The third (S₃) and fourth (S₄) heart sounds detected by phonocardiography are considered to represent the criterion standards of the gallop sounds, but their test characteristics have not been explored.

Objective To determine the diagnostic test characteristics of the S₃ and S₄ for prediction of left ventricular dysfunction using a computerized heart sound detection algorithm.

Design, Setting, and Participants Prospective study of 90 adult patients undergoing elective left-sided heart catheterization at a single US teaching hospital between August 2003 and June 2004. The mean age was 62 (SD, 13) years (range, 24-90 years) and 61 (68%) were male. Within a 4-hour period, participants underwent computerized heart sound phonocardiographic analysis, cardiac catheterization, transthoracic echocardiography, and blood sampling for assessment of an S₃, S₄, left ventricular end-diastolic pressure (LVEDP), left ventricular ejection fraction (LVEF), and B-type natriuretic peptide (BNP), respectively.

Main Outcome Measures Diagnostic test characteristics of the computerized phonocardiographic S₃ and S₄ using markers of left ventricular function as criterion standards.

Results Mean (SD) LVEDP was significantly elevated (18.4 [6.9] mm Hg vs 12.1 [7.3] mm Hg; P<.001), mean (SD) LVEF was reduced (49.4% [20.2%] vs 63.6% [14.8%]; P<.001), and median (interquartile range) BNP was elevated (330 [98-1155] pg/mL vs 86 [41-192] pg/mL; P<.001) in those with an S₃, S₄, or both compared with patients without a diastolic heart sound. The sensitivities of these heart sounds to detect an elevated LVEDP, reduced LVEF, or elevated BNP were 41%, 52%, and 32% for an S₃, and 46%, 43%, and 40% for an S₄, respectively. For abnormal levels of the same markers of ventricular function, the specificities of the S₃ were 92%, 87%, and 92%, while the specificities of the S₄ were 80%, 72%, and 78%, respectively.

Conclusions Neither the phonocardiographic S₃ nor the S₄ is a sensitive marker of left ventricular dysfunction. The phonocardiographic S₃ is specific for left ventricular dysfunction and appears to be superior to the moderate specificity of the phonocardiographic S₄.

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detect abnormal left ventricular function have not been examined.

We undertook a prospective study to correlate the presence of S3 and S4 heart sounds detected by computerized phonocardiography with invasive and non-invasive objective markers of left ventricular systolic and diastolic function in patients undergoing diagnostic cardiac catheterization.

**METHODS**

**Participants and Study Design**

Adult patients referred for non-emergent left-sided heart catheterization at the University of California San Francisco (UCSF) Medical Center were eligible for enrollment between August 2003 and June 2004. Exclusion criteria included age younger than 18 years, systolic blood pressure less than 90 mm Hg, intravenous vasopressor, inotropic, or vasodilator pharmacotherapy, cardiac rhythm other than a sinus or paced atrial rhythm, severe mitral regurgitation or stenosis, constrictive pericarditis, serum creatinine level of 4.0 mg/dL (354 µmol/L) or higher, severe pulmonary hypertension, and mechanical ventilation.

From systematic review of the clinical chart, patients’ primary diagnoses and significant comorbidities were recorded, including coronary artery disease (defined as ≥1 coronary artery with ≥70% diameter stenosis), systemic hypertension, chronic heart failure, aortic stenosis, mitral regurgitation, chronic renal insufficiency, hypertrophic obstructive cardiomyopathy, and chronic obstructive pulmonary disease. Study enrollment was prospectively set at 100 participants using cross-sectional sampling. All patients gave written informed consent prior to enrollment and the protocol was approved by the UCSF Committee on Human Research.

Blood was drawn from the arterial sheath for measurement of B-type natriuretic peptide (BNP) level using a membrane immunofluorescence assay (Biosite Inc, San Diego, Calif). Within 4 hours, cardiac catheterization, transthoracic echocardiography, and computerized heart sound phonocardiographic analysis were performed.

