pain, or who are admitted to a telemetry unit with chest pain. Also, the monitoring of diastolic heart sounds may be helpful to detect ischemia being used adjunctively with 24 hours Holter monitoring to evaluate patients with chest pain in outpatient settings.

The Audicor system is compatible with existing ECG machines and simply applied by replacing pre-existing 12-lead electrodes at the locations of V3 and V4 with two dual-purpose sensors, recording ECG as well as heart sound data. It is approved by Food and Drug Administration and currently available on the market. The heart sensors are disposable and the adherence time of heart sensors is also comparable to that of electrodes.

Limitations of the study

Although we found that a new or increased S3 or S4 occurred more frequently during ischemia induced by PCI than at baseline, our study results may not be

generalized to patients who experience ischemia by spontaneous coronary occlusion. The frequency of S3 and S4 that was reported in our study may be dependent on the duration of balloon inflation, which was an average of 30 seconds. The duration of balloon inflation in our study may not be sufficient to produce diastolic heart sounds as well as ST changes to the same extent as ischemia induced by spontaneous coronary occlusion. However, our findings of increased frequency of diastolic heart sounds during balloon inflation are comparable to the finding of one case study in which a subject developed a spontaneous occlusion of the proximal left anterior descending coronary artery during attempts to cannulate the left coronary artery [35]. The patient developed a significant ST elevation on anterior leads with severe dyspnea but did not report chest pain during the ischemia due to spontaneous coronary occlusions. A new S3 and S4 occurred during ischemia; especially, an S4 developed within 1 minute after spontaneous coronary occlusion.

Indeed, our study was performed with a small sample size of 24 for all subjects who had ECG evidence of ischemia during PCI and 19 subjects without ECG confounders. However, the McNemar test showed a significant increase in the frequency of diastolic heart sounds during coronary occlusion compared with that at baseline except for S4 when using 24 subjects including cases with and without ECG confounders. Power analysis also shows that our study results have enough power to conclude that the frequency of an S3 or S4 increased significantly during coronary occlusion compared to that at baseline with a power of between 70% and 98%; especially power increases when excluding cases with ECG confounders.

Conclusions

In summary, new or intensified diastolic S3 and S4 heart sounds measured with computerized acoustic cardiography develop in two-thirds of patients using the PCI model of acute coronary occlusion whether or not they develop standard ECG criteria for ischemia. We also found that all patients with chest pain, as well as nearly two-thirds with silent ischemia, develop a new or increased intensity of diastolic heart sounds during PCI-induced ischemia. These findings in our study suggest that the combined use of diastolic heart sounds with standard electrocardiography may improve the diagnosis of myocardial ischemia that is likely to develop into infarction.

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Legends

Figure 1. Placement of Audicor sensors.

Audicor sensors are substituted for the V3 and V4 electrodes when recording a standard 12-lead ECG. These special sensors acquire acoustic as well as ECG data.

Figure 2. Audicor recordings at baseline and during balloon inflation

A. Baseline. At baseline prior to PCI, there are neither ST-T wave criteria for ischemia nor diastolic heart sounds present. A nonspecific T wave abnormality is present but it does not reach ischemia criteria of a T wave nadir ≥1 mm below the isoelectric line.

B. During balloon inflation. During an 18-second balloon inflation in the mid left anterior descending coronary artery, ST segment elevation occurred in lead V3 (delta ST, 474μV). In addition, both an S3 and S4 developed.

Table 1. Sample Characteristics (n=24)

Mean age (yrs)	65.5±9.4 (47-82)
Female	25.0% (6/24)
Race	
Caucasian	13 (54.1%)
African-American	4 (16.7%)
Hispanic	3 (12.5%)
Asian/Pacific Islander	4 (16.7%)
Clinical presentation	
Possible ACS (non-STEMI or unstable angina)	58.3% (14/24)
Chronic stable angina	29.1% (7/24)
Diagnostic catheterization (pre-operative or other evaluation)	12.5% (3/24)
Medical history	
Coronary artery disease	75.0% (18/24)
Prior myocardial infarction	45.8% (11/24)
Diabetes Mellitus	58.3% (14/24)
Hypertension	70.8% (17/24)
Chronic Heart Failure	16.7% (4/24)
Angiographic extent of disease	
Single-vessel disease	37.5% (9/24)
Double-vessel disease	37.5% (9/24)
Triple-vessel disease	16.7% (4/24)
Four-vessel disease	8.3% (2/24)
Ejection fraction (%), mean (n=16)	55.3 ± 10.9
LVEDP (mmHg), mean (n=7)	17.5 ± 7.3

ACS=acute coronary syndrome; LVEDP=left ventricular end-diastolic pressure; STEMI: ST elevation myocardial infarction

Table 2. Diastolic heart sounds during PCI-induced ischemia

HS	Total N	Baseline Presence of HS		Balloon Occlusion New or ↑ intensity HS		P value*
		n	Percent	n	Percent	
All subjects						
S3	24	1	4.2%	9 (new S3=9)	37.5%	**0.021**
S4	24	5	20.8%	13 (new S4=12) (↑ intensity=1) (loss of S4=2)	54.2%	**0.077**
S3 or S4	24	5	20.8%	16 (new HS =13) (↑ intensity= 3) (loss of S3 or S4=1)	66.7%	**0.007**
Subjects without ECG confounders						
S3	19	1	5.3%	8 (new S3=8)	42.1%	**0.039**
S4	19	3	15.8%	13 (new S4=12) (↑ intensity=1) (loss of S4=1)	68.4%	**0.013**
S3 or S4	19	3	15.8%	15 (new HS=13) (↑ intensity=2)	78.9%	**0.002**

HS = heart sounds; NS= non-significant; *McNemar test

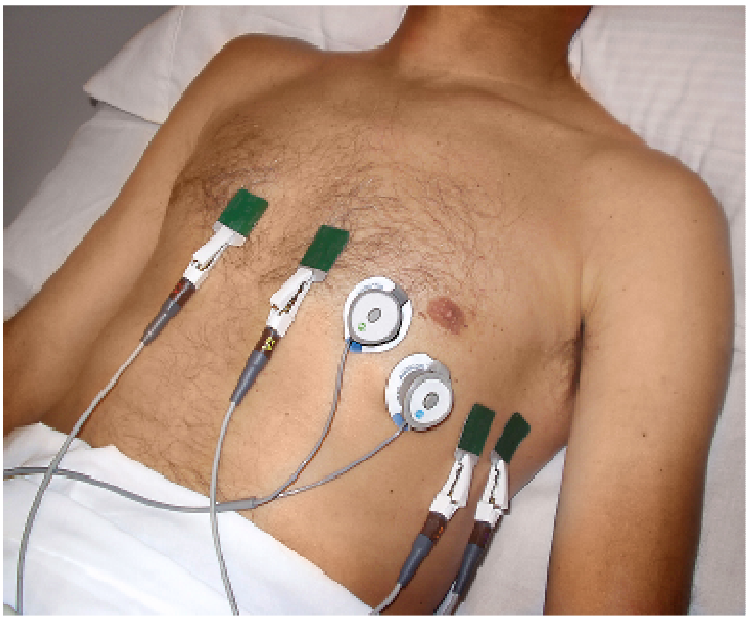
Table 3. Frequency of diastolic heart sounds in cases with and without clinical ST criteria for ischemia during PCI balloon occlusion

	ST change ≥100 μV in ≥ 2 contiguous leads			
	– Ischemia (n=15)		**+ Ischemia (n=9)**	
	n	%	n	%
New or ↑intensity, S3	5	33.3%	4	44.4%
New or ↑intensity, S4	8	53.3%	5	55.6%
New or ↑intensity, S3 or S4	10	66.7%	6	66.7%

Table 4. Prevalence of diastolic heart sounds in exercise-induced ischemia and acute myocardial infarction

Investigator Year	Measurement Method		S3	S4
	Auscultation	Phonocardiogram		
Exercise induced myocardial ischemia				
McNair[27], 1967	**X**		29/39 (74%)	–
Aronow[28], 1971		**X**	60/100 (60%)	94/100 (94%)
Cohn[17], 1973		**X**	6/41 (15%)	19/41 (46%)
Myocardial infarction				
Master[20], 1942		**X**	37/78 (47%)	65/78 (83%)
Stock[21], 1966	Either auscultation or phonocardiogram		16/37 (43%)	18/37 (49%)
Hill[22], 1969	**X**	**X**	48/87 (55%)	85/87 (98%)
Gould[23], 1972	**X**	**X**	2/20 (10%)	20/20 (100%)
Taylor [24], 1972		**X**	8/51 (15%)	31/51 (60%)
Turner[25], 1973		**X**	–	62/89 (70%)
Tierney[26], 1986	**X**		17/61 (28%)	

