Sequence of Electrocardiographic and Acoustic Cardiographic Changes and Angina during Coronary Occlusion and Reperfusion in Patients Undergoing Percutaneous Coronary Intervention

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Background: Previous studies have suggested that ventricular function may be impaired without or prior to electrocardiographic changes or angina during ischemia. Understanding of temporal sequence of electrical and functional ischemic events may improve the detection of myocardial ischemia.

Methods: A prospective study was performed in 21 subjects undergoing percutaneous coronary intervention (PCI) who had both ST amplitude changes >2 standard deviations above baseline on 12-lead electrocardiography (ECG), and new or increased third or fourth heart sound (S3 or S4) intensity measured by computerized acoustic cardiography. The sequence of the onset and resolution of these signs of ischemia were examined following coronary balloon inflation and deflation.

Results: Electrocardiographic ST amplitude and diastolic heart sound changes occurred contemporaneously, shortly after coronary occlusion (mean onset from balloon inflation; ST changes, 21 ± 17 seconds; S4, 25 ± 26 seconds; S3, 45 ± 43 seconds). In 40% of patients, a new or increased S3 or S4 developed earlier than ST changes. Anginal symptoms occurred in only 2 of the 21 subjects during ischemia with a mean onset time of 68 seconds. ST-segment changes resolved earliest (33 seconds after balloon deflation) while diastolic heart sounds (89 ± 146 seconds) and angina (586 ± 653 seconds) resolved later.

Conclusion: A new or intensified S3 and/or S4 occurred contemporaneously with electrocardiographic changes during ischemia. These diastolic heart sounds persisted longer than ST changes following coronary reperfusion. Acoustic cardiographic assessment of diastolic heart sounds may aid in the early detection of myocardial ischemia, particularly in those patients with an uninterpretable ECG.

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Early detection of myocardial ischemia in patients with acute coronary syndrome is essential to provide timely treatment and 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.^{1,2} Previous studies suggest that ventricular function can be severely impaired without

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ST-segment changes or angina during ischemia.^{3–12} During ischemia induced by percutaneous coronary intervention (PCI), about 40% of patients developed ventricular dysfunction without ischemic ST changes.^{6–8} In about 40% of patients who released excessive lactate that can damage the myocardial cells, angina did not develop during ischemia.¹³

Independent of electrocardiographic changes caused by the differences in electrical action potentials between ischemic and nonischemic cells, ventricular dysfunction has been shown to occur due to the loss of compliance of the ischemic zone of the left ventricle during ischemia.^{6–12} The combined use of electrical and functional changes of ischemia may help the early detection of ischemia and a timely provision of treatment, especially in patients with uninterpretable ECGs or those without angina.

In prior studies, ventricular dysfunction measured by a rise in ventricular filling pressure or abnormal wall motion on echocardiography was shown to occur earlier than ECG changes and angina during ischemia induced by PCI^{6–8} or exercise/atrial pacing,^{9–12} regardless of the duration or intensity of ischemia. Also, ventricular dysfunction persisted longer than ischemic ST changes after coronary reperfusion.^{7,13,14} Understanding the temporal changes of ST-segment deviation, ventricular dysfunction, and angina during myocardial ischemia continues to be clinically important. However, invasive measures of ventricular function are not readily available at the bedside for immediate and continuous assessment.

The assessment of diastolic third and fourth heart sounds (S3 and S4) determined by acoustic cardiography is a noninvasive measure of ventricular function. Previous studies have shown that diastolic heart sounds are highly correlated with ventricular dysfunction, such as elevation of left ventricular filling pressure or abnormal echocardiographic wall motion.^{15–17} Diastolic heart sounds have been shown to occur frequently during myocardial ischemia induced by exercise.^{18–21} In fact, two-thirds of patients without ECG changes develop diastolic heart sounds during ischemia^{18,19} due to the decreased compliance of the ventricle.

The aims of this study were twofold: (1) to investigate the sequence of ECG, acoustic cardiographic, and anginal signs during coronary occlusion induced during PCI, and (2) to determine the

sequence of resolution of these noninvasive signs of ischemia following reperfusion upon balloon deflation.

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 study enrollment.