Prior to angiography, left ventricular pressure was recorded. A BNP level higher than 100 pg/mL was prospectively specified as abnormal.14

**Invasive Left Ventricular Hemodynamics**

Patients underwent recording of left ventricular end-diastolic pressure (LVEDP) using a 6F pigtail catheter and a fluid-filled pressure transducer. Pressure was recorded using a 50–mm Hg scale at 50 mm/s paper speed. A physician, blinded to all clinical and diagnostic testing data, measured the post–A wave pressure. A minimum of 5 consecutive cardiac cycles were used to measure mean LVEDP. An LVEDP higher than 15 mm Hg was prospectively specified as abnormal.15,16

**Echocardiography**

Transthoracic echocardiographic data were obtained by an experienced echocardiographer (Acuson Sequoia, Mountain View, Calif, or SONOS 5500, Philips Medical Systems, Andover, Mass). Echocardiographic contrast (Optison, Amersham, Little Chalfont, England; 0.3-0.5 mL injected into a peripheral vein) was administered when required to improve endocardial border detection and enhance Doppler signals. Echocardiographic data were stored on magneto-optical disks and analyzed offline by a single experienced reader blinded to any clinical or study data. The average of 3 measurements was used for the analysis. End-diastolic and endsystolic volumes were calculated using the biplane method of discs17 and were then indexed to body surface area. These volumes were used to calculate left ventricular ejection fraction (LVEF). An LVEF less than 50% was prospectively defined as abnormal.

**Computerized Heart Sound Phonocardiographic Analysis**

A 3-minute audioelectrocardiographic tracing (Audicor, Inovise Medical Inc, Portland, Ore) was obtained (FIGURE 1). Audioelectrocardiographic leads were attached to the V1 and V4 positions and connected to a Marquette MAC 5000 (General Electric Healthcare Technologies, Waukesha, Wis). The audioelectrocardiographic data were stored electronically to a compact disc. A 10-second segment free of artifact was

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**Figure 1. Representative Normal and Abnormal Recordings**

Representative phonocardiographic recordings from the V4 position and electrocardiographic (ECG) recordings from the V6 position from a patient without a diastolic heart sound (normal) and from a patient with both a third and fourth heart sound (abnormal).
selected off-line by a technician, blinded to all clinical and diagnostic testing data, for a computer-generated report regarding presence of an S3/S4 heart sound. The Audicor software develops a confidence score between 0 and 1.0 for each heart sound based on the intensity, persistence, and frequency content, with a value of at least 0.5 indicating the presence of a diastolic heart sound.

**Statistical Analysis**

Data are presented as mean values and standard deviations for normally distributed continuous variables. Because BNP was highly right-skewed, this variable is presented as median and interquartile range (IQR) and analyses were performed on log-transformed values. Categorical data are presented as exact numbers and proportions. Sensitivity, specificity, and receiver operating characteristic (ROC) curves were calculated for S3 and S4 confidence scores as the predictors of elevated LVEDP, reduced LVEF, and elevated BNP using the predefined cutoffs. Continuous variables were compared using t tests and analysis of variance where appropriate. Categorical variables were compared using the Fisher exact test. All analyses were performed using STATA, version 8.2 (Stata Corp., College Station, Tex.).

**RESULTS**

One hundred patients were enrolled. Eight patients were excluded because of poor phonocardiographic sound quality. Because the phonocardiographic software cannot assess paced rhythms, 2 additional patients were excluded, leaving 90 patients for analysis.

