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Association of the Fourth Heart Sound with Increased Left Ventricular End-Diastolic Stiffness

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Abstract

Background—Although the fourth heart sound (S_4) is thought to be associated with a stiff left ventricle (LV), this association has never been proven. Recently, single-beat estimation of the end-diastolic pressure volume relationship (EDPVR) has been characterized ($P = \alpha V^\beta$), allowing the estimation of EDPVR in larger groups of patients. We hypothesized that the S_4 is associated with an upward- and leftward-shifted EDPVR, indicative of elevated end-diastolic stiffness.

Methods and Results—Ninety study participants underwent acoustic cardiographic analysis, echocardiography, and left heart catheterization. We calculated α and β coefficients to define the non-linear slope of the EDPVR using the single-beat method for measuring LV end-diastolic elastance. In the $P = \alpha V^\beta$ EDPVR estimation, α was similar ($p=0.31$) but β was significantly higher in the S_4 group (5.96 vs. 6.51, $p=0.002$), signifying a steeper, upward- and leftward-shifted EDPVR curve in subjects with an S_4 . The intensity of the S_4 was associated with both β ($r=0.42$, $p < 0.0001$) and $E/E' \div$ stroke volume index, another index of diastolic stiffness ($r=0.39$, $p=0.0008$). On multivariable analysis, β remained associated with the presence ($p=0.008$) and intensity ($p<0.0001$) of S_4 after controlling for age, sex, and ejection fraction.

Conclusions—The S_4 is most likely generated from an abnormally stiff LV, supporting the concept that the S_4 is a pathologic finding in older patients.

Keywords

phonocardiography; pathophysiology; hemodynamics; echocardiography

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INTRODUCTION

Since Potain's first description of the fourth heart sound (S_4) in the late 19th century (1), it has been known that the timing of the S_4 corresponds to atrial contraction. Investigators have shown that the S_4 is associated with the A wave on left atrial pressure tracing (2), increased height and rate of rise of A wave on apexcardiography (3), decreased ratio of early to late mitral inflow velocity on Doppler echocardiography (4), and increased atrial filling fraction (5). Because the S_4 has been associated with conditions that cause left ventricular (LV) diastolic stiffness such as aortic stenosis, ischemia, and left ventricular hypertrophy (6,7), many believe that the S_4 is due to decreased compliance, although this has never been proven. Because there is controversy regarding the clinical utility of the S_4 (8,9), and because its association with diastolic stiffness has never before been shown, we sought to prove the hypothesis that the S_4 is associated with increased end-diastolic stiffness.

METHODS

We performed a cross-sectional study of 100 unselected adult patients referred for non-emergent cardiac catheterization at the University of California, San Francisco Medical Center. The research protocol was approved by the University of California, San Francisco Committee on Human Research. All patients provided written informed consent prior to enrollment.

All adult patients who were undergoing left-heart catheterization were eligible for study. Exclusion criteria included age < 18 years old, systolic blood pressure < 90 mmHg, intravenous vasopressor and/or inotropic pharmacotherapy, cardiac rhythm other than a sinus or paced atrial rhythm, severe mitral regurgitation or stenosis, constrictive pericarditis, serum creatinine ≥ 4.0 mg/dL, severe pulmonary hypertension, or mechanical ventilation.

Within a 4-hour period, study participants underwent computerized heart sound detection using acoustic cardiography (Audicor, Inovise Medical, Inc., Portland, OR), 12-lead electrocardiography, transthoracic echocardiography, left heart catheterization, and blood sampling for BNP. Phonocardiography, electrocardiography, echocardiography, and invasive hemodynamics were all interpreted separately by physicians blinded to all clinical and diagnostic data.

All participants underwent a 3-minute acoustic cardiographic tracing (10) to determine presence or absence of the S_4 . The Audicor device records and interprets simultaneous digital ECG and heart sound data using unique dual-purpose sensors that acquire both electrical and acoustic data from the V_3 and V_4 positions. Using its computerized algorithm, the Audicor system first determines whether or not the S_4 is possibly present if it detects a deflection in the phonocardiographic waveform that corresponds to the timing of the S_4 (120–170 milliseconds after the onset of the P-wave). Then, based on the timing, intensity, persistence, and frequency of the extra heart sound, the Audicor system calculates an S_4 confidence score between 0 and 1.0. A confidence score ≥ 0.5 indicates the presence of the S_4 . For the purposes of our study, the acoustic cardiographic data was stored electronically. An artifact-free 10-second segment was selected off-line by a blinded biomedical engineer, and the computer-generated report determined the presence of an S_4 .

