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# Association Between Phonocardiographic Third and Fourth Heart Sounds and Objective Measures of Left Ventricular Function

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**T**IME-HONORED BEDSIDE AUSCULTATION with the stethoscope is an important clinical tool to help characterize heart sounds and identify abnormalities associated with cardiac dysfunction. Potain<sup>1</sup> first described the gallop rhythm in 1880, referring to the cadence produced by presence of abnormal diastolic cardiac sounds. These diastolic sounds refer to the presence of a third heard sound ( $S_3$ ) and/or fourth heart sound ( $S_4$ ). The auscultated  $S_3$  and  $S_4$  have long been used as clinical signs of heart disease, with diagnostic and prognostic importance.<sup>2-7</sup> However, the value of these physical findings has been diminished by reports of poor accuracy and interobserver reliability.<sup>8,9</sup>

As an objective instrument that supplies measurable data, the phonocardiogram has traditionally been the criterion (gold) standard tool for the detection of ventricular gallop sounds. Phonocardiography has been used to

**Context** The third ( $S_3$ ) and fourth ( $S_4$ ) 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  $S_3$  and  $S_4$  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  $S_3/S_4$ , 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  $S_3$  and  $S_4$  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  $S_3$ ,  $S_4$ , 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  $S_3$ , and 46%, 43%, and 40% for an  $S_4$ , respectively. For abnormal levels of the same markers of ventricular function, the specificities of the  $S_3$  were 92%, 87%, and 92%, while the specificities of the  $S_4$  were 80%, 72%, and 78%, respectively.

**Conclusions** Neither the phonocardiographic  $S_3$  nor the  $S_4$  is a sensitive marker of left ventricular dysfunction. The phonocardiographic  $S_3$  is specific for left ventricular dysfunction and appears to be superior to the moderate specificity of the phonocardiographic  $S_4$ .

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understand the mechanisms and associated clinical characteristics of diastolic sounds,<sup>10-13</sup> and results of phonocardiography have been used to determine the accuracy of physician auscultation.<sup>9</sup> However, the test characteristics of the phonocardiogram to

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detect abnormal left ventricular function have not been examined.

We undertook a prospective study to correlate the presence of  $S_3$  and  $S_4$  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

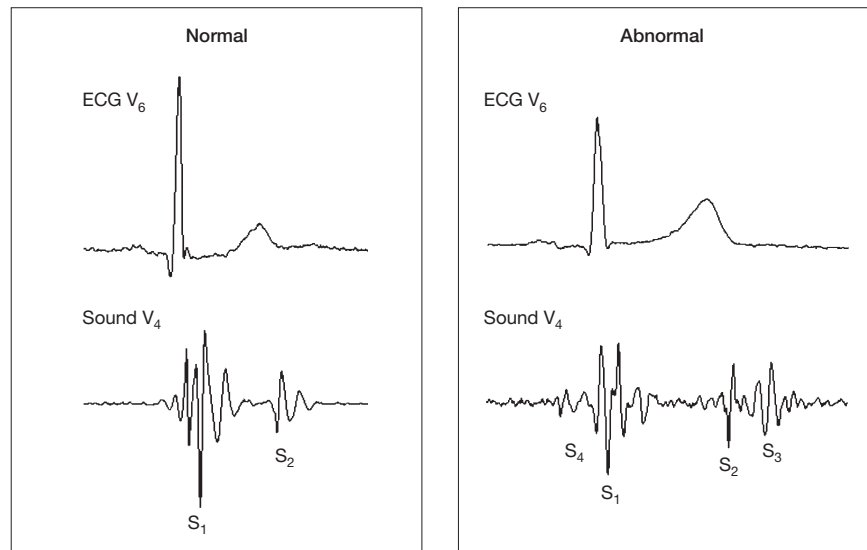
### Participants and Study Design

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  $\mu$ mol/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  $\geq 1$  coronary artery with  $\geq 70\%$  diameter stenosis), systemic hypertension, clinical 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.