The mean age was 62 (13) years (range, 24-90 years), and 61 (68%) were male. Twenty-six (29%) had diabetes, 72 (80%) had systemic hypertension, 32 (36%) had a clinical diagnosis of heart failure, and 16 (18%) were hospitalized for an acute coronary syndrome. Sixty-four patients (71%) had angiographic evidence of coronary artery disease, 40 (44%) had a prior percutaneous coronary intervention, and 17 (19%) had prior coronary artery bypass graft surgery. Five (6%) had moderate to severe calcific aortic stenosis and 2 (2%) had severe hypertrophic obstructive cardiomyopathy. The mean (SD) body surface area was 1.91 (0.26) m², the mean (SD) body mass index (calculated as weight in kilograms divided by the square of height in meters) was 29.0 (8.1), and the mean (SD) creatinine level was 1.47 (1.32) mg/dL (130 [117] μmol/L) (>1.5 mg/dL [>133 μmol/L] in 14 [16%]).

Computerized heart sound analysis detected no extra heart sound in 49 patients (54%), an S3 only in 12 patients (13%), an S4 only in 20 patients (22%), and both an S3 and an S4 in 9 patients (10%), so that there was an S3 and/or an S4 in 41 (46%).

Mean (SD) heart rate was 69/min (12/ min). Mean (SD) central aortic pressure was 131 (26) mm Hg for systolic pressure and 66 (13) mm Hg for diastolic pressure. Mean (SD) LVEDP was 15.0 (7.8) mm Hg (range, 1-31 mm Hg). Forty-one patients (46%) had an abnormal LVEDP (>15 mm Hg).

Seventy-nine patients had an adequate echocardiographic assessment of LVEF. Mean (SD) LVEF was 57% (19%) (range, 7%-85%). Twenty-three patients (28%) had an abnormal LVEF (<50%).

The median BNP was 133 pg/mL (IQR, 59-394 pg/mL; range, 5-4490 pg/mL; n=89). Fifty-two patients (58%) had an abnormal BNP (>100 pg/mL).

**Clinical Correlates of the Phonocardiographic S3 and S4**

There was no difference with respect to age, sex, or diabetes regarding the presence of diastolic heart sounds (TABLE 1). Patients with an isolated S4 tended to have a higher prevalence of coronary artery disease compared with those without a diastolic heart sound or those with an S3 alone. One third of patients with both an S3 and an S4 had an acute coronary syndrome, while only 6% of patients without a diastolic heart sound were undergoing cardiac catheterization for an acute coronary syndrome. The prevalence of systemic hypertension was highest in patients with an S3 or an S4 compared with patients without a diastolic heart sound. A clinical diagnosis of heart failure was significantly higher in patients with an S3 alone and those with both an S3 and an S4 compared with those with neither.

**Markers of Left Ventricular Function and the Phonocardiographic S3 and S4**

Patients with an S3 or S4 had a significantly higher LVEDP compared with patients without a diastolic heart sound.

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**Table 1. Baseline Demographic and Clinical Characteristics by Presence of Third and Fourth Heart Sounds**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Neither S3 nor S4 (n = 49)</th>
<th>S3 Only (n = 20)</th>
<th>S4 Only (n = 12)</th>
<th>S3 and S4 (n = 9)</th>
<th>S3 and/or S4 (n = 41)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>60.2 (12.7)</td>
<td>65.9 (13.4)</td>
<td>57.2 (11.8)</td>
<td>65.9 (16.7)</td>
<td>63.4 (12.7)</td>
<td>.18</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>33 (67)</td>
<td>15 (75)</td>
<td>8 (67)</td>
<td>5 (56)</td>
<td>28 (69)</td>
<td>.73</td>
</tr>
<tr>
<td>History, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>34 (69)</td>
<td>18 (90)</td>
<td>7 (58)</td>
<td>5 (56)</td>
<td>30 (73)</td>
<td>.11</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>6 (12)</td>
<td>5 (25)</td>
<td>2 (17)</td>
<td>3 (33)</td>
<td>10 (24)</td>
<td>.06</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12 (24)</td>
<td>7 (35)</td>
<td>5 (42)</td>
<td>2 (22)</td>
<td>14 (34)</td>
<td>.55</td>
</tr>
<tr>
<td>Hypertension</td>
<td>37 (76)</td>
<td>19 (95)</td>
<td>12 (100)</td>
<td>4 (44)</td>
<td>35 (85)</td>
<td>.004</td>
</tr>
<tr>
<td>Clinical heart failure</td>
<td>9 (18)</td>
<td>7 (35)</td>
<td>9 (75)</td>
<td>7 (78)</td>
<td>23 (56)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*P value is for a test of the hypothesis that there are no differences across the mutually exclusive groups (neither S3 nor S4, S4 only, S3 only, and both S3 and S4) using analysis of variance or the Fisher exact test.
(Table 2). For patients with both an S3 and an S4, the mean (SD) LVEDP was significantly elevated at 19.8 (5.1) mm Hg (Figure 2A). The differences in LVEDP between patients with an S3 alone, an S4 alone, or both were not statistically significant.