A convenience sample of subjects was enrolled from patients who were referred for nonurgent coronary angiography 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 nonischemic conditions (i.e., valvular heart disease, anemia, thyrotoxicosis, atrioventricular shunt, or tachycardia >120 bpm). 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

Computerized Acoustic Cardiography

The acoustic cardiographic heart sound detection system (Audicor, Inovise Medical Inc., Portland, OR, USA) has been approved by the US Food and Drug Administration (FDA) and is commercially available. It is designed to attach to standard 12-lead electrocardiographs although the newer system incorporates the electrocardiograph function. This allows the acoustic cardiograph to record and interpret ECG and heart sound data simultaneously using dual-purpose electrode sensors that acquire both ECG and acoustic data from the V₃ and V₄ locations. A Hewlett Packard XLI cardiograph (Philips, Andover, MA) was used to record 12-lead ECGs at a sampling rate of 1000 Hz. Continuous recordings of acoustic and ECG data were performed before and during cardiac catheterization and PCI and stored for off-line analysis. Using a proprietary software program (Inovise Medical),

mean values of 10-second data of ST amplitudes of all 12 ECG leads and heart sounds recorded before and during cardiac catheterization were provided for off-line analysis.

The computer algorithm within the acoustic cardiograph distinguishes diastolic heart sounds from normal heart sounds by their relative timing to ECG waves as well as their acoustic 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 to 10, with 10 as the most intense value. The algorithm diagnoses an S3 or S4 when their intensity reaches a value ≥ 5 . The validity of this algorithm has been confirmed in studies correlating S3 and S4 detection with measurement of ventricular function during cardiac catheterization such as decreased left ventricular ejection fraction, elevated left ventricular end-diastolic pressure, and/or increased B-type natriuretic peptide level.^{15,16} By contrast, human auscultation skills in clinical practice have proven to be unreliable.^{22,23} A prior study has demonstrated that acoustic cardiography is superior to clinical auscultation performed by cardiologists for the detection of ventricular dysfunction.²⁴

Procedure

The 12-lead ECG and acoustic cardiograph were applied to the chest with torso-positioned limb leads in the standard Mason-Likar configuration with acoustic cardiograph's dual-purpose sensors placed in 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 acoustic cardiograph 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 recorded chest pain or anginal equivalent symptoms during the procedure.

Selection of PCI Procedures for Analysis of the Sequence of Signs of Ischemia during Coronary Occlusion

One balloon inflation event 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 rotational atherectomy and/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 from 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- to 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 of, 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 precatheterization 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 preexisting 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 preexisting 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 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 (SPSS, Chicago, IL, USA) was used for statistical analysis.

RESULTS

A total of 80 patients, referred for coronary angiography due to cardiac symptoms suggestive of coronary artery disease or for screening for heart disease prior to surgery, underwent nonurgent coronary angiography and were attached to the acoustic cardiography. 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 ($n = 1$),

Table 1. Demographic and Clinical Characteristics ($n = 21$)

Mean age (years)	64.0 $\pm$ 10.5
Male	15 (71%)
Clinical presentation	
ACS (NSTEMI or unstable angina)	10 (48%)
Chronic stable angina	7 (33%)
Diagnostic catheterization (preoperative or other evaluation)	4 (19%)
Medical history	
Prior myocardial infarction	8 (38%)
Diabetes mellitus	12 (57%)
Hypertension	14 (67%)
Heart failure	1 (5%)
Angiographic extent of disease	
Single-vessel disease	8 (38%)
Two-vessel disease	7 (33%)
Three-vessel disease	5 (24%)
Four-vessel disease	1 (5%)
Ejection fraction (%), mean ($n = 16$)	56.4 $\pm$ 9.2
LVEDP (mmHg), mean ($n = 8$)	17.4 $\pm$ 7.3

ACS = acute coronary syndrome; LVEDP = left ventricular end-diastolic pressure; NSTEMI = non-ST elevation myocardial infarction.

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, five did not develop new or increased intensity diastolic heart sounds. Thus, the final sample size for the present analysis to determine the sequence of noninvasive signs of ischemia was 21 subjects.

