Articles

Implications of an Audible Third Heart Sound in Evaluating Cardiac Function

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We prospectively compared auscultatory findings of third heart sounds with radionuclide ventriculographic analysis of systolic and diastolic function. Cardiac auscultation was done to detect an S_3 in patients referred for radionuclide ventriculographic analysis of ventricular function. Of 49 adult men with the diagnosis of chronic, nonvalvular heart failure who were referred for the evaluation of heart failure, 22 (45%) at the time of the ventriculography had an S_3 present on examination. For the entire study group, the radionuclide ventriculography-derived ejection fraction was 33% ± 19.5 (mean ± SD) with a range of 6% to 74%. The peak ejection rate was 2.05 ± 1.09 end-diastolic volume per second with a range of 0.30 to 4.56. The peak filling rate was 1.97 ± 1.07 end-diastolic volume per second with a range of 0.44 to 3.94, and the time to peak filling rate was 0.18 ± 0.11 per second with a range of 0.05 to 0.61. The presence of an S_3 was associated with a reduced ejection fraction and also with impaired diastolic function as determined by the peak filling rate. The sensitivity and specificity for the S_3 in detecting abnormal systolic function (ejection fraction < 50%) were 51% and 90%, respectively, with a positive predictive value of 95% and a negative predictive value of only 32%. For an ejection fraction of less than 30%, the S_3 had a sensitivity and specificity of 78% and 88%. The presence of an S_3 was highly predictive of an abnormal ejection fraction. The absence of an S_3, however, is not uncommon in patients with a mildly impaired ejection fraction.

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The diastolic sound that occurs during rapid ventricular filling, synchronous to the rapid descent of the ventricular pressure wave, is called the third heart sound (S_3).[1-4] The S_3 temporally follows ventricular relaxation and occurs simultaneously with rapid ventricular filling. The origins of the sound remain undefined. Classic explanations have included the following:

- Early diastolic effects of the ventricle on the chest wall,
- Overfilling of the failing ventricle with partial tensing of the support of the valvular structures, and
- Rapid pressure decompression of residual fluid in the ventricle in early diastole.

The intensity of an S_3 is increased by rapid early diastolic filling, such as in cases of elevated atrial pressure–as in mitral regurgitation.[5] The S_3 is also frequently noted in hyperdynamic states, such as anemia and thyrotoxicosis, and in patients with an arteriovenous fistula. The intensity of the S_3 also increases during inotropic therapy.[6] In practice, the presence of an S_3 is often used by primary clinicians to suggest the presence of congestive heart failure, but the overall accuracy of the S_3 as an indicator for systolic or diastolic dysfunction is largely unknown.

Because the S_3 occurs during rapid ventricular filling, we hypothesized that the presence of an S_3 would predict abnormalities in the measurements of ventricular filling as determined by radionuclide ventriculography. Similarly, because the S_3 occurs after systole is completed, we hypothesized that the presence of an S_3 would not closely correlate to abnormalities of systolic function determined by radionuclide ventriculography.

The purpose of our study was to assess the relationship between the third heart sound and systolic and diastolic dysfunction as determined by radionuclide angiography. We were specifically seeking to determine the accuracy and reliability of an S_3 for detecting cardiac dysfunction in a group of patients referred for the evaluation of congestive heart failure.

Patients and Methods

Our study included 49 patients referred to the nuclear medicine department (Department of Veterans Affairs, Hines, Illinois, Medical Center) for radionuclide ventriculography with the diagnosis of nonvalvular chronic heart failure. On the day of the radionuclide ventriculographic study, all patients were examined separately by the same two internists (R.P., D.B.) for the presence of an S_3 using

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ABBREVIATIONS USED IN TEXT

EDV = end-diastolic volume
PER = peak ejection rate
PFR = peak filling rate
TPER = time to peak ejection rate
TPFR = time to peak filling rate

the bell of a good-quality stethoscope placed over the point of maximal impulse. If an S_3 was not audible in the supine position, the patient was auscultated in the left lateral decubitus position. In the event of a disagreement, a third physician at the medical center (a cardiologist) was asked to examine the patient. The hospital's human studies committee waived requirements for informed consent.

Radionuclide ventriculographic studies were performed using a modified in vivo technique for labeling autologous erythrocytes with 25 mCi of technetium Tc 99m. A small-field gamma camera was used to obtain the images with gating at 32 frames per cycle using a buffered frame mode acquisition. The left anterior oblique view with a 10-degree caudal tilt was used for calculating all radionuclide ventriculography measurements. Counts of 6.5 million were obtained for each left anterior oblique view. Using an automated edge detection method, the cinematographic images were analyzed to generate a time-activity curve for determining the ejection fraction, peak ejection rate (PER), peak filling rate (PFR), time to peak filling rate (TPFR), and time to peak ejection rate (TPER). Diastolic pressures were not normalized for the RR interval.