Patients with an LVEDP of more than 15 mm Hg had a higher prevalence of an S1 (41% vs 8%; P < .001) and an S4 (46% vs 20%; P = .01), a lower mean (SD) LVEF (50.4% [21.4%] vs 61.8% [14.6%]; P = .006), and a higher BNP (median, 329 pg/mL [IQR, 172-1002 pg/mL] vs 75 pg/mL [IQR, 39-133 pg/mL]; P < .001) than those with a normal LVEDP.

The LVEF was significantly lower for patients with an S3 alone, an S4 alone, and those with both an S3 and an S4 compared with those without a diastolic heart sound (Table 2 and Figure 2B). Patients with an LVEDP less than 50% had a higher prevalence of an S3 (52% vs 13%; P < .001) and an S4 (43% vs 28%; P = .20), a higher mean (SD) LVEDP (19.1 [7.5] mm Hg vs 13.7 [7.3] mm Hg; P = .003), and a higher BNP (median, 391 pg/mL [IQR, 151-1350 pg/mL] vs 96 pg/mL [IQR, 44-271 pg/mL]; P = .01) than those with a normal LVEDP. The BNP level tended to progressively increase comparing patients without a diastolic heart sound, those with an S3 alone, those with an S4 alone, and those with both an S3 and an S4 (Table 2).

**Test Characteristics of the Phonocardiographic S3 and S4**

In patients with an abnormal LVEDP, defined as more than 15 mm Hg, the presence of a very soft S3 (defined as a confidence score of 0.25) had a sensitivity of 54% and a specificity of 82%, while the clinically used confidence score of 0.50 had a sensitivity of 41% and a specificity of 94% (Figure 3A and Table 3). The S4 yielded a sensitivity of 46% with a specificity of 80%. The area under the ROC curve (AUROC) for the S3 confidence score was 0.76 (95% confidence interval [CI], 0.63-0.88; Figure 3A). The test performance for the S3 confidence score was slightly lower at 0.68 (95% CI, 0.57-0.79).

The test characteristics were similar based on an abnormal LVEF, defined as less than 50% (Table 3): both the S3 and the S4 had low sensitivities (52% and 43%, respectively), and the specificity of the S4 (87%) was superior to that of the S3 (72%). The AUROC for the S4 confidence score was 0.73 (95% CI, 0.62-0.84) and for the S4 confidence score was 0.62 (95% CI, 0.46-0.78) (Figure 3B).

The test characteristics of the phonocardiographic S3 and S4 using a BNP level of more than 100 pg/mL as the criterion standard for ventricular dysfunction also demonstrated low sensitivities (32% and 40%, respectively) and high specificities (92% and 78%, respectively; Table 3). The AUROCs for the S3 and S4 confidence scores as predictors of an elevated BNP were 0.65 (95% CI, 0.54-0.76) and 0.62 (95% CI, 0.50-0.73), respectively. The test characteristics for any diastolic heart sound (S3, S4, or both) had higher sensitivities but lower specificities, with no significant improvement in overall diagnostic accuracy (Table 3).
In our prospective study of 90 patients referred for elective cardiac catheterization, diastolic heart sounds as assessed by computerized phonocardiography had poor sensitivity for detection of left ventricular dysfunction. Although patients with either diastolic sound detected by computerized phonocardiographic heart sound analysis did have significantly higher LVEDP and BNP levels and lower LVEF measurements compared with those without a diastolic heart sound, overall diagnostic accuracy was modest, as evidenced by low AUROCs. The low sensitivities and AUROCs we observed indicate that diastolic heart sounds are not high-quality diagnostic tests for left ventricular dysfunction. Finally, the specificities of each sound to detect abnormalities in the objective markers of left ventricular function were consistently high, with the S₃ proving to be superior to the S₄ in separating patients based on abnormal left ventricular hemodynamics.