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



Representative phonocardiographic recordings from the  $V_4$  position and electrocardiographic (ECG) recordings from the  $V_6$  position from a patient without a diastolic heart sound (normal) and from a patient with both a third and fourth heart sound (abnormal).

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

### 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.<sup>15,16</sup>

### 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 end-systolic volumes were calculated using the biplane method of discs<sup>17</sup> 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  $V_3$  and  $V_4$  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

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

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

\*P value is for a test of the hypothesis that there are no differences across the mutually exclusive groups (neither S<sub>3</sub> nor S<sub>4</sub>, S<sub>4</sub> only, S<sub>3</sub> only, and both S<sub>3</sub> and S<sub>4</sub>) using analysis of variance or the Fisher exact test.

selected off-line by a technician, blinded to all clinical and diagnostic testing data, for a computer-generated report regarding presence of an S<sub>3</sub>/S<sub>4</sub> 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 S<sub>3</sub> and S<sub>4</sub> 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). A 2-tailed *P* < .05 was considered significant.

### 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) m<sup>2</sup>, 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 S<sub>3</sub> only in 12 patients (13%), an S<sub>4</sub> only in 20 patients (22%), and both an S<sub>3</sub> and an S<sub>4</sub> in 9 patients (10%), so that there was an S<sub>3</sub> and/or an S<sub>4</sub> 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 S<sub>3</sub> and S<sub>4</sub>

There was no difference with respect to age, sex, or diabetes regarding the presence of diastolic heart sounds (TABLE 1). Patients with an isolated S<sub>4</sub> tended to have a higher prevalence of coronary artery disease compared with those without a diastolic heart sound or those with an S<sub>3</sub> alone. One third of patients with both an S<sub>3</sub> and an S<sub>4</sub> 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 S<sub>3</sub> or an S<sub>4</sub> compared with patients without a diastolic heart sound. A clinical diagnosis of heart failure was significantly higher in patients with an S<sub>3</sub> alone and those with both an S<sub>3</sub> and an S<sub>4</sub> compared with those with neither.

### Markers of Left Ventricular Function and the Phonocardiographic S<sub>3</sub> and S<sub>4</sub>

Patients with an S<sub>3</sub> or S<sub>4</sub> had a significantly higher LVEDP compared with patients without a diastolic heart sound

**Table 2.** Hemodynamic, Echocardiographic, and BNP Characteristics by Presence of Third and Fourth Heart Sounds

Characteristics*	Neither S <sub>3</sub> nor S <sub>4</sub> (n = 49)	S <sub>4</sub> Only (n = 20)	S <sub>3</sub> Only (n = 12)	S <sub>3</sub> and S <sub>4</sub> (n = 9)	S <sub>3</sub> and/or S <sub>4</sub> (n = 41)	P Value†
Heart rate, beats/min	69 (11)	64 (11)	77 (14)	70 (10)	69 (11)	.02
Systolic aortic pressure, mm Hg	131 (22)	146 (26)	117 (24)	119 (33)	131 (31)	.007
Central aortic pressure, mm Hg	94 (16)	95 (19)	87 (17)	88 (21)	91 (19)	.41
LVEDP, mm Hg	12.1 (7.3)	18.0 (6.9)	18.0 (8.2)	19.8 (5.1)	18.4 (6.9)	.001
LVEF, %	63.6 (14.8)	54.7 (20.5)	44.2 (20.4)	46.1 (18.8)	49.4 (20.2)	.002
LVMI, g/m <sup>2</sup>	114 (41)	112 (30)	121 (26)	132 (48)	118.9 (33.5)	.71
BNP, median (IQR), pg/mL	86 (41-192)	213 (75-655)	492 (109-1100)	904 (292-1350)	330 (98-1155)	<.001

Abbreviations: BNP, B-type natriuretic peptide; IQR, interquartile range; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index (determined by echocardiography).

\*Data are presented as mean (SD) unless otherwise noted.