Transthoracic echocardiographic data (Acuson Sequoia, Siemens, Malvern, PA or SONOS 5500, Philips Medical Systems, Andover, MA) was obtained by an experienced echocardiographer in 88 participants and analyzed off-line by a single experienced reader blinded to any clinical or study data. Echocardiographic contrast (Optison®, Amersham, Little Chalfont, United Kingdom; 0.3 to 0.5 mL injected into a peripheral vein) was administered when required to improve endocardial border detection. End-diastolic and end-systolic volumes were calculated using the biplane method of discs (11), and were then indexed to body

surface area. A biplane, area-length formula was used to calculate left atrial volume (12). The E/E' ratio was defined as the ratio of the peak early diastolic mitral inflow velocity (measured with pulsed-wave Doppler) to the peak early diastolic mitral annular tissue velocity (sample volume placed at the lateral mitral annulus) (13). Stroke volume was calculated non-invasively by measuring the left ventricular outflow tract (LVOT) diameter (in the parasternal long axis view) and LVOT velocity time integral (VTI) by pulse-wave Doppler (in the apical 5-chamber view), using the following equation: stroke volume = (LVOT diameter / 2)² × π × LVOT VTI (14).

Participants underwent recording of LV diastolic pressures using a 6-French pigtail catheter and a properly-zeroed fluid-filled pressure transducer prior to the administration of any radiographic contrast. Pressure was recorded using a 50 mmHg scale at 50 mm/sec paper speed. A physician, blinded to the phonocardiographic and echocardiographic data, measured various time-points in diastole in the left ventricular pressure tracing, including the early diastolic pressure (nadir of LV pressure after mitral valve opening), mid-diastolic pressure (LV pressure at mid-point between the early diastolic pressure and the onset of the A-wave), pre-A wave diastolic pressure, peak A wave diastolic pressure, and post-A wave diastolic pressure (LVEDP). We defined the peak LV filling rate (slope of the pressure curve in early diastole) as pre-A wave LV diastolic pressure minus the early LV diastolic pressure divided by the time difference between these two points. A minimum of five consecutive cardiac cycles was used to determine these measurements that were also averaged over the respiratory cycle.

Left ventricular end-diastolic stiffness (also known as LV end-diastolic elastance) was defined as the slope of the end-diastolic pressure-volume relationship (EDPVR) on pressure-volume analysis. We measured slope of the EDPVR by four different methods (Figure 1): invasive LV end-diastolic pressure ÷ echocardiographic LV end-diastolic volume (EDP/EDV); invasive LV end-diastolic pressure ÷ Doppler-derived stroke volume (EDP/SV); tissue Doppler E/E' ÷ Doppler-derived stroke volume (E/E'/SV) (15); and the single-beat method of EDPVR estimation, described by the following equation: $EDP = \alpha EDV^\beta$ (16). For the single-beat method, we calculated group-averaged EDV₂₀ based on mean α and β coefficients, as suggested by Burkhoff et al (17). This value represents the predicted end-diastolic volume at an end-diastolic pressure of 20 mmHg. A smaller EDV₂₀ denotes increased end-diastolic stiffness.

Continuous data with a normal distribution was displayed as mean ± standard deviation. Right-skewed data, such as BNP, was displayed as the median and interquartile range. Nominal data was displayed as exact numbers and proportions. Differences in baseline demographic and clinical characteristics, echocardiographic variables, and left ventricular hemodynamic variables were calculated according to presence or absence of S₄ and were determined with unpaired *t* tests or the Mann-Whitney test for continuous variables and chi-square analysis-of-contingency table using the Fisher's exact test for dichotomous variables, where appropriate. We calculated Pearson correlation coefficients to determine whether various indices of diastolic stiffness correlated with S₄ confidence score. We used multivariable linear regression to determine independent predictors of the S₄ confidence score. A separate model was constructed for each of the following predictors: EDP/SV, E/E'/SV, β -coefficient of the non-linear EDPVR equation, and A-wave height on invasive LV pressure tracing. Age, sex, history of heart failure, LV ejection fraction, left atrial volume, and BNP were entered into each model as covariates. All statistical analyses were performed using Stata version 9.2 (Stata Corporation, College Station, TX).