The auscultated third and fourth heart sounds are known to be associated with abnormal left ventricular hemodynamics. An auscultated gallop sound has been shown to be associated with a worse prognosis in patients undergoing noncardiac surgery, in those with asymptomatic left ventricular dysfunction, and in those with overt heart failure. Several studies have reported test characteristics of the auscultated S₃ or S₄ to detect abnormal markers of left ventricular function, including elevated LVEDP, echocardiographic measurements of left atrial filling, LVEF, and BNP levels. One small, blinded study examined the test characteristics of the auscultated S₃, yielding an 84% sensitivity and 75% specificity for an elevated atrial filling fraction, and in those with overt heart failure.

Table 3. Test Characteristics for Computerized Heart Sound Detection

<table>
<thead>
<tr>
<th></th>
<th>LVEDP &gt;15 mm Hg</th>
<th>LVEF ≤50%</th>
<th>BNP &gt;100 pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S₃</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>41 (26-58)</td>
<td>52 (31-73)</td>
<td>32 (20-46)</td>
</tr>
<tr>
<td>Specificity</td>
<td>92 (80-98)</td>
<td>87 (76-94)</td>
<td>92 (78-98)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>81 (58-95)</td>
<td>57 (34-78)</td>
<td>85 (62-97)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>65 (53-76)</td>
<td>84 (73-92)</td>
<td>48 (36-60)</td>
</tr>
<tr>
<td>Accuracy</td>
<td>69 (58-78)</td>
<td>78 (68-86)</td>
<td>56 (45-67)</td>
</tr>
<tr>
<td><strong>S₄</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>46 (31-63)</td>
<td>43 (23-66)</td>
<td>40 (26-54)</td>
</tr>
<tr>
<td>Specificity</td>
<td>80 (66-90)</td>
<td>72 (59-82)</td>
<td>78 (61-90)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>66 (46-82)</td>
<td>34 (18-54)</td>
<td>72 (52-87)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>64 (51-76)</td>
<td>79 (66-88)</td>
<td>47 (34-60)</td>
</tr>
<tr>
<td>Accuracy</td>
<td>64 (54-74)</td>
<td>64 (54-74)</td>
<td>55 (44-66)</td>
</tr>
<tr>
<td><strong>S₃ and/or S₄</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>68 (52-82)</td>
<td>74 (52-90)</td>
<td>57 (42-70)</td>
</tr>
<tr>
<td>Specificity</td>
<td>73 (59-85)</td>
<td>64 (52-76)</td>
<td>72 (55-86)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>68 (52-82)</td>
<td>42 (26-58)</td>
<td>75 (59-87)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>73 (59-85)</td>
<td>88 (75-95)</td>
<td>53 (38-67)</td>
</tr>
<tr>
<td>Accuracy</td>
<td>71 (61-80)</td>
<td>67 (56-76)</td>
<td>63 (52-73)</td>
</tr>
</tbody>
</table>

Abbreviations: BNP, B-type natriuretic peptide; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction.

*Data are presented as percentage (95% confidence interval).