Sample Characteristics

Clinical characteristics and angiographic findings for the 21 subjects are displayed in Table 1. In these 21 subjects, the mean duration of balloon occlusion was 29.5 ± 5.7 seconds. The mean maximal ST amplitude change from baseline to coronary occlusion was $138.7 \pm 141.8 \mu\text{V}$. Nineteen subjects' ischemic events were induced by PCI balloon occlusion (angioplasty, $n = 12$; stent deployment, $n = 7$). One patient received rotational atherectomy. The remaining subject underwent presurgical diagnostic coronary angiography and had spontaneous vasospastic occlusion of the proximal left anterior descending coronary during diagnostic coronary angiography. This case is described in detail elsewhere.²⁶ This subject developed ST-segment elevation in leads I, aVL, V₂₋₅ that persisted until emergency stent placement was performed. The subject also

Figure 1. Electrocardiographic and acoustic cardiographic changes in lead V3 at baseline (panel A), onset of ECG changes (B), onset of S4 (C), and onset of S3 (D). The time from left anterior descending coronary artery occlusion due to rotational atherectomy is shown for panels B, C, and D.

developed both S3 and S4 heart sounds as well as the anginal-equivalent symptom of acute dyspnea. Among the 21 subjects, three patients had baseline ST deviation due to left ventricular hypertrophy but none had a bundle branch block. Baseline S3 and S4 were present in three patients (S3 only in 1; S4 only in 1; both S3 and S4 in 1).

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 (S3 only in 4; S4 only in 10; both S3 and S4 in 7); whereas, ST changes meeting clinical criteria $\geq 100 \mu\text{V}$ above the baseline were observed in 9 out of 21 subjects (43%). Angina occurred in only 2 of the 21 subjects during coronary occlusion.

Sequence of the Onset of Noninvasive Signs of Ischemia during Coronary Occlusion

The electrocardiographic and acoustic diastolic heart sound changes in a representative patient during left anterior descending coronary artery occlusion due to rotational atherectomy are shown in Figure 1. In this case, electrocardiographic ST changes occurred first, followed by the development of an S4 and last an S3. The timing of electrocardiographic and acoustic cardiographic changes and angina in each subject is described in Table 2. The mean time of the onset of ST changes and the development of a new or increased S3

Table 2. The Timing of Electrocardiographic and Acoustic Cardiographic Changes and Angina during Coronary Occlusion (n = 21)

Subject Number	Coronary Artery and Location	Duration of Occlusion (sec)	Lead with Maximal ST Change	Maximal Delta ST (μ V)	Time to ECG Deviation Onset (>2SD; sec)	Time to New or $\uparrow$ S3 Onset (sec)	Time to New or $\uparrow$ S4 Onset (sec)	Time to New or $\uparrow$ S3/S4 Onset (sec)	Time to Angina (sec)
1	LAD, proximal	32	V2	+64.0	63	43	53	43	—
2	RCA, distal	29	V3	−205.0	9	40	—	40	—
3	Left main	30	III	−90.3	12	52	—	52	—
4	Left main	—	III	−333.7	10	140	50	50	—
5	RCA, proximal	26	V6	−18.0	19	9	—	9	—
6	LCx, mid	37	V4	−27.8	50	—	10	10	—
7	LAD, mid	34	V4	+355.0	12	12	22	12	—
8	LAD, mid	32	III	−16.8	30	—	10	10	—
9	LAD, proximal	34	II	−101.0	41	31	31	31	—
10	LAD, proximal	34	V4	−42.3	55	—	105	105	—
11	LAD, mid	26	V2	+91.4	12	22	12	12	—
12	LCx, proximal	24	V3	+42.4	4	4	14	4	—
13	LAD, mid	32	V3	+166.0	4	—	24	24	32
14	LAD, mid	—	V3	+496.0	11	121	21	21	—
15	RCA, mid	32	AVF	+22.5	30	—	20	20	—
16	LAD, proximal	30	V3	+415.7	11	21	11	11	103
17	LCx, distal	38	III	+39.5	13	—	13	13	—
18	OM, proximal	19	V2	−44.2	12	2	—	2	—
19	RCA, mid	16	V3	+126.2	7	47	—	47	—
20	LCx, distal	26	III	+135.0	12	—	2	2	—
21	LCx, mid	29	V2	−80.7	23	—	2	2	—

S3 = third heart sound; S4 = fourth heart sound; LAD = left anterior descending; RCA = right coronary artery; LCx = left circumflex; OM = obtuse marginal.

or S4 from the PCI procedures is summarized in Table 3. There was no significant difference between the onset of ST-segment deviation onset and diastolic heart sounds. Both ST amplitude changes >2 SD and new or increased diastolic heart sounds began to occur within 20–45 seconds after coronary occlusion. In the case with spontaneous coro-

nary occlusion, ST amplitude changes >2 SD developed 10 seconds after initial coronary occlusion, followed by the new development of an S4 (50 seconds) and an S3 (140 seconds).