RESULTS

Of the 100 patients enrolled, eight patients were excluded due to poor acoustic cardiographic sound quality and two patients were excluded due to presence of paced rhythms, which could

not be assessed by the available software. Thus, 90 patients comprised this study cohort. Overall, the mean age was 62 ± 14 years, 35% were female, 29% were diabetic, 36% had heart failure, 67% had coronary heart disease, and 80% had hypertension. Two percent of the cohort had hypertrophic cardiomyopathy and 5% had moderate or greater aortic stenosis. Seventeen percent had normal coronary arteries and normal LV end-diastolic pressure. The mean LV ejection fraction was $57 \pm 19\%$ (range 7–85%) and mean LVEDP was 15.0 ± 7.6 mmHg (range 1–31 mmHg).

Computerized heart sound analysis detected an S_4 in 29 patients (32%). There were only 3 patients under the age of 40 years, and only one of these patients had an S_4 . Those with an S_4 were older and there was a trend towards increased acute coronary syndrome and heart failure in the S_4 group (Table 1). Subjects with an S_4 had increased ventricular and atrial volumes but LV mass index was no different than those without an S_4 (Table 2). Those with an S_4 also had higher E/E' ratio and BNP but those with and without an S_4 did not differ significantly in terms of other, more traditional diastolic parameters (Table 3). On invasive hemodynamic testing, subjects with an S_4 had higher LV filling pressures, especially the A wave height (Table 4, Figure 2).

Table 5 lists the four indices of diastolic stiffness and the correlation coefficient for each parameter compared with the S_4 confidence score. The EDP/SV, E/E'/SV, and β (stiffness) coefficient of the single-beat EDPVR method all correlated with the S_4 confidence score, whereas the EDP/EDV ratio did not. Figure 3 shows the mean EDPVR curve (and group-averaged EDV₂₀) for subjects with and without an S_4 . Figure 3 shows that on average, patients with an S_4 had a leftward- and upward-shifted EDPVR curve, signifying that these patients had stiffer ventricles. Because the β -coefficient, but not the α -coefficient, correlated with the S_4 , it was important to show that the EDV₂₀ (the calculated EDV at an idealized EDP of 20 mmHg) was smaller in patients with an S_4 compared with those without an S_4 . This finding shows that when the α - and β -coefficients are examined together in the equation $EDP = \alpha EDV^\beta$, they combine to produce an EDPVR curve that is leftward and upward shifted in the S_4 patients. Finally, Table 6 shows results of the multivariable analysis, showing that increased end-diastolic stiffness was independently associated with the S_4 confidence score.

DISCUSSION

The importance of the S_4 has been debated in the past; some believe that the S_4 is present in the majority of elderly, thereby decreasing its utility (6,7,9). Our study supports the concept that the S_4 is an abnormal finding, and it is the first S_4 study to our knowledge which quantifies LV diastolic stiffness using various different parameters. We showed that the S_4 is independently associated with increased diastolic stiffness. Specifically, we found that several diastolic stiffness parameters, including the EDP/SV and E/E'/SV ratios, and a leftward- and upward-shifted EDPVR curve, were all independently associated with the S_4 . By performing a comprehensive invasive- and non-invasive study of the S_4 , we were able to go beyond prior studies which were limited by studying only mitral inflow characteristics on echocardiography (4,5,18), or which included smaller numbers of patients (2,4,5).

Of the various LV diastolic stiffness parameters, we speculate that the EDP/EDV ratio did not correlate to the S_4 because this ratio does not approximate the EDPVR curve very well. As shown in Figure 1, the EDPVR curve begins its upward trajectory at approximately once volume is greater than end-systolic volume. Rather than EDV, using stroke volume in the denominator of EDPVR slope estimation appears to be more accurate.

In our study, we found that the S_4 was associated with both increased LV diastolic stiffness and increased height of the A wave on invasive LV pressure tracing. Prior studies have shown

that an increased A wave on LV diastolic pressure tracing is related to either elevated end-diastolic chamber stiffness or increased left atrial volume transport (19). Therefore, the association of increased A wave height with the S₄ further supports our finding that the S₄ is associated with increased LV end-diastolic stiffness.