COMMENT

In our prospective study of 90 patients referred for elective cardiac catheterization, diastolic heart sounds as assessed by computerized phonocardiography had poor sensitivity for detection of left ventricular dysfunction. Although patients with either diastolic sound detected by computerized phonocardiographic heart sound analysis did have significantly higher LVEDP and BNP levels and lower LVEF measurements compared with those without a diastolic heart sound, overall diagnostic accuracy was modest, as evidenced by low AUROCs. The low sensitivities and AUROCs we observed indicate that diastolic heart sounds are not high-quality diagnostic tests for left ventricular dysfunction. Finally, the specificities of each sound to detect abnormalities in the objective markers of left ventricular function were consistently high, with the S₃ proving to be superior to the S₄ in separating patients based on abnormal left ventricular hemodynamics.

The auscultated third and fourth heart sounds are known to be associated with abnormal left ventricular hemodynamics. An auscultated gallop sound has been shown to be associated with a worse prognosis in patients undergoing noncardiac surgery, in those with asymptomatic left ventricular dysfunction, and in those with overt heart failure.

Several studies have reported test characteristics of the auscultated S₃ or S₄ to detect abnormal markers of left ventricular function, including elevated LVEDP, echocardiographic measurements of left atrial filling, LVEF, and BNP levels. One small, blinded study examined the test characteristics of the auscultated S₃, yielding an 84% sensitivity and 75% specificity for an elevated atrial filling fraction, and in those with overt heart failure. In our study, the specificities of each sound to detect abnormalities in the objective markers of left ventricular function were consistently high, with the S₃ proving to be superior to the S₄ in separating patients based on abnormal left ventricular hemodynamics. The auscultated third and fourth heart sounds are known to be associated with abnormal left ventricular hemodynamics. An auscultated gallop sound has been shown to be associated with a worse prognosis in patients undergoing noncardiac surgery, in those with asymptomatic left ventricular dysfunction, and in those with overt heart failure.

Several studies have reported test characteristics of the auscultated S₃ or S₄ to detect abnormal markers of left ventricular function, including elevated LVEDP, echocardiographic measurements of left atrial filling, LVEF, and BNP levels. One small, blinded study examined the test characteristics of the auscultated S₃, yielding an 84% sensitivity and 75% specificity for an elevated atrial filling fraction in 41 patients. An important limitation to the S₃ studies involves the auscultators’ lack of blinding to the patients’ clinical conditions; nonetheless, they demonstrated low sensitivities (31%-51%) and high specificities (90%-
97%) in detecting an abnormal level of the chosen hemodynamic marker.\(^4\)\(^,\)\(^10\)\(^,\)\(^22\)
As a caveat to all of these studies, the generalizability and applicability of the true test characteristics are difficult to determine given substantial interobserver variability and poor accuracy of physician auscultation.\(^8\)\(^,\)\(^9\)\(^,\)\(^23\)

As an objective unbiased instrument that supplies measurable data, the phonocardiogram has been viewed as the criterion standard for detection of S3 and S4. Phonocardiography has been used to elucidate the hemodynamic mechanisms of the S3 and S4\(^2\)\(^,\)\(^10\)\(^-\)\(^13\)\(^,\)\(^16\)\(^,\)\(^24\) and has served to provide objective evidence of the S3 and S4 in studies on auscultation.\(^9\)\(^,\)\(^23\) However, to the best of our knowledge, the test characteristics of the phonocardiographic S3 and S4 have not been previously reported.

In the present study, we compared the phonocardiographic S3 and S4 with 3 clinically relevant objective markers of left ventricular function: LVEDP, LVEF, and BNP levels. Clinically, an S3 alone was associated with hypertension and heart failure, an S4 alone was associated with coronary disease and hypertension, and the combination of the sounds tended to have a higher prevalence in those with acute coronary syndromes or heart failure. Sex and presence of diabetes were not related to the prevalence of these diastolic heart sounds.

The level of each marker of left ventricular function was significantly more abnormal in patients with an S3 alone compared with those without an S3. Patients with an S4 alone tended to have a lower LVEF and higher BNP compared with those with an S4 alone. Those with an S4 alone had a significantly higher LVEDP and BNP compared with those without an S4. Finally, patients exhibiting both diastolic sounds had the highest LVEDP and BNP levels.