In the two subjects who reported symptoms during ischemia, angina occurred 67.5 ± 50.2 seconds following coronary occlusion and was preceded by

Table 3. 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 $\uparrow$ S3	New or $\uparrow$ S4	New or $\uparrow$ S3 or S4	Angina
Time of onset (seconds)	21.0 $\pm$ 17.4 (n = 21)	45.0 $\pm$ 43.1 (n = 12)	25.0 $\pm$ 25.9 (n = 16)	25.2 $\pm$ 25.3 (n = 21)	67.5 $\pm$ 50.2 (n = 2)
Ischemic events during PCI (n = 19)					
Time of onset (seconds)	22.1 $\pm$ 17.9 (n = 19)	27.9 $\pm$ 17.3 (n = 10)	23.5 $\pm$ 26.8 (n = 14)	24.2 $\pm$ 25.9 (n = 20)	67.5 $\pm$ 50.2 (n = 2)
Ischemic events during rotational atherectomy (n = 1)					
Time of onset (seconds)	11	121	21	21	—
Ischemic events during spontaneous coronary occlusion (n = 1)					
Time of onset (seconds)	10	140	50	50	—

S3 = third heart sound; S4 = fourth heart sound.

Table 4. The Timing of Resolution of Electrocardiographic and Acoustic Cardiographic Changes and Angina after Coronary Reperfusion (n = 18)

Subject Number	Time to Resolution of ECG Deviation (sec)	Time to Resolution of S3 (sec)	Time to Resolution of S4 (sec)	Time to Resolution of S3 and S4 (sec)	Time to Resolution of Angina (sec)
1	66	96	6	96	98
2	86	26	66	66	1657
3	12	32	–	32	–
7	28	18	8	18	–
8	8	–	8	8	–
9	15	5	235	235	530
10	20	–	60	60	–
11	9	9	59	59	–
12	5	89	79	89	–
13	22	–	12	12	25
14	17	7	27	27	–
15	53	133	133	133	–
16	17	–	17	17	620
17	15	–	5	5	–
18	113	13	–	13	–
19	31	51	–	51	–
20	6	–	56	56	–
21	64	–	627	627	–
Mean ± SD	32.6 ± 31.0	47.4 ± 43.8	95.1 ± 165.7	89.1 ± 145.6	586.0 ± 652.7

S3 = third heart sound; S4 = fourth heart sound.

ECG and diastolic heart sound changes. Subjects who developed angina during ischemia were more likely to develop other ischemic signs earlier than those without angina (ST = 7.5 vs 22.4 seconds; S3 or S4 = 17.5 vs 26.1 seconds) and have greater ST changes during ischemia (mean: 290.9 vs 112.7 μ V; P = NS), although the duration of coronary occlusion was similar in both groups (31 vs 29 seconds).

Sequence of Resolution of Noninvasive Signs of Ischemia Following Reperfusion

Eighteen (angioplasty, n = 13; stent deployment, n = 5) 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. Because of these requirements, the data regarding ischemic resolution often were obtained following balloon deflations, which were different from the balloon events presented in Table 2. 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 defla-

tion, both diastolic heart sounds and ST amplitude changes normalized in all 18 subjects.

The timing of the disappearance of noninvasive signs of ischemia after balloon deflation in each subject is described in Table 4. The mean time for ST amplitude changes (32.6 seconds) to normalize tended to be earlier compared to the time for resolution of both S3 and S4 heart sounds (89.1 seconds; P = 0.09). In 13 (78%) of the 18 subjects, ST amplitude changes normalized earlier than (n = 11) or at the same time as (n = 2) diastolic heart sound changes. Five subjects developed symptoms of ischemia (chest pain, 4; nausea, 1) during balloon occlusion. In all five subjects, symptoms persisted after ECG and heart sound changes had normalized.