†P value is for a test of the hypothesis that there are no differences across the mutually exclusive groups (neither S<sub>3</sub> nor S<sub>4</sub>, S<sub>4</sub> only, S<sub>3</sub> only, and both S<sub>3</sub> and S<sub>4</sub>) using analysis of variance or the Fisher exact test.

(TABLE 2). For patients with both an S<sub>3</sub> and an S<sub>4</sub>, the mean (SD) LVEDP was significantly elevated at 19.8 (5.1) mm Hg (FIGURE 2A). The differences in LVEDP between patients with an S<sub>3</sub> alone, an S<sub>4</sub> alone, or both were not statistically significant.

Patients with an LVEDP of more than 15 mm Hg had a higher prevalence of an S<sub>3</sub> (41% vs 8%;  $P < .001$ ) and an S<sub>4</sub> (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 S<sub>3</sub> alone, an S<sub>4</sub> alone, and those with both an S<sub>3</sub> and an S<sub>4</sub> compared with those without a diastolic heart sound (Table 2 and Figure 2B). Patients with an LVEF less than 50% had a higher prevalence of an S<sub>3</sub> (52% vs 13%;  $P < .001$ ) and an S<sub>4</sub> (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 LVEF. The BNP level tended to progressively increase comparing patients without a diastolic heart sound, those with an S<sub>4</sub> alone, those with an S<sub>3</sub> alone, and those with both an S<sub>3</sub> and an S<sub>4</sub> (Table 2).

### Test Characteristics of the Phonocardiographic S<sub>3</sub> and S<sub>4</sub>

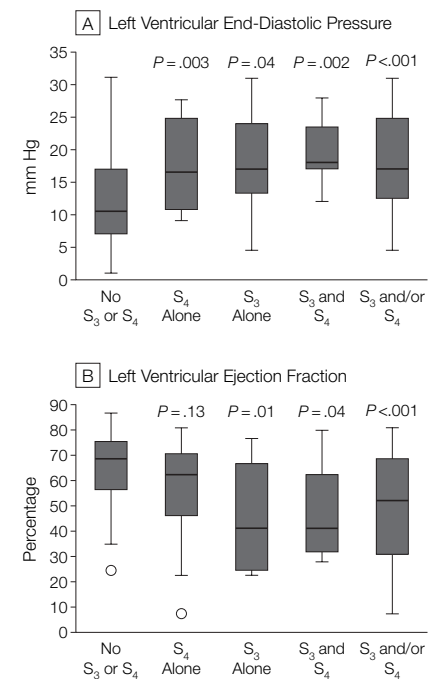
In patients with an abnormal LVEDP, defined as more than 15 mm Hg, the

presence of a very soft S<sub>3</sub> (defined as a confidence score of 0-0.25) 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 3 and TABLE 3). The S<sub>4</sub> yielded a sensitivity of 46% with a specificity of 80%. The area under the ROC curve (AUROC) for the S<sub>3</sub> confidence score was 0.76 (95% confidence interval [CI], 0.63-0.88; Figure 3A). The test performance for the S<sub>4</sub> 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 S<sub>3</sub> and the S<sub>4</sub> had low sensitivities (52% and 43%, respectively), and the specificity of the S<sub>3</sub> (87%) was superior to that of the S<sub>4</sub> (72%). The AUROC for the S<sub>3</sub> confidence score was 0.73 (95% CI, 0.62-0.84) and for the S<sub>4</sub> confidence score was 0.62 (95% CI, 0.46-0.78) (Figure 3B).