Unlike prior studies, we found that patients with an S₄ had similar LV mass. This may reflect our elderly cohort with multiple cardiac comorbidities, which could have made finding differences in LV mass difficult. In addition, we measured LV mass and not LV wall thickness, which may have been associated with the S₄ due to differences in concentric and eccentric hypertrophy. Our findings may also be due to the use of acoustic cardiographic S₄ instead of auscultatory S₄. The acoustic cardiographic S₄, similar to phonocardiography, may detect more truly pathologic S₄ sounds (and not simply a split S₁) (18) and therefore may detect increased LV filling pressures at the end of diastole, and increased ventricular volumes, as found in our study. Interestingly, in a recent large epidemiologic study of 2,802 patients with heart failure (20), there was a trend towards increased prevalence of the S₄ in those with reduced ejection fraction compared with those with preserved ejection fraction (p=0.13), which may suggest that the S₄ is clinically found even in patients with low ejection fractions and larger ventricular volumes.

Patients with an S₄ did not differ significantly from those without an S₄ in terms of mitral inflow parameters measured by echocardiography. Early diastolic filling (Doppler E wave velocity) decreases with impaired relaxation and increases with elevated LV filling pressures. Thus, early diastolic filling properties (from which LV relaxation is derived non-invasively) are not the ideal method for determining intrinsic stiffness of the LV. In addition, the S₄ occurs in late diastole and is therefore more dependent on ventricular physiologic factors at the end of diastole. Finally, although not statistically significant, E velocity was slightly higher in the S₄ group, and starting in mid-diastole and continuing on to end-diastole, LV pressures were higher in the S₄ group. For these reasons, and based on the primary findings of our study, S₄ appears to be related to intrinsic diastolic stiffness of the LV.

Our study is limited by the lack of simultaneous echocardiographic-Doppler and invasive LV pressure measurements. However, all phonocardiographic and echocardiographic studies were done within four hours of left-heart catheterization. The lack of simultaneous measurements would only bias these associations between the S₄ and LV diastolic stiffness parameters toward the null. Our study is also limited by the use of a fluid-filled (and not micromanometer) catheter for measurement of invasive LV pressures which decreases precision of measurements. We also could not calculate tau (the time constant for isovolumic relaxation) which may have added further insight into the pathophysiology of the S₄. In addition, although the correlation between the S₄ confidence score and parameters of LV diastolic stiffness were highly significant, the correlation coefficients were modest. However, it is possible that the S₄ confidence score and echocardiographic findings do not correlate in a linear fashion, and other factors, such as body habitus, may have attenuated the correlation between S₄ confidence score and LV diastolic stiffness. Finally, an important limitation of our study is possible selection bias since all patients were referred for cardiac catheterization.

In conclusion, the S₄ is most likely generated from an abnormally stiff LV, supporting the concept that the S₄ is a pathologic finding in older patients. Based on the results of our study, detection of the S₄ with the Audicor acoustic cardiographic system may help the clinical diagnosis of patients with increased LV diastolic stiffness, and detection of the S₄ has the potential to be a simple non-invasive method to test the effect of current and future therapies on LV diastolic stiffness.

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Figure 1. Methods for Estimating Left Ventricular End-Diastolic Stiffness

LV = left ventricular, EDPVR = end-diastolic pressure volume relationship, EDP = end-diastolic pressure, SV = stroke volume, EDV = end-diastolic volume. The slope of the EDPVR relationship can be estimated by the single-beat method ($EDP = \alpha EDV^\beta$), EDP/SV , E/E' (as a surrogate of EDP; see text) / SV, and EDP/EDV .

Figure 2. Differences in Left Ventricular Filling Pressures in Diastole – No S₄ vs. S₄

LV = left ventricle, EDP = end-diastolic pressure. Pressures in subjects with an S₄ were higher from mid-to-end diastole. * = P<0.05; † = P<0.005

Figure 3. Differences in Left Ventricular End-Diastolic Pressure-Volume Relationship – No S₄ vs. S₄

EDV₂₀ = group-averaged end-diastolic volume at left ventricular end-diastolic pressure of 20 mmHg. Patients with an S₄ had an upward and leftward-shifted end-diastolic pressure volume relationship (signifying increased end-diastolic stiffness), as shown by the decreased group-averaged EDV₂₀ in the S₄ group.