Correlation between Ventricular Function and the Onset of Noninvasive Ischemic Signs

Among patients who developed a new or increased S3 during ischemia (n = 11), patients with an S3 intensity score ≥ 8.0 tended to develop ST changes (11.7 vs 21.6 seconds; P = 0.43) and diastolic heart sounds earlier (15.0 vs 33.0 seconds; P = 0.22) than patients with an intensity score < 8.0 .

Patients with a higher intensity of S3 tended to have greater maximal delta ST than those with a lower intensity score for S3 (271.6 μ V vs 128.7 μ V; $P = 0.13$).

DISCUSSION

Findings from this study suggest that sudden occlusion of a coronary artery produces both ECG changes and new and/or increased intensity of diastolic heart sounds (S3 and/or S4) within 20–45 seconds of the coronary occlusion due to balloon inflation. In roughly 40% of our subjects, diastolic heart sounds occurred earlier than ischemic ST changes. Our findings demonstrate that the onset of chest pain or anginal-equivalent symptoms is infrequent and is typically the last sign in the sequence of ischemia. Symptoms were absent altogether in more than 90% of our subjects who had both ECG and acoustic cardiographic signs of ischemia.

Our findings differ from previous investigations^{6–12} that show abnormalities of ventricular function occur earlier than ECG changes during acute coronary occlusion as a result of PCI^{6–8} or during ischemia resulting from exercise or atrial pacing.^{9–12} Previous investigators reported that the earliest indication of ischemia during PCI was diastolic dysfunction (fall in dP/dT; 2–12 seconds), followed by systolic dysfunction (wall motion abnormalities on echocardiogram: 5–20 seconds) and elevation of left ventricular end-diastolic pressure (18 seconds). These functional changes preceded ECG changes that occurred (15–30 seconds) and angina (35–40 seconds), if it occurred at all. Also, Sugishita's study¹⁰ showed that abnormal ventricular wall motion on echocardiogram occurred earlier than (82%) or at the same time as (13%) ischemic ST-T wave changes on ECG (30 $\pm$ 15 seconds vs 90 $\pm$ 60 seconds; $P < 0.001$) during ischemia due to exercise.

There are several explanations for discrepancies with prior reports on the sequence of functional and ECG signs of ischemia. Unlike previous investigations that used a single ECG lead or fewer than 12 ECG leads,^{6–8} we obtained continuous recordings of all 12 ECG leads during PCI procedure period. When applied leads do not face the localized ischemic zone in that occluded coronary artery, ischemia may not be detected. It is possible that prior investigators underestimated ECG changes as monitored by fewer than 12 ECG leads or by noncontinuous monitoring. Another explanation of the find-

ing of diastolic heart sounds occurring later than ECG changes is our use of external, noninvasive acoustic cardiographic methods. The noninvasive measurement of an S3 or S4 may require more time than the direct measurement of left ventricular end-diastolic pressure from the inside of the heart.

Previous studies using ST-segment Holter monitoring have reported that 70–90% of ischemic episodes occur silently without angina.^{27,28} However, Chierchia and colleagues²⁸ found that during asymptomatic episodes, ventricular dysfunction occurred to the same extent as during symptomatic episodes. In their study, an increase in ventricular filling pressure was observed in 60% of those asymptomatic episodes. Similarly, Helfant¹³ reported that 8 of 21 patients (38%) had abnormal lactate metabolism but they did not develop angina during ischemia induced by atrial pacing. Also, they did not find any correlation between abnormal lactate metabolism and ECG changes. These findings suggest that myocardial cell damage can occur without ECG changes or angina. In our study, among the 21 subjects who underwent percutaneous coronary intervention, ST changes meeting clinical criteria ≥ 100 μ V above baseline were observed in only 43% and chest pain was reported in only 2 of the 21 subjects during coronary occlusion; whereas, new or increased intensity of S3 or S4 developed in all subjects.

A previous study¹² observed that the degree of ventricular dysfunction correlated with an increase in lactate production. It was observed that an elevation in left ventricular end-diastolic pressure that persisted for more than 1 minute, or the presence of angina, tended to accompany abnormal lactate metabolism and significant ST changes.¹² Similarly, we observed that patients with a higher intensity of scores for S3 and/or S4 during ischemia developed ST changes and diastolic heart sounds earlier after balloon inflation and that the ST changes were greater. Also, we observed that patients with angina were more likely to have greater ST changes and to develop ischemic ST changes and diastolic heart sounds earlier during ischemia than those without angina.