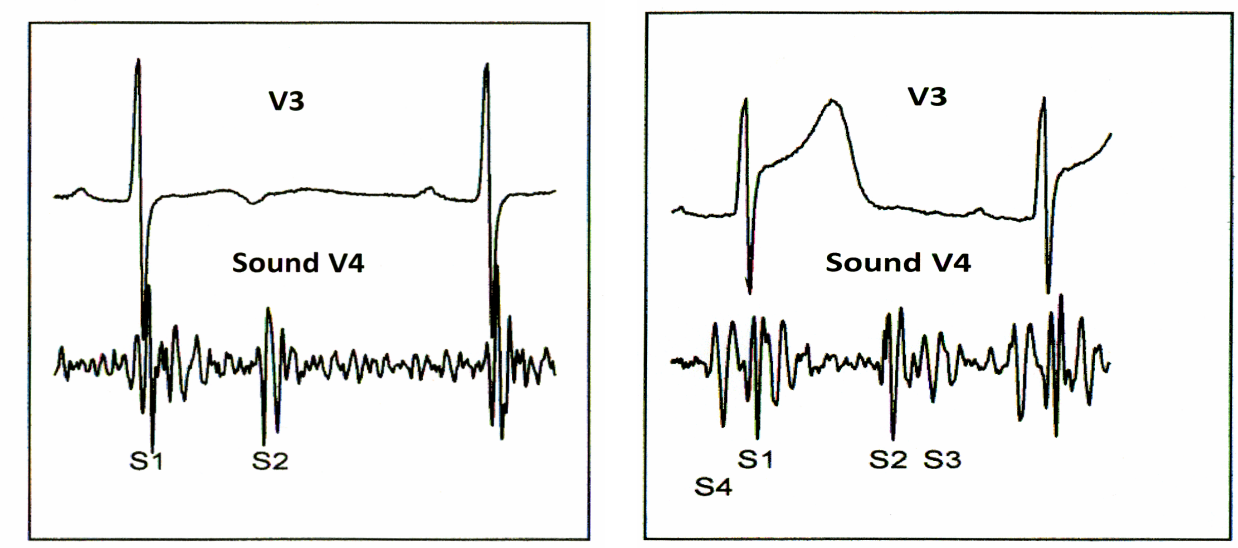
Figure 1. Placement of Audicor sensors.



Audicor sensors are substituted for the V3 and V4 electrodes when recording a standard 12-lead ECG. These special sensors acquire acoustic as well as ECG data.

Figure 2. Audicor recordings at baseline and during balloon inflation

A. Baseline **B. Balloon inflation**



C. At baseline prior to PCI, there are neither ST-T wave criteria for ischemia nor diastolic heart sounds present. A nonspecific T wave abnormality is present but it does not reach ischemia criteria of a T wave nadir ≥1 mm below the isoelectric line.

D. During an 18-second balloon inflation in the mid left anterior descending coronary artery, ST segment elevation occurred in lead V3 (delta ST, 474 μV). In addition, both an S3 and S4 developed.

Paper 2

Diastolic Heart Sounds as an Adjunctive Diagnostic Tool with ST criteria for Acute Myocardial Ischemia

Lee, E., Michaels, A.D., Selvester, R.H., & Drew, B.J. Diastolic heart sounds as a predictor of acute myocardial ischemia.

Abstract

Aims/Methods: To investigate whether diastolic third or fourth heart sounds (S3 or S4) predict acute myocardial ischemia, a prospective comparison study was conducted in a group with ischemia induced by percutaneous coronary intervention (n=19) and a non-ischemia group (n=18) without coronary artery disease. Diastolic heart sounds were detected with a novel computerized acoustic cardiographic system.

Results: Of 37 patients, the mean age was 59.4 ± 11.8 years and 51.4% were male. An S4 was more sensitive (73.7%) in predicting ischemia than an S3 (52.6%) or standard ST-T criteria (47.4%). All subjects with standard ST-T wave criteria had an S3 or S4. All subjects without an S3 or S4 also did not have standard ST-T wave criteria for ischemia. Using logistic regression, both an S3 and S4 were shown to predict ischemia ($p<0.05$), independent of ST-T criteria. The prediction of ischemia was improved by 31.6% when the presence of an S3 or S4 was added to ST-T wave criteria. The presence of an S3 or S4, especially an S4, combined with standard ST-T wave criteria was the best predictor of myocardial ischemia. The absence of an S3 and S4 was helpful to rule out myocardial ischemia.

Conclusion: The use of acoustic cardiography to detect an S3 or S4 may augment the ECG detection of ischemia and may help to rule out the presence of myocardial ischemia when both an S3 and S4 are not present.

Key words: heart sounds, electrocardiography, phonocardiography, acoustic cardiography, Myocardial ischemia, sensitivity, specificity

Introduction

The standard 12-lead electrocardiogram (ECG) is the primary tool for the diagnosis of acute myocardial ischemia. However, 45%-55% of patients who present to an emergency department with chest pain and are subsequently diagnosed with acute myocardial infarction (MI) on the basis of elevated serum troponin have an initial ECG that is non-diagnostic of acute myocardial ischemia [1-3].

Changes in ventricular function may occur during acute myocardial ischemia independent of electrical changes. Abnormal wall motion of the ischemic zone on echocardiogram [4-5] and a rise in left ventricular filling pressure [6-10] have been used to identify acute myocardial ischemia, adjunctively with ECG criteria. However, these measurements are not readily available to diagnose transient or evolving acute myocardial ischemia in the immediate care setting.

Continuous non-invasive bedside monitoring of ventricular function may improve the early detection of acute myocardial ischemia when used in conjunction with the standard 12-lead ECG. Diastolic third and fourth heart sounds (S3 and S4) have been shown to correlate with direct measurement of left ventricular dysfunction, such as abnormal elevation of left ventricular filling pressure or abnormal wall motion [11-18]. Previous studies have shown that diastolic heart sounds occur more frequently in patients with transient myocardial ischemia [17-20] and acute MI [21-27] than in normal subjects. Furthermore, during myocardial ischemia induced by exercise [18-20], diastolic heart sounds occur even when ST-T waves are normal or non-specific for ischemia. However, previous studies of diastolic heart sounds have two major limitations. First, they did not consider the presence of pre-existing diastolic heart sounds and thus their conclusions

regarding frequency and its significance of diastolic heart sounds during myocardial ischemia or acute MI are questionable. Second, diastolic heart sounds were measured by a cumbersome phonocardiographic instrument that is impractical or unavailable in clinical settings or by auscultation, which has been shown to be unreliable because of poor agreement with phonocardiography and other observers [28, 29]. In addition, from these previous studies, it is uncertain whether diastolic heart sounds augment the diagnosis of myocardial ischemia independent of ST-T wave changes.

It has recently become possible to detect diastolic heart sounds with a computerized acoustic cardiographic system that is simple to use in clinical settings. The aims of the present study were (1) to use acoustic cardiography to compare the diagnostic test characteristics (i.e. sensitivity, specificity, overall accuracy) of diastolic heart sounds and standard ST-T wave criteria as methods for detecting acute myocardial ischemia induced during acute coronary occlusion due to percutaneous coronary intervention (PCI) balloon inflation, and (2) to investigate whether diastolic heart sounds augment the diagnosis of myocardial ischemia, independent of standard ST-T wave criteria.

Methods

Research Design, Sample, and Setting

A prospective observational comparison study was conducted in the adult cardiac catheterization laboratory at the University of California, San Francisco. We recruited convenience sample of patients undergoing non-urgent diagnostic coronary angiography with possible PCI. Exclusion criteria included patients with 1) non-English speaking, 2) acute ST elevation MI, 3) hemodynamic instability requiring urgent cardiac

catheterization, 4) inability to develop an S4 (atrial fibrillation or flutter), 5) likelihood of having diastolic heart sounds due to non-ischemic conditions (i.e., valvular heart disease, anemia, thyrotoxicosis, atrioventricular shunt, or tachycardia >120bpm), and 6) ECG confounders for ischemia (i.e. bundle branch block, left ventricular hypertrophy with secondary abnormality, early repolarization, or paced rhythm). The study was approved by the University of California, San Francisco Committee on Human Research and written informed consent was obtained prior to study enrollment.

Instruments

Acoustic cardiography. The Audicor system (Inovise Medical, Portland, OR) is applied to standard 12-lead electrocardiographs. This compatibility allows the Audicor system simultaneously to record and interpret ECG and heart sound data using dual-purpose electrode sensors that detect both ECG and acoustic data from the V_3 and V_4 electrode locations. The Hewlett Packard XLi cardiograph (Philips, Andover, MA) was used to record 12-lead ECGs at a sampling rate of 1000 Hz. A simultaneous recording of acoustic and ECG data was made continuously before and during cardiac catheterization and PCI and stored for off-line analysis.