Prespecified and conventionally accepted levels of each marker of ventricular function (LVEDP > 15 mm Hg, LVEF < 50%, and BNP > 100 pg/mL) were prospectively defined as abnormal, and these abnormal levels served as criterion standards to determine the test characteristics of the phonocardiographic S3 and S4. Both sounds demonstrated consistently low sensitivities to detect an abnormal level of any of the markers (ranging from 32% to 52%). This suggests that neither sound should be used to screen for the presence of an abnormal LVEDP, LVEF, or BNP level. More generally, absence of the sounds does not appear to rule out ventricular dysfunction.

The specificities of the S3 were consistently high, ranging from 87% to 92%, suggesting that, if present, an S3 can be useful to rule in a diagnosis of ventricular dysfunction. The specificities of the S4 to detect an abnormal marker of ventricular function were consistently lower than those of the S3 but remained moderately high (72%-80%). The test characteristics of any diastolic heart sound (S3 and/or S4) showed an increase in sensitivity (57%-74%) but a reduction in specificity (64%-73%) compared with using either heart sound alone.

The test characteristics of the phonocardiogram may vary depending on the cutoff used to designate a positive S3 or S4. Our particular phonocardiogram was an audioelectrocardiographic tracing that created a computer-generated confidence score for each heart sound between 0 and 1.0; a value of at least 0.50 was prospectively specified as indicative of a diastolic heart sound. As demonstrated by the AUROCs (Figure 3), this cutoff generally yielded the highest accuracy. Reducing the cutoff to 0.25 or higher, which likely includes the detection of some sounds not audible to the human ear, provided somewhat higher sensitivities for the presence of elevated LVEDP (54% for the S3 and 56% for the S4) but resulted in a modest reduction in specificity (82% for the S3 and 76% for the S4).

The findings of this study should not be extrapolated to patients with conditions known to have a high prevalence of these diastolic sounds that would have been excluded from the study, such as severe mitral regurgitation or constrictive pericarditis. Because an S3 can be physiologic in younger people (particularly those <40 years old), our findings should not be used to interpret the meaning of an S3 in younger patients. A significant limitation of the study likely represents a limitation of phonocardiography in general or perhaps any instrument that requires high-quality data for accurate interpretation—8 patients were excluded in our study because of poor quality of the phonocardiographic tracings. A final limitation is that there is no single universally accepted tool for phonocardiography; however, we did use prospectively defined cutoffs for both the phonocardiographic tracings and hemodynamic parameters.

In conclusion, the absence of a phonocardiographic S3 or S4 is not sufficient to exclude ventricular dysfunction. If present, the phonocardiographic S3 and S4 are specific for an elevated LVEDP, a depressed LVEF, and an elevated BNP level. The S3 appears to have superior test characteristics compared with the S4 in identifying patients with abnormal left ventricular function.

Author Contributions: Dr Michaels had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Marcus, Gerber, Vessey, Chatterjee, Michaels.

Acquisition of data: Gerber, McKeown, Jordan, Huddleston, Foster, Michaels.

Analysis and interpretation of data: Marcus, Gerber, McKeown, McCulloch, Michaels.

Drafting of the manuscript: Marcus, Michaels.

Critical revision of the manuscript for important intellectual content: Marcus, Gerber, McKeown, Vessey, Jordan, Huddleston, McCulloch, Foster, Chatterjee, Michaels.

Statistical analysis: McCulloch, Michaels.

Administrative, technical, or material support: Huddleston, Michaels.

Study supervision: Foster, Chatterjee, Michaels.

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Cardiac Catheterization Laboratory for their technical assistance; and Patti Arand, Nancy Forman, and Robert Warner of Inovise Medical Inc for training and technical support.

REFERENCES

The life of every man is a diary in which he means to write one story, and writes another; and his humblest hour is when he compares the volume as it is with what he vowed to make it.
—J. M. Barrie (1860-1937)