After reperfusion, ECG changes normalized promptly, preceding the return of ventricular function as evidenced by the disappearance of new or intensified diastolic heart sounds. These findings are similar to those in ischemia studies during atrial pacing¹³ or exercise.¹⁴ Electrocardiographic

and hemodynamic changes normalized earlier than resolution of ventricular function and angina after the cessation of exercise or atrial pacing. Hauser and colleagues⁷ 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.

Ambrosio¹⁴ suggested that delay in the recovery of contractile function after resolution of exercise-induced angina may indicate evidence of myocardial stunning. Helfant¹³ observed that angina and abnormal lactate metabolism improved 10 minutes after the discontinuation of pacing. In our study, diastolic heart sounds, the S3 and S4 disappeared earlier than angina in the five patients who developed angina during balloon inflation and, similar to previous studies, angina was resolved about 10 minutes after balloon deflation.

Nonischemic conditions (e.g., body position changes, ECG confounders such as left ventricular hypertrophy or left bundle branch block) may cause ST-segment changes. The appearance of new or intensified diastolic heart sounds may help to confirm that observed ST-segment fluctuations are, in fact, due to ischemia when evaluating a patient presenting with chest pain. In our study, all three patients who had ECG confounders developed a new or increased S3 and S4 during an average of 26 seconds of balloon occlusion, whereas only one patient met the clinical criteria for ST changes $\geq 100 \mu\text{V}$ above the baseline.

Patients who present with symptoms suggestive of acute coronary syndrome often have other cardiac disease such as ventricular hypertrophy or congestive heart failure. In these nonischemic conditions, patients may have an S3 and S4 at baseline without ischemia. In our study, all three patients who had baseline S3 or S4 developed a new or increased intensity of S3 or S4 during ischemia, independent of ECG changes. These study results suggested that a new or increased intensity of S3 and S4 occurred during ischemia even when there are preexisting heart sounds, showing that the responsiveness of diastolic heart sounds was sensitive enough to detect ischemia.

Clinical Implications

Computerized acoustic cardiography provides a simultaneous recording of both acoustic and ECG

data continuously. Acoustic data may be provided using continuous variables, rather than dichotomous results. Acoustic cardiography may improve the noninvasive detection of transient or evolving myocardial ischemia, permitting the timely treatment of patients who present with chest pain in the prehospital, emergency room, or in-hospital settings. Adding acoustic cardiography may be particularly helpful in the evaluation of patients with an ECG confounded by ventricular hypertrophy, ventricular pacing, or bundle branch block.

Our study showed that diastolic heart sounds occurred contemporaneously with ST changes but earlier than angina in a majority of our subjects during PCI-related coronary occlusion. Abnormal diastolic heart sounds persisted longer following coronary reperfusion even after ST changes were normalized. In silent myocardial ischemia, the presence of diastolic heart sounds may help to detect and confirm the presence of myocardial ischemia when the ECG is uninterpretable. Also, our study suggests that patients may experience ventricular dysfunction even after coronary perfusion is restored and ST changes are normalized. The presence of S3 or S4 after resolution of angina may indicate severe loss of ventricular function. In these patients, more aggressive treatment for ventricular dysfunction may be required.

Study Limitations

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

CONCLUSION

This study showed that electrocardiographic ST-segment changes and new or intensified diastolic heart sounds occur at approximately the same time and promptly after ischemia within roughly 20–45 seconds of coronary occlusion. Electrocardiographic ST changes were the first to resolve during coronary reperfusion, followed by diastolic heart sounds and angina. Our study suggests that the noninvasive measurement of abnormal ventricular

function by acoustic cardiography provides diagnostic information regarding acute myocardial ischemia, independent of the heart's electrical activity. The presence of diastolic heart sounds may help rapid clinical decision making to detect myocardial ischemia, particularly when ST changes are confounded by conduction disease, pacing, or ventricular hypertrophy as well as to provide appropriate treatment for coronary reperfusion and functional restoration resulting from myocardial ischemia.

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