The Audicor system's computer algorithm identifies normal and diastolic heart sounds by the timing of the heart sounds relative to ECG waves as well as the characteristics of the heart sounds (i.e. frequency, amplitude, intensity). For example, an S3 is diagnosed when a low-pitched sound is consistently detected approximately 120-180 milliseconds after the onset of the second heart sound. In contrast, an S4 is diagnosed when a low-pitched heart sound is detected during late diastole and 120-180 milliseconds

after the onset of the P wave and before the Q wave. Sounds that consistently occur with proper timing and frequency for an S3 or S4 are rated from 0-10, with 10 as the strongest value. The algorithm diagnoses the presence of an S3 or S4 when the intensity reaches a value ≥ 5.0. The ability of the Audicor algorithm to detect diastolic heart sounds was validated in a prior study comparing the detection of an S3 and S4 to hemodynamic parameters for measuring ventricular function obtained at cardiac catheterization [13]. Also, its validity was reported in a study comparing diastolic heart sounds with Tissue Doppler imaging, echocardiographic findings, and B-type natriuretic peptide [15].

Procedure

Acoustic and ECG data were gathered solely by a research nurse before and during cardiac catheterization and PCI. The 12-lead ECG and Audicor system were applied to the chest with torso-positioned limb leads in the standard Mason-Likar configuration [30] with Audicor dual-purpose sensors at the location of leads V3 and V4. For research purposes, a small device was attached to the Audicor system that produced a temporary flat line segment on the V3 or V4 ECG lead when a switch was depressed. This allowed the research nurse to mark the precise timing of balloon inflation and deflation. The research nurse also noted any chest pain or anginal equivalent symptoms before and during PCI balloon inflation.

Comparison groups with and without acute myocardial ischemia

After undergoing cardiac catheterization and angiography, patients were classified into two groups. The ischemia group had an ST amplitude change at the J point >2

standard deviations (SD) over the baseline in ≥ 2 contiguous ECG leads during PCI balloon occlusion. Contiguous limb leads were defined in the Cabrera sequence of aVL, I, negative (inverted) aVR, II, aVF, and III. The use of the 2 SD criterion guaranteed that ST amplitude during balloon inflation was significantly different from that prior to balloon inflation with a 95% confidence interval and an alpha of 0.05. The non-ischemia group underwent coronary angiography and had normal coronary arteries or clinically insignificant lesions that did not require PCI.

Measurement of standard ST-T wave criteria and diastolic heart sounds

A software program, FIAT Tools (Inovise Medical, Portland, OR), was used to analyze ECG wave as well as acoustic data obtained from the Audicor system. Automated continuous median 10-second data was provided for both ECG and acoustic data recorded before and during cardiac catheterization and PCI in each patient.

The new universal criteria for MI were used to define the criteria for ischemia [31] that is likely to develop into infarction. The presence of ST-T wave criteria for ischemia was defined when one of the following was present: (a) ST elevation at the J point in ≥2 contiguous leads with cut-off points of ≥2 mm in males or ≥1.5 mm in females in leads V_2-V_3 or ≥1 mm in other leads or (b) horizontal or down-sloping ST segment depression ≥0.5 mm in ≥2 contiguous leads or (c) T wave inversion ≥1 mm in ≥2 contiguous leads. The presence of diastolic heart sounds was defined when the intensity reached a value of ≥5 by the algorithm of the Audicor system.

In the non-ischemia group, standard ST-T wave criteria and diastolic heart sounds were evaluated from the first 30 consecutive 10-second 12-lead ECGs and acoustic data

prior to catheter insertion. These ECG and heart sound criteria were considered present when they were observed consistently in 80% of the first 30 recordings. This measurement allowed for the minimization of variation due to noise. In the ischemia group, standard ST-T wave criteria and diastolic heart sounds were determined at the point of maximal ST amplitude change during PCI balloon coronary occlusion.

Statistical Analysis

Frequencies and proportions were used to describe the prevalence of diastolic heart sounds and standard ST-T wave criteria in the ischemia and non-ischemia groups. The chi-square test and logistic regression were used to investigate whether the presence of an S3 or S4 was predictive of myocardial ischemia and whether they were predictive of myocardial ischemia independent of ST-T wave criteria. Proportions were used to describe the sensitivity, specificity, and overall accuracy of ST-T wave criteria and diastolic heart sounds for predicting acute myocardial ischemia. Overall accuracy was obtained from the formula: [n (True Positive) + n (True Negative)/ N (all subjects)]. Also, a receiver operating characteristic (ROC) area under the curve was used to compare the overall accuracy of the combinations of ST-T wave criteria and diastolic heart sounds to detect myocardial ischemia.

For further analysis, one variable (i.e., heart sounds_ST score, HS_ST score) was obtained from the combination of diastolic heart sounds and ST-T wave criteria. The score reflects that the absence of diastolic heart sounds is a likely predictor of the absence of myocardial ischemia. The variable was scored from 1 and 4, with 4 as the highest score representing a likelihood of having myocardial ischemia. (1- no ST-T wave criteria

with absence of S3 and S4, 2- presence of ST-T wave criteria but absence of S3 and S4, 3- no ST-T wave criteria but presence of S3 or S4, 4- presence of ST-T wave criteria and S3 or S4).

Results

Sample Characteristics

A total of 80 patients who were referred for cardiac catheterization for symptoms suggestive of coronary artery disease, or for pre-surgical or other screening for heart disease underwent non-urgent cardiac catheterization and were attached to the Audicor system. Of the 80 patients, 43 patients were excluded from the present analysis for the following reasons: coronary artery bypass surgery performed instead of PCI (n=20); leads taken off due to hemodynamic instability (n=2) or difficulty visualizing the coronary artery because of the non-radiolucent acoustic sensors (n=3); failure of data storage (n=1); cancellation of the procedure (n=3); missing data regarding timing of balloon inflation and deflation (n=1); PCI without the requisite >2 SD ST amplitude change from baseline during balloon occlusion (n=1); ECG evidence of acute myocardial ischemia at baseline prior to cardiac catheterization (n=1); left ventricular hypertrophy with secondary ST-T wave abnormality (n=6); bundle branch block (n=3); and early repolarization (n=2).

Of the remaining 37 patients, 19 comprised the ischemia group because they underwent PCI and had a ST amplitude change at the J point >2 SD from baseline in ≥ 2 contiguous ECG leads during balloon occlusion. The remaining18 patients comprised the non-ischemia group because they were found to have normal coronary arteries or non-

significant coronary lesions that did not warrant PCI and have no ECG evidence of ischemia.

The clinical and angiographic characteristics of patients in the ischemia and non-ischemia groups are displayed in Table 1. Patients in the ischemia group were more likely to be older and male than those in the non-ischemia group. About 60% of the patients in the ischemia group were referred for cardiac catheterization due to symptoms suggestive of acute coronary syndrome. In contrast, about 70% of the non-ischemia patients were referred for cardiac catheterization for diagnostic screening or pre-operatively. The ischemia group was more likely to have a history of coronary artery disease or prior MI.

Presence of Baseline Diastolic Heart Sounds

No significant difference was found in the prevalence of an S3 or S4 at the baseline between the two groups (3 cases in ischemia group, 4 cases in non-ischemia group). Among the 18 patients in the non-ischemia group, four patients had an S3 or S4 at baseline (S3-1, S4-3). The patient with a baseline S3 had a history of congestive heart failure with an ejection fraction < 40%. One of three patients with a baseline S4 had a history of congestive heart failure. Another patient with a baseline S4 had a left ventricular end-diastolic pressure (LVEDP) of 24 mmHg. However, the remaining patient with a baseline S4 did not show any significant ventricular dysfunction or a history of heart disease.

In the ischemia group of 19 patients, the mean duration of balloon inflation was 28.0 ± 7.8 seconds and the mean ST amplitude change was 184.6 ± 186.4 μV. Among these 19 patients, a baseline S3 or S4 was present in three (S4 only, 2; S3 and S4, 1). The

patient with both an S3 and S4 at baseline showed a significant increase in the intensity of S4 during balloon inflation, although the S3 did not increase significantly during ischemia. In one of the two patients with a pre-existing S4, a new S3 developed during ischemia although the pre-existing S4 disappeared. In the second patient with a baseline S4, the pre-existing S4 did not increase in intensity nor did an S3 develop during ischemia.

No significant association was found between diastolic heart sounds during coronary balloon inflation and clinical characteristics in the ischemia group, except in the following cases. In cases with congestive heart failure, the pre-existing S3 or S4 were less likely to increase in intensity > 2SD during ischemia ($p=0.035$). This observation is difficult to generalize results due to the small sample size of only 2 patients with congestive heart failure. Also, cases with presence with a prior MI developed a new S3 or S4 during ischemia, although significance was not found in the correlation between the presence of prior MI and the development of diastolic heart sounds ($p>0.05$). Among the 19 patients in the ischemia group, 8 patients had a prior MI. Of those 8 patients, a baseline S3 or S4 was present in only one patient and it did not increase in intensity > 2 SD during balloon inflation. The remaining 7 patients did not have a baseline S3 or S4 but developed new diastolic heart sounds during ischemia.