The normal limits for PFR, TPFR, and PER were determined in the nuclear medicine laboratory using 35 subjects referred for multigated acquisition as part of a pre-chemotherapy assessment, who were found to have ejection fractions of greater than 50% and no evidence of infarction or hypertrophy on electrocardiography.

Data Analysis

The sensitivity, specificity, positive predictive value, and negative predictive value of an audible S_3 for predicting ejection fractions of less than 0.50 or 0.30, abnormal PFR (< 1.6 end-diastolic volume [EDV] per second), abnormal TPFR (> 0.360 seconds), and abnormal PER (< 2.3 EDV per second) were calculated. The student's *t* test was used to compare mean values of the ejection fraction, PER, PFR, and TPFR for patients with or without an S_3 (Table 1).

Results

All 49 patients enrolled in the study were men. Ages ranged from 49 to 74 years with a mean of 61.3 years. The mean age of patients with an audible S_3 was significantly less than those without an S_3 (56.6 versus 65.0 years). The mean ejection fraction of all patients referred was 33.1 ± 19.5 (mean ± SD). As a group, however, those patients with an audible S_3 had significantly lower ejection fractions compared with those without an S_3 (19.0 ± 13.3 versus 44.9 ± 16.6 [$P < .001$]). The PER for all referred patients was 2.05 ± 1.09 EDV per second, with a significantly slower PER for those patients with an S_3 than for those without an S_3 (1.37 ± 0.98 versus 2.35 ± 0.91 [$P < .001$]). The PFR among the patients with an S_3 was 1.50 ± 1.01 EDV per second, compared with 2.38 ± 1.01 for those without an S_3 ($P = .005$). The mean TPFR was significantly different for those with an S_3 versus those without (0.148 ± 0.086 second versus 0.215 ± 0.131 second [$P = .05$]) (see Table 1).

The sensitivity, specificity, positive predictive value, and negative predictive value of an audible S_3 for ejection fractions of less than 50% or less than 30%, an abnormal PER, an abnormal PFR, and an abnormal TPFR are given in Table 2. Ten patients had ejection fractions of more than 50%. Of the remaining 39 patients, 23 had ejection fractions of less than 30%. On examination, 21 patients had an audible S_3. Of these, 20 had ejection fractions of less than 50% (positive predictive value of 95%) and 18 patients had ejection fractions of less than 30%. Of the 28 patients who did not have an S_3 on physical examination, only 9 had a normal ejection fraction (negative predictive value of 32%), but 23 of these patients had ejection fractions of greater than 30% (negative predictive value of 82%).

The correlation between the peak ejection rate and the ejection fraction was calculated by least-square linear regression with $r = 0.89$, $P < .001$. Similarly, a correlation between the peak filling rate and the ejection fraction was documented with $r = 0.73$, $P < .001$.

Discussion

We undertook this study to examine the value of a third heart sound in predicting poor left ventricular perfor-

TABLE 1.—*Radionuclide Ventriculography (MUGA) Variables and Age Distribution in Patients With and Without a Third Heart Sound*

Variable	S_3 Present*		P Value
	Yes	No	
Age, yr	56.5 ± 12.6	65 ± 9.2	<.05
Ejection fraction, %	19 ± 13.3	44.9 ± 16.6	<.001
Peak ejection rate, EDV/sec	1.37 ± 0.98	2.35 ± 0.91	<.001
Peak filling rate, EDV/sec	1.5 ± 1.01	2.381 ± 1.014	.005
Time to peak filling rate, sec	0.148 ± 0.086	0.215 ± 0.131	.05

EDV = end-diastolic volume, MUGA = multigated acquisition

*Values are mean ± SD.

TABLE 2.—*Sensitivity, Specificity, and Predictive Values for Ejection Fraction Indices in Patients With a Third Heart Sound*

	Sensitivity		Specificity		Positive Predictive Value		Negative Predictive Value	
Index	%	*(95% CI)*	%	*(95% CI)*	%	*(95% CI)*	%	*(95% CI)*
EF < 50%, n = 39	51	(33-67)	90	(56-100)	95	(76-100)	32	(16-52)
EF < 30%, n = 23	78	(56-92)	88	(70-98)	86	(64-97)	82	(63-94)
Abnormal PER	64	(44-81)	78	(56-92)	78	(56-92)	64	(44-81)
Abnormal PFR	61	(39-80)	73	(52-88)	66	(43-85)	68	(47-84)
Abnormal TPFR	0	(0-71)	54	(33-69)	0	(0-16)	89	(72-98)

CI = confidence interval, EF = ejection fraction, PER = peak ejection rate, PFR = peak filling rate, TPFR = time to peak filling rate

mance. The reliability of this finding as an indication of left ventricular dysfunction has not been carefully studied with modern diagnostic methods. The presence of an S_3 has traditionally been associated with poor ventricular systolic performance; however, we had expected that the S_3 might be more closely associated with abnormalities of the diastolic index because of its synchrony with diastole.