Table 1

Baseline Demographic and Clinical Characteristics by Presence of Fourth Heart Sound

Characteristic	No S ₄ N=61	S ₄ N=29	P-value
Age (years)	60 ± 12	66 ± 14	0.048
Female (%)	33	31	0.87
Body mass index (kg/m ²)	29.0 ± 7.7	27.6 ± 5.5	0.35
Acute coronary syndrome (%)	13	28	0.093
Coronary artery disease (%)	67	79	0.24
Diabetes (%)	28	31	0.76
Heart failure (%)	30	48	0.082
Hypertension (%)	80	79	0.91
Serum creatinine (mg/dL)	1.48 ± 1.42	1.44 ± 1.11	0.91

Values are means ± standard deviation.

Table 2

Echocardiographic and B-Type Natriuretic Peptide Characteristics by Presence of Fourth Heart Sound

Characteristic	No S ₄ (N=61)	S ₄ (N=29)	P-value
LV ejection fraction (%)	60 ± 18	52 ± 20	0.076
LV end-diastolic volume index (ml/m ²)	54 ± 24	76 ± 39	0.0028
LV end-systolic volume index (ml/m ²)	24 ± 21	43 ± 38	0.007
Left atrial volume index (ml/m ²)	28 ± 11	34 ± 14	0.047
Left ventricular mass index (g/m ²)	115 ± 39	118 ± 3	0.77
B-type natriuretic peptide (pg/mL) median (IQR)	107 (43–300)	292 (96–1210)	0.041

Values are means ± standard deviation unless stated otherwise.

Table 3

Diastolic function parameters

Characteristic	No S ₄ (N=61)	S ₄ (N=29)	P-value
Early mitral inflow velocity (m/s)	0.8±0.2	0.9±0.3	0.12
Late (atrial) mitral inflow velocity (m/s)	0.8±0.2	0.8±0.2	0.22
Early/late mitral inflow velocity (E/A) ratio	1.1±0.5	1.2±0.5	0.40
Pulmonary venous flow systolic/diastolic ratio	1.3±0.5	1.1±0.4	0.14
Early mitral inflow velocity/early mitral annular velocity (E'/E') ratio	6.6±3.7	9.0±6.2	0.042

Values are means ± standard deviation.

Table 4
Hemodynamic Characteristics by Presence of Fourth Heart Sound

Characteristic	No S ₄ N=61	S ₄ N=29	P-value
Heart rate (beats/min)	71 ± 12	66 ± 11	0.064
Systolic aortic pressure (mmHg)	128 ± 23	137 ± 31	0.12
Mean aortic pressure (mmHg)	93 ± 16	93 ± 19	0.96
Early LV diastolic pressure (mmHg)	6.6 ± 5.6	8.3 ± 4.6	0.14
LV mid-diastolic pressure (mmHg)	7.9 ± 5.9	10.6 ± 5.4	0.039
LV pre-A wave diastolic pressure (mmHg)	8.9 ± 6.2	11.6 ± 5.2	0.048
LV peak A wave diastolic pressure (mmHg)	14 ± 8.0	20.3 ± 7.4	0.0006
LV end-diastolic pressure (mmHg)	13.3 ± 7.8	18.5 ± 6.4	0.0022
A wave height (difference between LV peak A wave and pre-A wave pressure; mmHg)	5.1 ± 3.9	8.7 ± 4.6	0.0002
LV diastolic pressure slope during rapid filling phase (pre-A wave)	21.7 ± 29.0	28.7 ± 35.1	0.31

Values are means ± standard deviation.

Table 5Correlation of S₄ Confidence Score with Parameters of Diastolic Stiffness

Diastolic Stiffness Parameter	Correlation Coefficient	P-value
End-diastolic pressure / end-diastolic volume	0.17	0.13
End-diastolic pressure / stroke volume	0.42	0.0001
Ratio of early mitral inflow to early mitral annular velocity (E/E') / stroke volume	0.38	0.001
Single-beat method ($EDP = \alpha EDV^\beta$)		
• α -coefficient	-0.07	0.53
• β -coefficient	0.28	0.014

Table 6
Independent Multivariate Predictors of S₄ Confidence Score

Multivariate Predictor	β -Coefficient [†]	P-value
End-diastolic pressure / stroke volume	0.09	<0.0001
E/E' / stroke volume	0.08	0.015
β (stiffness constant)	0.09	0.003
Invasive A-wave height	0.07	<0.0001

* Adjusted for age, sex, history of heart failure, ejection fraction, left atrial volume, and BNP

[†] Per 10% increase of predictor variable