Standard ST-T wave criteria and diastolic heart sounds: prevalence significance for detection of myocardial ischemia

Of the 37 patients, standard ST-T wave criteria for ischemia were present in 52.6% (10/19) of the ischemia group during PCI balloon occlusion and in none of the

non-ischemia group. An S3 or S4 occurred in 84.2% (16/19) of the ischemia group and in 22.2% (4/18) of the non-ischemia group. Both standard ST-T wave criteria and diastolic heart sounds occurred more frequently in patients with ischemia than without ischemia. Diastolic heart sounds were found more frequently than standard ST-T wave criteria in the ischemia group during PCI balloon occlusion. Using logistic regression, patients with an S3 or S4 were 18.7 times more likely to have myocardial ischemia than patients without an S3 or S4 (p=0.001). Independent of standard ST-T wave criteria, both an S3 and S4 showed a significant contribution to detect the presence of myocardial ischemia (p= 0.034 for S3, p=0.015 for S4, P=0.032 for S3 or S4).

In the ischemia group (n=19), 9 patients (47.4%) did not develop standard ST-T wave criteria for ischemia during PCI balloon occlusion. Of these 9 patients with non-diagnostic ECGs during balloon occlusion, an S3 or S4 occurred in 6 (66.7%). Of the 19 patients in the ischemia group, only 3 did not have an S3 or S4. These three patients also did not have standard ST-T wave criteria during balloon occlusion.

Diagnostic characteristics of standard ST-T criteria and diastolic heart sounds for detecting myocardial ischemia

The sensitivity, specificity, and overall accuracy of standard ST-T wave criteria and diastolic heart sounds for detecting acute myocardial ischemia are presented in Table 2. Compared with standard ST-T wave criteria (52.6%), the presence of an S3 or S4 was more sensitive for detecting myocardial ischemia (84.2%). An S4 was more sensitive for predicting myocardial ischemia than an S3 (73.7% versus 47.4%); whereas the absence of an S3 was a better detector of the absence of myocardial ischemia (94.4%), compared

with the absence of an S4 (83.3%). Among the 37 patients, 17 patients did not have diastolic heart sounds. All 17 patients without diastolic heart sounds did not have the standard ST-T wave criteria.

When adding an S3 or S4 to the standard ST-T wave criteria, the sensitivity for detecting myocardial ischemia was improved by 31.6% (p=0.001), but specificity was decreased by 22.2%. The overall accuracy of prediction of myocardial ischemia was improved from 75.7% to 81.1% when using combined ECG and heart sound information other than ECG information alone. Similarly, using a ROC curve (Figure 1), the area under the curve increased when adding diastolic heart sounds, especially an S4, to standard ST-T wave criteria. Furthermore, the overall accuracy of detection of myocardial ischemia improved when using the HS_ST score, reflecting that the absence of S3 and S4 is indicative of the absence of myocardial ischemia independent of ST-T wave criteria.

In further analysis, using the criterion of a delta ST change $\geq$ 0.5mm in $\geq$ 2 contiguous leads, the addition of an S3 or S4 improved sensitivity of detection of myocardial ischemia by 21% and overall accuracy by 10.8% with a decrease in specificity 22.2%. Using binary logistic regression, an S4 was shown to improve the detection of myocardial ischemia independent of ST criteria $\geq$ 0.5mm (p=0.025); however, the presence of an S3 did not significantly increase the detection of myocardial ischemia, independent of ST criteria $\geq$ 0.5mm (p=0.078). Using the ROC curve, the area under the curve also increased when adding the presence of S4 to ST criteria $\geq$ 0.5mm. Furthermore, the best model for improving overall accuracy of detection of myocardial ischemia was found when using the HS_ST score with ST criteria $\geq$ 0.5mm.

Discussion

Findings from this study show that diastolic heart sounds, especially an S4, are valuable for detecting the presence of myocardial ischemia using the PCI model of acute coronary occlusion. The PCI model used in this study is ideal to investigate electrical and acoustic changes during myocardial ischemia that, like acute coronary syndrome, results primarily from an interruption of myocardial oxygen supply due to sudden coronary artery occlusion. Also, the PCI model allows investigators to obtain electrical and acoustic data without noisy signals which is a major problem during exercise-induced myocardial ischemia. In addition, exercise increases heart rate which can cause false positive diastolic heart sounds.

In our study, we found the combined use of diastolic heart sounds with standard ST-T wave criteria improved the sensitivity (by 31.6%) and overall accuracy (by 5.4%) for predicting acute myocardial ischemia although it reduced specificity by about 20%. Also, our study showed that the presence of an S4 improved the detection of myocardial ischemia when combined with standard ST-T wave criteria as well as a lower ST threshold criterion of an ST change ≥0.5mm of the baseline in ≥ 2 contiguous leads. Using the HS_ST score, we also found that the absence of an S3 and S4 was helpful to rule out myocardial ischemia even when combined with the lower threshold ST criterion.

Several investigators have reported that diastolic heart sounds occur frequently during exercise-induced myocardial ischemia [17-20], which is a simulation of the mechanism in chronic stable angina (i.e., myocardial oxygen demand that exceeds supply). Table 3 shows the prevalence of diastolic heart sounds and ischemic ST-T

changes during exercise-induced ischemia reported in the literature, as measured by early phonocardiography equipment [17,20] or by auscultation [18, 19]. These previous studies showed that, during ischemia induced by exercise, an S4 (46.3%-94%) also occurred more frequently than an S3 (14.6%- 74%) or ST-T wave criteria (59%). For example, Aronow and colleagues [20] observed that among 100 patients with angina induced by a Master's two-step exercise test, an S4 developed in 94; whereas S3 and ST-T wave changes developed only in 60 and 53, respectively. Our study extends the findings of these prior studies by using the PCI model of acute MI. Compared with standard ST-T wave criteria (sensitivity, 52.6%), an S4 was more sensitive (73.7%) than the ECG or an S3 (sensitivity, 47.4%), for the detection of acute myocardial ischemia.

Previous investigators have shown that diastolic heart sounds often occur when ST-T wave criteria for ischemia are not present [19-20]. Aronow and colleagues [20] observed that an S4 developed without significant ST changes in 17% of 49 patients who developed angina during exercise. Similarly, McNair [19] observed that an S3 was present in 46% of 39 patients with angina who had non-significant ECG changes during exercise testing. These findings suggested that the diagnosis of myocardial ischemia might be improved when combining the use of diastolic heart sounds with ST-T wave changes. Our study confirms these findings. In our study, among 19 patients in the ischemia group, 6 (31.6%) developed diastolic heart sounds without standard ST-T wave criteria for ischemia. Both an S3 and S4 were found to be detective of myocardial ischemia independent of standard ST-T wave criteria using binary logistic regression ($p<0.05$). Also, the presence of an S3 or S4 augmented the sensitivity of standard ST-T wave criteria for ischemia by 31.6% in detecting myocardial ischemia.

In our total sample of 37 patients, 10 developed standard ST-T wave criteria for ischemia during balloon occlusion. In these10 patients with ST-T wave changes, diastolic heart sounds were present in all (S3 only=2, S4 only=7, S3 and S4 =1). Of our total sample, 27 did not have standard ST-T wave criteria for ischemia and of these, 9 (33.3%) had balloon occlusions that were likely to represent ischemia (>2 SD ST amplitude change from baseline). Diastolic heart sounds were present in 6 of these 9 patients (66.7%) without standard ECG criteria for ischemia.

In studies [17-20] of diastolic heart sounds during exercise in normal subjects, the absence of diastolic heart sounds (specificity) was 89% - 100% for an S3 and 71% - 96% for an S4. In contrast, the specificity of ischemic ST-T wave criteria was lower ranging from 62% - 96%. In these studies, the absence of an S3 was more specific for the absence of myocardial ischemia than an S4 or ST-T wave criteria. Our study confirmed these findings during PCI-induced myocardial ischemia. We found that the specificity of an S3 (94.4%) was minimally lower than the standard ST-T wave criteria but higher than an S4 (83.3%).

Patients for whom angiography with possible PCI is indicated are likely to have co-morbidity such as congestive heart failure or prior MI, which may cause diastolic heart sounds without ischemia. Thus, in our study, adding an S3 or an S4 to ST-T wave criteria reduced the specificity for the detection of myocardial ischemia by 20%, compared with the use of standard ST-T wave criteria alone. In our study, an S3 or S4 was found in 4 of 18 patients without ischemia (1 with S3, 3 with S4). In these 4 cases, three patients had either prior MI or poor left ventricular function with elevated LVEDP. However, one remaining individual in the non-ischemia group with an S4 had no heart

disease or ventricular dysfunction. These prevalence results of diastolic heart sounds in the non-ischemia group of our study are similar to those in another Audicor study [32] with normal subjects without angina symptoms. Using the Audicor system, Collins and colleagues [32] reported that an S3 occurred in 6.9% and an S4 in 20.1 % in normal subjects without cardiac symptoms. Diastolic heart sounds can occur due to abnormal ventricular function without acute myocardial ischemia as the cause. Therefore, diastolic heart sounds should be evaluated in conjunction with a patient's symptoms and ECG criteria for ischemia.