The third heart sound occurs early in diastole following mitral valve opening. Nonetheless, we found the presence of an S_3 to be more closely associated with abnormalities of ejection phase indices, such as the ejection fraction and peak ejection rate, than with the diastolic index of the peak filling rate. Comparing the percentage of patients with an S_3 in each multigated-acquisition-measurements group for normal versus abnormal indices showed that the presence of an S_3 was closely associated with an ejection fraction of less than 50%, less than 30%, and the peak ejection rate (χ^2, $P = .01$, $P < .001$, and $P = .001$, respectively). The association with the peak filling rate and the time to peak filling rate was not as strong, however (χ^2, $P = .025$ and $P = .08$, respectively).

The results with the greatest practical clinical importance are those that show the reliability of an S_3 for predicting cardiac dysfunction. The positive predictive value of an S_3 for identifying patients with an ejection fraction of less than 0.50 is excellent (95%, with a 95% confidence interval of 76% to 100%). The corresponding negative predictive value is only 32%, however, indicating that physicians cannot reliably exclude at least mild systolic dysfunction when an S_3 is not heard. The corresponding specificity and sensitivity are 90% and 51%, respectively, for identifying ejection fractions of less than 0.50. For detecting severely reduced ejection fractions of less than 0.30, the positive predictive value of an S_3 is still good at 86% and the negative predictive value, as expected, is much better at 82%. Therefore, in the absence of an audible third heart sound, a clinician can, with good confidence, exclude the presence of severe systolic dysfunction (defined as an ejection fraction of less than 30%). As a consequence of the excellent specificity and the high positive predictive value of an audible S_3 for identifying ejection fractions of less than 0.50, a clinician can be highly confident that systolic dysfunction is present when a third heart sound is heard. The sensitivity and negative predictive value of the S_3 are also high for patients with severe systolic dysfunction. Whereas predictive values can be criticized for their dependence on disease prevalence, these values are effectively used by clinicians in making medical decisions, although some estimation of disease likelihood (prevalence) is made before test results are obtained. It should be noted that there was roughly an even split in our population between patients with severe systolic dysfunction (23) and those without severe systolic dysfunction (26), although our population included a somewhat smaller number with normal systolic function (10).

Although the S_3 occurs in diastole, its association with the index of diastolic dysfunction, as determined by gated blood pool scanning, is modest. The presence of an S_3 can predict abnormal peak filling rates, with a positive predictive value of 66% and a specificity of 73%. The value of the presence of an S_3 in positively predicting abnormally delayed time to peak filling rate is 0% with a specificity of 54%. Therefore, although the presence of an S_3 appears to have some association with abnormally slow filling rates, it is not associated with a delayed time to peak filling rate.

The idea that the heart sound heard in early diastole may be associated closely with abnormalities of systole is intriguing. Early rapid ventricular filling occurs following the mitral valve opening. Despite the rapid influx of blood to the ventricle, pressure continues to decline. Indeed, 40% to 60% of the total ventricular volume is completed at or before the time that ventricular pressure reaches minimum. Because a notable amount of ventricular filling occurs early in the rapid filling phase and is thought to be simultaneous with the occurrence of an S_3, we thought that diastolic filling variables, determined by radionuclide ventriculography, would be intimately associated with auscultation findings of an S_3, which occurs simultaneously with this early rapid filling. Late ventricular filling and atrial kick-dependent ventricular filling are the late diastolic events. The contribution of ventricular filling (preload) that occurs during early diastole is dependent, in part, on the time course of ventricular relaxation and the atrioventricular pressure gradient. Thus, events that contribute to early rapid ventricular filling occur during isovolumic relaxation, before mitral valve opening. This, therefore, may link measurements of systolic events to auscultatory and measurable findings of diastole.

There is precedent in the basic physiology literature to consider early ventricular filling as a systolic event. Brutsaert and Rademakers have proposed that the traditional concepts of a well-defined end to ejection and discreet onset of diastole be abandoned.[7] Their concept of systole and diastole recognizes that the early filling reflects the rate and completeness of ventricular relaxation, both be-

fore and immediately following mitral valve opening. This concept then links late systolic events, through relaxation, to early filling.

Our study is limited by the use of an audible S_3, as opposed to the use of diagnostic phonocardiography. For practicing physicians, an auscultated S_3 is a more appropriate and relevant measure in terms of patient care. Furthermore, the use of radionuclide angiography to assess the derivative values of ventricular function is critically dependent on acquisition and edge-detection algorithms.[8] The diastolic measurements are also dependent on the mitral valvular function, atrioventricular pressure gradient, and perhaps the heart rate. Nonetheless, these findings provide insight into the pathogenesis of the clinically appreciable S_3 and give a good indication of the reliability and accuracy of the S_3 for predicting various degrees of cardiac systolic and diastolic dysfunction.

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