The test characteristics of the phonocardiographic S<sub>3</sub> and S<sub>4</sub> 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 S<sub>3</sub> and S<sub>4</sub> 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 (S<sub>3</sub>, S<sub>4</sub>, or both) had higher sensitivities but lower

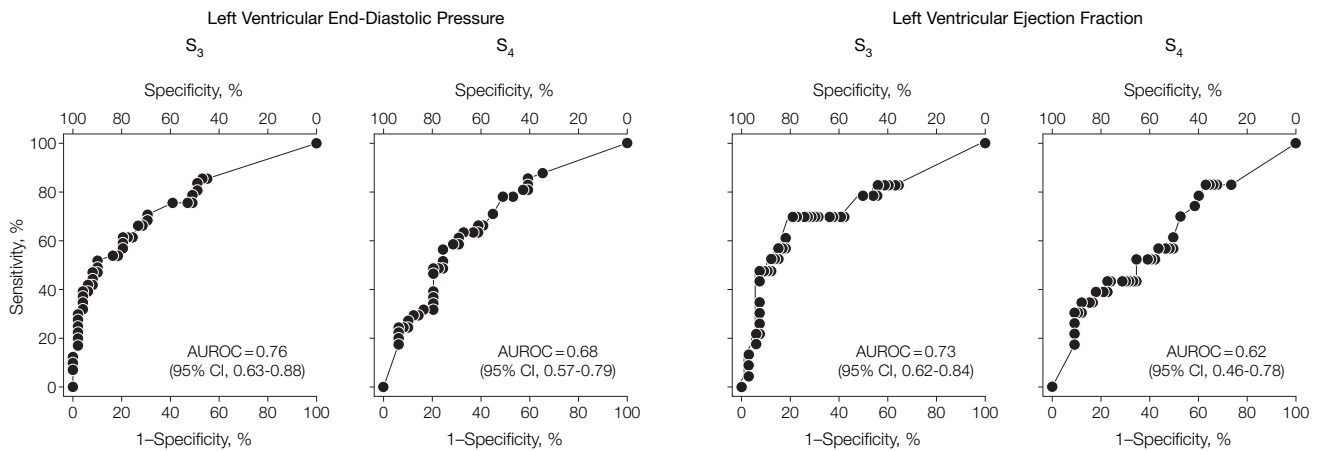
**Figure 2.** Median Left Ventricular End-Diastolic Pressure and Left Ventricular Ejection Fraction for Patients Based on Phonocardiographic Presence of a Third and/or Fourth Heart Sound



The box-and-whisker plots show the median and interquartile range (box), the upper hinge (75th percentile plus 1.5 times the interquartile range) (upper error bars), the lower hinge (25th percentile plus 1.5 times the interquartile range) (lower error bars), and outlier values (circles) outside the hinges. The P values represent comparisons with the group without diastolic heart sounds. There were no other statistically significant between-group comparisons.

specificities, with no significant improvement in overall diagnostic accuracy (Table 3).

**Figure 3.** Receiver Operating Characteristic Curves for Various Cutoffs of the Third and Fourth Heart Sound Confidence Scores in Differentiating Patients with Normal or Abnormal LVEDP and LVEF



A normal left ventricular end-diastolic pressure (LVEDP) was defined as 15 mm Hg or less and a normal left ventricular ejection fraction (LVEF) was defined as 50% or more. Marked portions of the curves indicate the sensitivity and specificity when using the given confidence cutoff for an S<sub>3</sub> or S<sub>4</sub>. AUROC indicates r statistic for the area under the receiver operating characteristic curve; CI, confidence interval.

**Table 3.** Test Characteristics for Computerized Heart Sound Detection\*

	LVEDP >15 mm Hg	LVEF <50%	BNP >100 pg/mL
<b>S<sub>3</sub></b>			
Sensitivity	41 (26-58)	52 (31-73)	32 (20-46)
Specificity	92 (80-98)	87 (76-94)	92 (78-98)
Positive predictive value	81 (58-95)	57 (34-78)	85 (62-97)
Negative predictive value	65 (53-76)	84 (73-92)	48 (36-60)
Accuracy	69 (58-78)	78 (68-86)	56 (45-67)
<b>S<sub>4</sub></b>			
Sensitivity	46 (31-63)	43 (23-66)	40 (26-54)
Specificity	80 (66-90)	72 (59-82)	78 (61-90)
Positive predictive value	66 (46-82)	34 (18-54)	72 (52-87)
Negative predictive value	64 (51-76)	79 (66-88)	47 (34-60)
Accuracy	64 (54-74)	64 (54-74)	55 (44-66)
<b>S<sub>3</sub> and/or S<sub>4</sub></b>			
Sensitivity	68 (52-82)	74 (52-90)	57 (42-70)
Specificity	73 (59-85)	64 (52-76)	72 (55-86)
Positive predictive value	68 (52-82)	42 (26-58)	75 (59-87)
Negative predictive value	73 (59-85)	88 (75-95)	53 (38-67)
Accuracy	71 (61-80)	67 (56-76)	63 (52-73)