The clinical significance of an S3 or S4 in normal subjects has been evaluated in terms of ventricular function [17] and long-term outcomes [33-34]. Cohn [17] observed that patients with a normal angiogram but who developed diastolic heart sounds after exercise had a greater increase in LVEDP than those who did not develop diastolic heart sounds, although the difference was not statistically significant. Aronow and colleagues [33] found that coronary artery disease developed more frequently in normal subjects with an S4 (10.3%) than in those without diastolic heart sounds (1.4%) during a 30-month follow-up period. Similar findings are demonstrated in our study. In patients without ischemia in our study, LVEDP in patients with an S3 or S4 was greater than that in patients without an S3 or S4 (19.5± 21.5 versus 14.5± 5.3) and left ventricular ejection fraction was lower in non-ischemic patients with diastolic heart sounds than without (56.5 ± 21.5 versus 58.9 ± 11.6); however, these differences were not statistically significant.

Our study showed that 7 out of 8 patients in the ischemia group who had a history of prior MI (87.5%) developed a new S3 or S4 during ischemia. This finding indicates

that diastolic heart sounds may be responsive enough to reflect the presence of acute myocardial disease and functional change and, thus, may help to detect the presence of myocardial ischemia even where there is pre-existing ventricular dysfunction and heart disease. However, these findings may not be generalized due to the small sample size. Further study is needed with a greater sample size to investigate the significance of diastolic heart sounds for the detection of myocardial ischemia in patients with co-morbidity.

The results of our study may not be generalized to patients who experience ischemia by spontaneous coronary occlusion. The duration of balloon inflation, an average of 28 seconds in our study, may not be sufficient to induce diastolic heart sounds as well as ST changes to the same extent as ischemia induced by spontaneous coronary occlusion. Further research is needed in patients who present to the emergency department with chest pain to determine whether the presence of diastolic heart sounds could augment the ECG in the detection of myocardial ischemia that may develop into MI without timely treatment.

Clinical implications

Detection of myocardial ischemia is challenging due to its transient nature. Many patients who come to the emergency room for the evaluation for acute coronary syndrome present after chest pain has subsided or they have already been treated with nitroglycerin prior to arrival. Thus, the 12-lead ECG taken upon arrival at the emergency room does not reflect effectively electrical activity during myocardial ischemia.

Furthermore, the 12-lead ECG has been shown to be limited in its ability to detect myocardial ischemia with a sensitivity of only 45-55%.

Acoustic cardiography can be used easily in conjunction with an existing electrocardiography machine; as well it can provide the continuous recording of simultaneous acoustic and electrocardiographic data. Also, the cost of heart sensors is comparable to that for the electrodes for a 12-lead ECG. These benefits of acoustic cardiography may complement echocardiography as a continuous measurement of ventricular function and may help to detect myocardial ischemia, either transient or evolving to infarction. Especially in the pre-hospital setting, acoustic cardiography may assist health care provides to make "real-time decisions" and to provide timely treatment of patients who present with chest pain in the emergency room. In addition, acoustic cardiography may help to detect myocardial ischemia in patients who are admitted to a telemetry unit with chest pain or for whom chest pain should be evaluated using 24-hour Holter monitoring in an outpatient setting.

Conclusion

In summary, our study shows that the presence of diastolic S3 or S4 heart sounds may be diagnostic of myocardial ischemia induced by PCI, independent of standard ST-T wave criteria. The presence of an S3 or S4, especially an S4, along with standard ST-T wave criteria for ischemia increases the sensitivity for the detection of ischemia by 31.6%, with an increase in overall accuracy. However, the addition of an S3 or S4 to standard ST-T wave criteria decreases specificity for the prediction of ischemia by 22.2%. In our study, ST changes in the ischemia group met the standard ST-T wave

criteria in only about half of patients (10/19, 52.6%). Our study suggests that the combined use of diastolic heart sounds and lower threshold ST criteria ≥ 0.5mm may be useful to detect myocardial ischemia. Also, we have found that the absence of diastolic heart sounds helps to rule out the presence of myocardial ischemia and thus improves the overall accuracy of diagnosis of myocardial ischemia. The combined use of diastolic heart sounds as measured by acoustic cardiography with ECG criteria may improve the early detection of acute myocardial ischemia, either transient or evolving to myocardial infarction, and, thus, help to provide timely treatment.

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Table 1. Sample characteristics

Characteristics	**Non-ischemia (n=18)**	**Ischemia (n=19)**	**P-value**
Age, mean (years)	54.8 ± 12.5	63.8 ± 9.4	0.017
Gender (Female)	27.8% (5/18)	73.7% (14/19)	0.009
Clinical Presentation Possible ACS Chronic Stable Angina Diagnostic catheterization	 22.2% (4/18) 5.6% (1/18) 72.2% (13/18)	 57.9% (11/19) 31.6% (6/19) 10.5% (2/19)	0.004
Hx of CAD	11.1% (2/18)	73.7% (14/19)	0.001
Hx of prior MI	5.6% (1/18)	42.1% (8/19)	0.025
Hx of HTN	72.2% (13/18)	68.4% (13/19)	0.503
Hx of CHF	27.8% (5/18)	10.5% (2/19)	0.210
Hx of DM	22.2% (4/18)	52.6% (10/19)	0.118
Ejection fraction, mean (%)	58.2 ±14.2 (n=14)	56.1± 8.4 (n=13)	0.642
LVEDP, mean (mmHg)	15.3 ± 5.5 (n=12)	17.6 ± 7.3 (n=7)	0.458
Baseline S3	5.6% (1/18)	5.3% (1/19)	1.0
Baseline S4	16.7% (3/18)	15.8% (3/19)	1.0
Baseline S3 or S4	22.2% (4/18)	15.8% (3/19)	0.693

ACS= acute coronary syndrome; CAD= coronary artery disease; MI= myocardial infarction; HTN= hypertension; CHF= congestive heart failure; DM= diabetes mellitus; LVEDP = left ventricular end diastolic pressure; S3= third heart sound; S4= fourth heart sound

Table 2. Standard ST-T wave criteria and diastolic heart sounds as predictors of acute myocardial ischemia (n=37)

	Sensitivity Ischemia Group (n =19)	**Specificity Non-ischemia Group (n=18)**	**Overall Accuracy (n=37)**	**Odds Ratio (95% CI)**	**P-value**
Standard ST-T criteria	52.6% (10/19)	100.0% (18/18)	75.7% (28/37)	N/A**	< 0.001***
S3	47.4% (9/19)	94.4% (17/18)	70.3% (26/37)	15.3 (1.7-139.3)	0.015*
S4	73.7% (14/19)	83.3% (15/18)	78.4% (29/37)	14.0 (2.8-69.8)	0.001*
S3 or S4	84.2% (16/19)	77.8% (14/18)	81.1% (30/37)	18.7 (3.6-98.2)	0.001*
Predictability of combined ECG and heart sound criteria					
Standard ST-T+S3	73.7% (14/19)	88.9% (16/18)	81.1% (30/37)	22.4 (3.7-134.1)	0.001*
Standard ST-T+S4	84.2% (16/19)	83.3% (15/18)	83.8% (31/37)	26.7 (4.6-153.2)	0.000*
Standard ST-T +S3 or S4	84.2% (16/19)	77.8% (14/18)	81.1% (30/37)	18.7 (3.6-98.2)	0.001*

* P value of logistic regression

** Odds ratio unavailable due to “zero” case of ST-T criteria in non-ischemia group

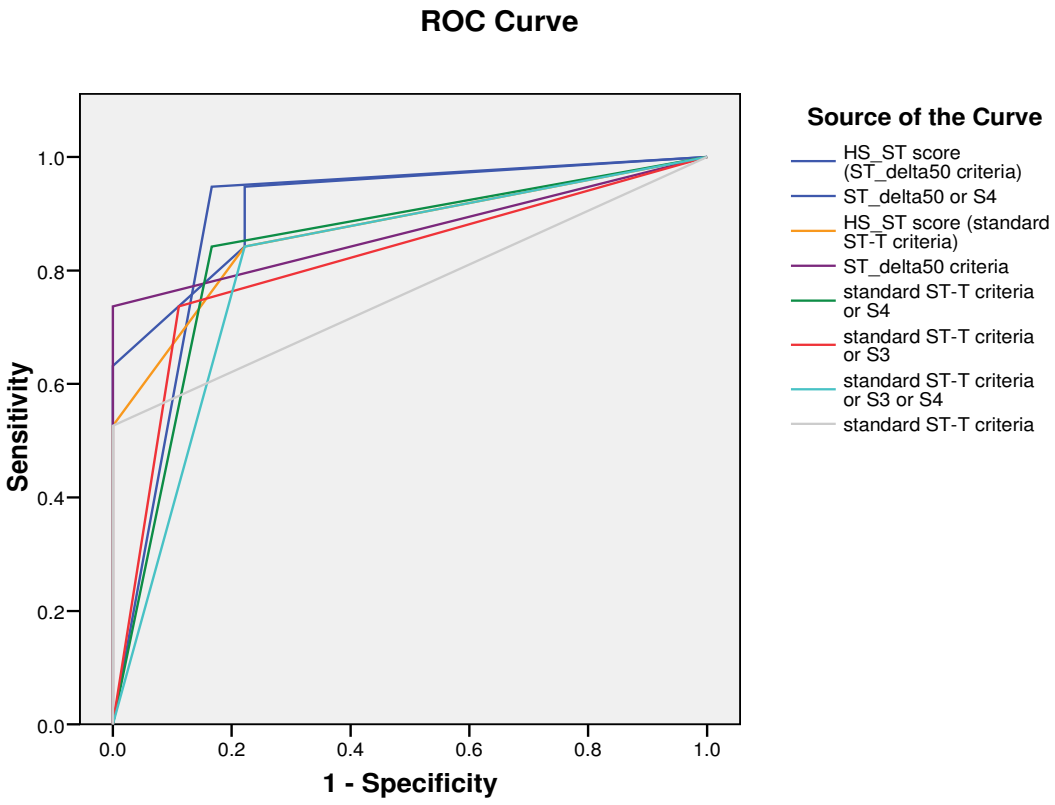
*** P value of Fisher’s exact test

Table 3. Sensitivity and specificity of ST-T wave criteria and diastolic heart sounds for predicting myocardial ischemia reported in the literature

Author Year	Method	N	Heart Sound Measure	Sensitivity	Specificity
Aronow[20] 1971	Master's two step test	100 with angina 100 normal subjects	PCG	ST-T criteria: 59% (59/100) S3:60% (60/100) S4:94% (94/100)	ST-T criteria: 96% (96/100) S3:89% (89/100) S4:71% (71/100)
Cohn[17] 1973	Handgrip exercise	41= CP with CAD 20= CP but negative angiogram	PCG	S3:14.6% (6/41) S4:46.3% (19/41) S3-S4: 54.0% (22/41)	S3:100.0% (20/20) S4:85.0% (17/20) S3-S4:85.0% (17/20)
McNair[19] 1967	Master's two-step exercise	39 with angina 52 normal subjects	AUS	ST-T criteria: 31% (12/39) S3:74% (29/39) S4:7.7% (3/39)	ST-T criteria: 94.3% (49/52) S3:100% (52/52) S4:96.2% (50/52)
Tavel[18] 1996	TMT exercise	292 with (+) perfusion defect 830 with (–) perfusion defect	AUS	ST-T criteria: 40% (27/68) S3:38.7% (113/292)	ST-T criteria: 62% (38/61) S3:90.3% (486/538)

MI= myocardial infarction; HS= heart sound; CP= chest pain; TMT= treadmill test; PCG= phonocardiogram; AUS= auscultation; S3=third heart sound; S4= fourth heart sound

Figure1. Prediction of ST-T criteria and diastolic heart sounds for myocardial ischemia



Variables	Area under the curve
HS_ST score (ST_delta50 criteria)	0.921
ST_delta50 criteria or S4	0.890
HS_ST score (Standard ST-T criteria)	0.868
ST_delta50 criteria	0.868
Standard ST-T criteria or S4	0.838
Standard ST-T criteria or S3	0.813
Standard ST-T criteria or S3 or S4	0.810
Standard ST-T criteria	0.763

Paper 3

Ischemic Cascade: Sequence of Electrocardiographic and Acoustic Cardiographic Changes and Anginal Symptoms During Coronary Occlusion

Lee, E., Michaels, A.D., Selvester, R.H., & Drew, B.J. Ischemic cascade: sequence of electrocardiographic and acoustic cardiographic changes and anginal symptoms during coronary occlusion.

Abstract

Background: Previous studies have suggested that ventricular function may be impaired without or prior to ECG changes during ischemia. Using diastolic third and fourth heart sounds (S3 and S4), a non-invasive measurement of ventricular function, our study investigated whether diastolic heart sounds occur earlier than electrical changes or angina during ischemia.

Methods: To determine the sequence of ECG, diastolic heart sounds, and anginal ischemic symptoms, a prospective observational study was performed in 21 subjects undergoing cardiac catheterization and percutaneous coronary interventional (PCI) procedures. Subjects had both ST-segment amplitude changes >2 standard deviations above the baseline, as well as new or increased intensity S3 or S4 measured by computerized acoustic cardiography. The sequence of resolution of these noninvasive signs of ischemia was also examined following balloon deflation.

Results: Electrocardiographic ST amplitude changes were the earliest sign of ischemia (mean onset, 21 seconds), and they were also the first to resolve after balloon deflation. New or increased intensity diastolic heart sounds followed ECG changes (mean onset, S4, 24.7 seconds; S3, 38.1 seconds). Anginal symptoms occurred in only 2 of the 21 subjects during ischemia with a mean onset time of 67.5 seconds.

Conclusion: ECG signs of ischemia preceded functional changes as measured by new or intensified S3 and/or S4. Angina is the last event in the ischemic cascade and in the vast majority of subjects.

Key words: myocardial ischemia, phonocardiography, acoustic cardiography, electrocardiography, heart sounds

Introduction

Early detection of myocardial ischemia in patients with acute coronary syndrome is essential to provide timely treatment and to prevent subsequent cardiac disability or death. Although the 12-lead electrocardiogram (ECG) has been considered the gold standard for detection of myocardial ischemia that is likely to develop into infarction, nearly half of patients presenting to an emergency department with chest pain who subsequently develop biomarker evidence of infarction have an initial nondiagnostic ECG [1-3]. Animal studies suggest that ventricular function may be impaired without significant ST segment changes during ischemia [4-6]. In humans, the ECG shows evidence of ischemia induced by percutaneous coronary intervention (PCI) in 36 - 53% of cases, whereas signs of ventricular dysfunction are present in 90-100% of cases [7-8].

"Ischemic cascade" refers to the temporal sequence of events during acute myocardial ischemia. In the previous studies, ventricular dysfunction measured by a rise in ventricular filling pressure or abnormal wall motion on echocardiogram was present in 85-100% of cases [8, 10-11] and was shown to occur earlier than ECG changes or chest pain during ischemia induced by PCI [7-11] or exercise [12-13] regardless of the duration or intensity of ischemia. However, these measures of ventricular function are either invasive or not readily available at the bedside for immediate and continuous assessment.

The presence of diastolic heart sounds (the third and fourth heart sounds; S3 and S4) is a non-invasive measure of ventricular function. In previous studies, diastolic heart sounds have been shown to be highly correlated with ventricular dysfunction such as elevation of left ventricular filling pressure or abnormal wall motion [14-21]. Diastolic heart sounds have been shown to occur frequently during myocardial ischemia induced

by exercise [20-23]. In fact, about two thirds of patients without ECG changes have been shown to develop diastolic heart sounds during ischemia [22-23] due to the decreased compliance of the ventricle. The aims of the present study were twofold: (1) to investigate the sequence of ECG, diastolic heart sounds, and anginal signs of ischemia during coronary occlusion induced by PCI procedures, and (2) to determine the sequence of resolution of these noninvasive signs of ischemia following reperfusion.

Methods

Research design, setting, and sample

A prospective observational study was performed in the cardiac catheterization laboratory at the University of California, San Francisco. The study was approved by the institution's Committee on Human Research and written informed consent was obtained prior to cardiac catheterization.

A convenience sample of subjects was enrolled from patients who were referred for non-urgent cardiac catheterization with possible PCI. Patients were excluded if they had acute ST elevation myocardial infarction requiring primary PCI or were hemodynamically unstable requiring urgent cardiac catheterization. Also excluded were patients who were unable to develop an S4 (atrial fibrillation or flutter) or patients likely to have diastolic heart sounds due to non-ischemic conditions (i.e., valvular heart disease, anemia, thyrotoxicosis, atrioventricular shunt, or tachycardia >120bpm). However, patients with ECG confounders for ischemia (i.e., bundle branch block, left ventricular hypertrophy with secondary ST-T wave abnormality) were not excluded.

Instruments

Acoustic cardiography. The Audicor heart sound detection system (Inovise Medical, Portland, OR) is designed to attach to standard 12-lead electrocardiographs. This compatibility allows the Audicor system to record and interpret ECG and heart sound data simultaneously using dual-purpose electrode sensors that acquire both ECG and acoustic data from the V_3 and V_4 locations. A Hewlett Packard XLi cardiograph (Philips, Andover, MA) was used to record 12-lead ECGs at a sampling rate of 1000 Hz. Continuous recording of acoustic and ECG data was performed before and during cardiac catheterization and PCI and stored for off-line analysis.

The Audicor system's computer algorithm distinguishes diastolic heart sounds from normal heart sounds by their relative timing to ECG waves as well as their characteristics (i.e. frequency, amplitude). The S3 is a low-pitched sound that occurs in early diastole approximately 120-180 milliseconds after the onset of the second heart sound. The S4 occurs during late diastole approximately 120-180 milliseconds after the onset of the P wave and before the Q wave. Sounds that consistently occur at the proper time for an S3 or S4 are rated from 0-10, with 10 as the loudest value. The algorithm diagnoses an S3 or S4 when their intensity reaches a value ≥ 5. The validity of the Audicor algorithm has been confirmed in studies correlating S3 and S4 detections with measurement of ventricular function during cardiac catheterization [14] and in a study that correlated diastolic heart sounds with decreased left ventricular ejection fraction or abnormal wall motion and increased B-type natriuretic peptide level [15].