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 S<sub>3</sub> proving to be superior to the S<sub>4</sub> 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.<sup>4,18,19</sup> An auscultated gallop sound has been shown to be associated with a worse prognosis in patients undergoing noncardiac surgery,<sup>20,21</sup> in those with asymptomatic left ventricular dysfunction,<sup>6</sup> and in those with overt heart failure.<sup>6,7</sup>

Several studies have reported test characteristics of the auscultated S<sub>3</sub> or S<sub>4</sub> to detect abnormal markers of left ventricular function, including elevated LVEDP,<sup>16</sup> echocardiographic measurements of left atrial filling,<sup>19</sup> LVEF,<sup>4</sup> and BNP levels.<sup>22</sup> One small, blinded study examined the test characteristics of the auscultated S<sub>4</sub>, yielding an 84% sensitivity and 75% specificity for an elevated atrial filling fraction in 41 patients.<sup>19</sup> An important limitation to the S<sub>3</sub> 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.<sup>4,16,22</sup> 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.<sup>8,9,23</sup>

As an objective unbiased instrument that supplies measurable data, the phonocardiogram has been viewed as the criterion standard for detection of  $S_3$  and  $S_4$ . Phonocardiography has been used to elucidate the hemodynamic mechanisms of the  $S_3$  and  $S_4$ <sup>2,10-13,18,24</sup> and has served to provide objective evidence of the  $S_3$  and  $S_4$  in studies on auscultation.<sup>9,23</sup> However, to the best of our knowledge, the test characteristics of the phonocardiographic  $S_3$  and  $S_4$  have not been previously reported.

In the present study, we compared the phonocardiographic  $S_3$  and  $S_4$  with 3 clinically relevant objective markers of left ventricular function: LVEDP, LVEF, and BNP levels. Clinically, an  $S_3$  alone was associated with hypertension and heart failure, an  $S_4$  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  $S_3$  alone compared with those without an  $S_3$ . Patients with an  $S_3$  alone tended to have a lower LVEF and higher BNP compared with those with an  $S_4$  alone. Those with an  $S_4$  alone had a significantly higher LVEDP and BNP compared with those without an  $S_4$ . 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  $S_3$  and  $S_4$ . 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  $S_3$  were consistently high, ranging from 87% to 92%, suggesting that, if present, an  $S_3$  can be useful to rule in a diagnosis of ventricular dysfunction. The specificities of the  $S_4$  to detect an abnormal marker of ventricular function were consistently lower than those of the  $S_3$  but remained moderately high (72%-80%). The test characteristics of any diastolic heart sound ( $S_3$  and/or  $S_4$ ) 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  $S_3$  or  $S_4$ . 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  $S_3$  and 56% for the  $S_4$ ) but resulted in a modest reduction in specificity (82% for the  $S_3$  and 76% for the  $S_4$ ).

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. Be-

cause an  $S_3$  can be physiologic in younger people (particularly those <40 years old),<sup>25</sup> our findings should not be used to interpret the meaning of an  $S_3$  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  $S_3$  or  $S_4$  is not sufficient to exclude ventricular dysfunction. If present, the phonocardiographic  $S_3$  and  $S_4$  are specific for an elevated LVEDP, a depressed LVEF, and an elevated BNP level. The  $S_3$  appears to have superior test characteristics compared with the  $S_4$  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.

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**Statistical analysis:** McCulloch, Michaels.

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

**Study supervision:** Foster, Chatterjee, Michaels.

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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)