Procedure

The 12-lead ECG and Audicor system were applied to the chest with torso-positioned limb leads in the standard Mason-Likar configuration [24] with Audicor dual-purpose sensors placed at the V3 and V4 locations. Radiolucent ECG lead wires and electrodes were used to allow for angiographic visualization of the coronary arteries; however, the two heart sound sensors were not radiolucent. For research purposes, a small device was attached to the Audicor system that produced a temporary flat line segment on the V3 or V4 ECG lead when a switch was depressed. This allowed the research nurse to mark the precise timing of balloon inflations and deflations, and other coronary interventions. The research nurse also noted chest pain or anginal equivalent symptoms during PCI balloon inflation.

Selection of PCI procedures for analysis of the sequence of signs of ischemia during coronary occlusion

One procedure was selected for each subject to serve as a model of acute myocardial ischemia due to coronary occlusion. Several coronary procedures were considered including PCI balloon occlusion with angioplasty or stent deployment and interruption of coronary blood flow during rotablator or intracoronary ultrasound [25]. In order to select the coronary procedures most likely to represent ischemia, only subjects who had an ST amplitude change (delta ST) at the J point of greater than 2 standard deviations (SD) over the baseline in ≥1 ECG lead during the procedure were included in the analysis. The use of the 2 SD criterion guaranteed that ST amplitude during the coronary intervention was significantly different than that at baseline with a 95%

confidence interval (alpha = 0.05). To minimize baseline variation due to noise, the baseline ST amplitude was calculated from an average of 30 consecutive 10-second 12-lead ECGs over a 3-5 minute period before catheters were inserted. To investigate the sequence of ischemic events such as ECG changes, diastolic heart sounds, and angina, for each subject, the first event with both delta ST >2 SD and new or increased intensity diastolic heart sounds was selected.

The onset of ischemic ECG changes was defined as the point after balloon inflation or other coronary intervention when ST amplitude exceeded 2 SD above the pre-catheterization baseline in the ECG lead with maximal delta ST. The onset of positive diastolic heart sounds was measured at the point when the intensity of the diastolic heart sound (a) reached a score of 5 or (b) exceeded 2 SD above the baseline in the presence of pre-existing diastolic heart sounds. The onset of chest pain/anginal equivalent symptoms was determined in "real time" by the research nurse who stood next to the subject's head during the coronary procedures.

Selection of PCI procedures for analysis of the sequence of resolution of signs of ischemia during coronary reperfusion

To determine how long each noninvasive sign of ischemia persisted after coronary reperfusion, the last balloon inflation/deflation episode was selected for analysis. If the last balloon inflation did not induce both delta ST >2 SD and diastolic heart sounds, then analysis was performed on a PCI event with both ST amplitude and diastolic heart sound changes that also had at least a 1-minute reperfusion interval after balloon deflation before subsequent coronary interventions.

The timing of the disappearance of ST amplitude changes after balloon deflation was measured at the point when the delta ST reached <2 SD from the baseline value. The disappearance of diastolic heart sounds after balloon deflation was measured at the point when the intensity of the diastolic heart sound (a) reached a score <5 or (b) became <2 SD above baseline in the presence of pre-existing diastolic heart sounds. The timing of the relief of chest pain/anginal equivalent symptoms was assessed prospectively by the research nurse eliciting the patient's self report.

Statistical analysis

The time interval from the onset of coronary intervention inducing ischemia during cardiac catheterization to the appearance of ST changes, appearance or increase in diastolic heart sounds, and occurrence of angina was measured in seconds. A paired *t*-test was used to investigate whether the timing of changes in diastolic heart sounds was different from the onset of ST changes or angina. Also, a paired *t*-test was used to investigate whether the timing of normalization was different for ST changes, diastolic heart sounds, and angina with an alpha of 0.05. For all statistical analyses, a two-tailed p-value < 0.05 was considered statistically significant. SPSS 15.0 was used for statistical analysis.

Results

A total of 80 patients, referred for cardiac catheterization due to cardiac symptoms suggestive of coronary artery disease or for screening for heart disease prior to surgery, underwent non-urgent cardiac catheterization and were attached to the Audicor

system. Fifty-four patients were excluded for the following reasons: coronary artery bypass surgery performed instead of PCI (n=20); negative angiographic findings (n=25); leads taken off due to hemodynamic instability (n=1) or inability to visualize the coronary artery during the procedure (n=3); lack of data storage (n=1); cancellation of the procedure (n=3); and missing data regarding timing of balloon inflation and deflation (n=1). The remaining 26 patients had ST amplitude changes >2 SD during PCI; however, 5 did not develop new or increased intensity diastolic heart sounds so the sequence of noninvasive signs of ischemia could not be determined. Thus, the final sample size for the present analysis was 21.

Sample characteristics

Clinical characteristics and angiographic findings for the 21 subjects are displayed in Table 1. Twenty subjects' ischemic events were induced by PCI balloon occlusion (angioplasty, n=15; stent deployment, n=4), or rotablator use (n=1). The mean duration of balloon occlusion was 29.5 ± 5.7 seconds. The mean maximal ST amplitude change from baseline to coronary occlusion was 102.7 ± 109.0 μV. Three patients had the ST deviation at the baseline secondary to left ventricular hypertrophy. In a 21st subject undergoing pre-surgical diagnostic cardiac catheterization, we had the unique opportunity to observe a spontaneous occlusion of the proximal left anterior descending coronary. This case is described in detail elsewhere [26]. However, this subject developed ST segment elevation in leads I, aVL, V_{2-5} with reciprocal ST depression in leads II, III, aVF, and V_6 that persisted until emergency stent placement was performed. The subject also developed both S3 and S4 heart sounds as well as the anginal equivalent symptom of

acute dyspnea. The subject did sustain a limited acute myocardial infarction with positive serum biomarkers; however, following urgent treatment, the subject had a good outcome.

Among the 21 subjects, baseline S3 and S4 were present in three patients (1: S3 only, 1: S4 only, 1: S3 and S4). During coronary occlusion, a new or increased intensity of S3 developed in 11 subjects and a new or increased intensity of S4 developed in 17 subjects (4: S3 only, 10: S4 only, 7: S3 and S4). Angina occurred in only two of the 21 subjects during coronary occlusion. In these two subjects, the mean duration of balloon inflation was 31.0 ± 1.4 seconds and the mean ST amplitude change was 165.5 ± 17.7μV.

Ischemic cascade: sequence of the onset of noninvasive signs of ischemia during coronary occlusion

ST amplitude changes >2 SD began to occur an average of 21.0 seconds after coronary occlusion whereas new or increased intensity diastolic heart sounds occurred an average of 25.2 seconds after coronary occlusion (Table 2). This average 4.2 second difference was not statistically significant (paired t-test, p =0.42). In the case with spontaneous coronary occlusion, ST amplitude changes >2 SD developed at 10 seconds after initial coronary occlusion, followed by new development of and an S4 (50 seconds) and an S3 (140 seconds) when the onset of coronary occlusion was specified as the time before any acute ST changes. Of the 21 subjects, diastolic heart sound changes occurred earlier than ST changes in 8 (38.1%), at the same time as ST changes in 4 (19.0%), and later than ST changes in 9 (42.9%).

In the two subjects who reported symptoms during ischemia, angina occurred an average 67.5 seconds following coronary occlusion and was preceded by ECG and

diastolic heart sound changes. Specifically, one subject developed ST changes >2SD at 4 seconds, a new S4 at 24 seconds, and angina at 34 seconds after balloon inflation. The second subject developed both ST changes >2 SD and a new S4 at 11 seconds, a new S3 at 21 seconds, and angina at 103 seconds after balloon inflation.

Sequence of resolution of noninvasive signs of ischemia following reperfusion

Eighteen of the 21 patients who developed both ST amplitude and diastolic heart sound changes had the required 1-minute reperfusion interval from balloon deflation to subsequent intervention that was required for assessment of the disappearance of ischemic signs. All 18 of the selected episodes had coronary reperfusion due to balloon deflation following angioplasty, n=13 or stent deployment, n=5. The mean duration of balloon occlusion was 28.2 ± 6.7 seconds. The mean maximal ST amplitude changes during occlusion were 149.6± 130.8 μV (range: 21 – 496 μV). A new or increased intensity of S3 occurred in 10 patients and a new of increase S4 occurred in 14 patients (4- S3 only, 8- S4 only, 6- S3 and S4). The average interval between balloon deflation and subsequent balloon inflation or other coronary intervention was 144.4 ± 74.4 seconds (range: 60 - 310 seconds). After balloon deflation, both diastolic heart sound and ST amplitude changes normalized in all 18 subjects. Angina occurred in 5 of the 18 subjects during the selected coronary procedure.

Mean time for ischemic signs to disappear following balloon deflation is shown in Table 3. The mean time for ST amplitude changes to normalize was 32.6 seconds whereas the resolution of both S3 and S4 heart sounds averaged 92.4 seconds after balloon deflation (p=0.088). In 14 (77.8%) of the 18 subjects, ST amplitude changes

normalized earlier than (n=12) or at the same time as (n=2) diastolic heart sound changes. In the remaining 4 patients, diastolic heart sound changes resolved earlier than ST amplitude changes.

Five subjects developed symptoms of ischemia (chest pain, 4; nausea, 1) during balloon occlusion. In all 5 subjects, symptoms persisted after ECG and heart sound changes had normalized. Mean time to symptom relieve after balloon deflation was 586.0 ± 652.7 seconds.

Discussion

Findings from this study suggest that sudden occlusion of a coronary artery produces ECG changes as the earliest manifestation of ischemia, with new or increased intensity of diastolic heart sounds (S3 and/or S4) occurring a few seconds later. Our findings demonstrate that the onset of chest pain or anginal equivalent symptoms is the last sign in the ischemic cascade and symptoms were missing altogether in more than 90% of our subjects who had both ECG and heart sound signs of ischemia. In addition to using the artificial PCI model of ischemia, we had the unique opportunity to observe one subject who had a spontaneous occlusion of the proximal left anterior descending coronary artery resulting in acute myocardial infarction. In this subject, ECG changes also preceded development of an S3 and S4 by about one minute.

Our findings differ from previous investigations [7-11] that show abnormalities of ventricular function occur earlier than ECG changes during acute coronary occlusion. Investigators reported that the earliest indication of ischemia during PCI was diastolic dysfunction (fall in dP/dT) within 2-12 seconds, followed by systolic dysfunction (wall

motion abnormalities on echocardiogram) within 5-20 seconds and elevation of left ventricular end-diastolic pressure within 18 seconds. These functional changes preceded ECG changes that occurred within 15-30 seconds and angina that occurred in 35-40 seconds, if it occurred at all.

A possible explanation for our disagreement with prior reports on the sequence of functional and ECG signs of ischemia may be that, unlike previous investigations that used a single ECG lead or less than 12 ECG leads (or did not specify ECG leads) or failed to record continuously (i.e. a snap-shot or series of ECGs) [20-23], we obtained continuous recordings of all 12 ECG leads during the entire diagnostic cardiac catheterization and PCI procedure period. Ischemia due to abrupt occlusion of a major epicardial coronary artery produces ST segment changes only in several ECG leads that face the localized ischemic myocardium in that vessel's distribution. Thus, it is possible that prior investigators underestimated ECG changes due to single lead monitoring or non-continuous multi-lead monitoring. The other possibility is that the Audicor detection of new or increased S3 or S4 is delayed beyond the early increase in LVEDP or wall motion abnormalities on echocardiogram.

Electrocardiographic changes with myocardial ischemia are due to direct effects of ischemia on the cellular action potential [27]. The cellular action potential of ischemic cells shows a loss in resting membrane potential and a shorter action potential duration. Differences in electrical potentials between ischemic and non-ischemic cells create a gradient especially during phases 3 and 4 of the action potential and result in current flow that produces ST segment changes on the body surface ECG.

Because many non-ischemic conditions (e.g., body position changes with continuous ECG monitoring) can cause ST segment changes, the appearance of new or intensified diastolic heart sounds helps to confirm that observed ST segment fluctuations are, in fact, due to ischemia. Such confirmation of combined ECG and heart sound information would be expected to improve the diagnostic accuracy of the ECG alone when evaluating a patient presenting to an emergency department with chest pain.

Our findings are in agreement with previous studies [7-11] that demonstrate angina is the final event in the ischemic cascade when it is present. During ischemia induced by PCI, angina has been reported to occur about 35 to 90 seconds after balloon inflation and about 15-30 seconds after ECG changes or measures of ventricular dysfunction. We observed that when angina occurred, its onset began an average of 67.5 seconds after balloon inflation, following ST amplitude and diastolic heart sound changes.

Previous studies using ST-segment Holter monitoring have reported that about 70-90% of ischemic episodes occur silently without angina [28-32]. However, Chierchia and colleagues [32] found that even during asymptomatic episodes, ventricular dysfunction occurred to the same extent as during symptomatic episodes. In their study [32], ischemia occurred silently without angina in 84% of 283 episodes of ischemia documented by ECG changes. Also, an increase in ventricular filling pressure was observed in 60% of those asymptomatic episodes. These finding are supported by our study using acoustic cardiography. In our study, during balloon coronary occlusions of approximately 30 seconds, 19 of 21 patients did not develop angina; however, all 19 developed new or increased intensity diastolic heart sounds.

In follow-up studies [33-34], silent ischemia was associated with a higher incidence of cardiac death, non-fatal MI, and coronary artery bypass surgery or PCI than those with angina symptoms. Such undesirable outcomes may have resulted from the failure to detect and treat ischemia. Ventricular function may be impaired to the same extent in subjects with and without angina symptoms during ischemia.

In our study, after reperfusion, ECG changes normalized earlier than the return of ventricular function as evidenced by the disappearance of new or intensified diastolic heart sounds. Three previous investigative groups [8, 10-11] observed that echocardiographic changes begin to normalize about 10 –22 seconds after PCI balloon deflation. Hauser and colleagues [8] reported that, after balloon deflation, angina symptoms resolved first, followed by ECG changes and echocardiographic changes. In contrast, we found that angina persisted after balloon deflation even after ECG and diastolic heart sound changes had disappeared.

Study limitations/ Further study

The small sample size limited our ability to detect statistically significant differences in timing of noninvasive signs of ischemia. A future study is needed to compare the sequence of noninvasive signs of ischemia in patients who are evaluated in the emergency room with acute coronary syndrome and to determine the diagnostic value of combined acoustic and electrocardiographic signs of ischemia.

Conclusion

The current study indicates that electrocardiographic ST segment changes are the first noninvasive measure to appear and disappear during coronary occlusion and reperfusion. New or increased intensity diastolic heart sounds measured by acoustic cardiography accompany ECG changes of ischemia a few seconds later and serve to confirm the diagnosis of ischemia for patients without anginal symptoms. Angina is the last event in the ischemic cascade and in the vast majority of subjects, does not occur at all during PCI-related coronary occlusion.

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Table 1. Sample Characteristics (n=21)

Mean age (yrs)	64.0 ± 10.5
Male	15 (71.4%)
Clinical presentation	
Possible ACS (non-STEMI or unstable angina)	10 (47.6%)
Chronic stable angina	7 (33.3%)
Diagnostic catheterization (pre-operative or other evaluation)	4 (19.1%)
Medical history	
Coronary artery disease	14 (66.7%)
Prior myocardial infarction	8 (38.1%)
Diabetes Mellitus	12 (57.1%)
Hypertension	14 (66.7%)
Chronic Heart Failure	1 (4.8%)
Angiographic extent of disease	
Single-vessel disease	8 (38.1%)
Double-vessel disease	7 (33.3%)
Triple-vessel disease	3 (23.8%)
Four-vessel disease	1 (4.8%)
Ejection fraction (%), mean (n=16)	56.4 ± 9.2
LVEDP (mmHg), mean (n=8)	17.4 ± 7.3

ACS= acute coronary syndrome; LVEDP= left ventricular end-diastolic pressure;

STEMI= ST elevation myocardial infarction

Table 2. Sequence of noninvasive signs of ischemia during coronary occlusion

Subjects with ST change > 2 SD with new or increased S3 or S4 (n=21)					
Sign	ST >2 SD	New or ↑S3	New or ↑S4	New or ↑ S3 or S4	Angina
Time of onset (seconds)	21.0 ± 17.4 (n=21)	38.1 ± 39.6 (n=11)	24.7 ± 25.1 (n=17)	25.2 ± 25.3 (n=21)	67.5 ± 50.2 (n=2)
Ischemic events during PCI (n=20)					
Time of onset (seconds)	21.5 ± 17.6 (N=20)	27.9± 17.3 (n=10)	23.1 ± 25.0 (n=16)	24.0 ± 25.2 (n=20)	67.5 ± 50.2 (N=2)
Ischemic events during spontaneous coronary occlusion (n=1)					
Time of onset (seconds)	10	140	50	50	(+) SOB/ (-) CP (onset: unclear)

S3- third heart sound; S4- fourth heart sound; SOB- shortness of breath; CP- chest pain

Table 3. Disappearance of noninvasive signs of ischemia after balloon deflation (n=18)

Sign	ST	S3	S4	S3 & S4	Angina
Time to disappearance (seconds)	32.6 ± 31.0 (n=18)	47.4 ± 43.8 (n=10)	94.4 ± 166.2 (n=14)	92.4 ± 144.0 (n=18)	586.0 ± 652.7 (n=5)

S3- third heart sound; S4- fourth heart sound

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6-6-08 — Date