Clinical Significance and Hemodynamic Correlates of the Third Heart Sound Gallop in Aortic Regurgitation

A Guide to Optimal Timing of Cardiac Catheterization

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SUMMARY The hemodynamic and clinical data of 42 patients with chronic significant aortic regurgitation and 31 normal subjects were examined. Of the patients with aortic regurgitation, 28 had a third heart sound (S₃) gallop and 14 did not. There was no significant difference in the severity of regurgitation between the patients with or without an S₃ gallop. However, all patients with an S₃ gallop had an abnormally increased left ventricular residual volume and depressed contractile state. These findings were supported by the hemodynamic data of two patients who underwent cardiac catheterization before and after the development of an S₃ gallop.

We conclude that the S₃ gallop in patients with chronic AR reflects left ventricular dysfunction, rather than more severe degrees of regurgitation per se, and may therefore be useful for selecting patients for cardiac catheterization and consideration for prosthetic aortic valve replacement.

PATIENTS with aortic regurgitation (AR) can redistribute blood flow and increase forward effective stroke volume by reducing the regurgitant volume during exercise. Therefore, they may remain asymptomatic for many years, even in the presence of significant left ventricular (LV) dysfunction, and cardiac decompensation is usually far advanced by the time radiographic enlargement, wide pulse pressure and electrocardiographic abnormalities become apparent. Furthermore, the impairment in ventricular performance is frequently irreversible and may not improve significantly despite aortic valve replacement.

A higher perioperative and late surgical mortality and increased morbidity has been described in patients with AR and associated congestive heart failure, cardiomegaly on preoperative chest x-ray, depressed ejection fraction, and increased LV end-systolic volume (ESV) or end-diastolic pressure (EDP). AR is usually easily diagnosed and quantitated at the bedside. However, the clinical recognition of early LV dysfunction is difficult despite the use of accepted noninvasive techniques.

The ventricular (S₃) gallop, which has been acknowledged as an indicator of cardiac decompensation for a century, has uncertain significance in patients with chronic, isolated AR without overt congestive heart failure. While some authors have associated this sound with LV dysfunction, others believe it only reflects more severe degrees of regurgitation or have not examined its significance in patients with AR. Few published hemodynamic data are available in such patients. The present study was designed to evaluate the meaning and clinical value of the S₃ gallop in patients with AR.

Materials and Methods

The records of 55 consecutive patients with chronic, hemodynamically significant AR (greater than 25% regurgitation) were examined retrospectively and prospectively. All patients were referred to the Medical College of Georgia for cardiac catheterization, cineangiography and possible aortic valve replacement on the basis of established clinical criteria. The following were considered as grounds for exclusion of 13 patients from the study: unsatisfactory LV cineangiograms that prevented reliable estimates of chamber volume and function in three, diastolic hypertension of greater than 90 mm Hg in two, more than trivial mitral regurgitation or stenosis in two, aortic stenosis with a calculated valve area of less than 2 cm² in two, significant coronary artery disease with angiographic evidence of greater than 50% diameter narrowing of any major coronary artery in one patient, atrial fibrillation in one, and lack of documentation by one or more senior cardiology faculty members about the presence or absence of an audible S₃ gallop in two patients. Forty-two patients, 35 male and seven female, qualified for inclusion. The patients ranged in age from 16–65 years (mean 36 years). Twenty-four patients had a congenital bicuspid aortic valve. Fourteen had a history of rheumatic fever and one a history of infective endocarditis. Two patients had Marfan's syndrome and one had probable luetic heart disease. A separate group of 31 patients (mean age 31 years) with atypical chest pain underwent diagnostic catheterization and were found to be free of organic heart disease; they were the normal control.

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subjects. The New York Heart Association (NYHA) functional classification was used to grade symptoms.

The arterial systolic and diastolic blood pressures (BPs) were measured at rest with a sphygmomanometer. Standard 12-lead ECGs were interpreted by the criteria of Romhilt and Estes, five points being diagnostic and four suspicious for LV enlargement. The transverse diameter of the heart was evaluated with chest x-ray films taken at a standard distance of 6 feet and the cardiothoracic ratios were calculated. Twenty-nine patients underwent exercise stress testing using the Bruce treadmill protocol. Published data for normal middle-aged men and women, supplemented by our own unpublished data for younger patients, were used for comparison. The absence or presence of an S3 gallop was determined by examining the patient in the left lateral decubitus position with the bell of the stethoscope lightly and precisely applied to the point of maximal impulse. In the reported cases, no difficulty was encountered in separating a loud, transient S3 gallop from an Austin-Flint rumble.

Right- and left-heart catheterizations were performed in all patients. Pressures were obtained in the standard fashion through fluid-filled catheters connected to a Statham P23Db strain-gauge transducer, and recorded on a DR-8 Electronics for Medicine recorder, after suitable calibration using a mercury manometer. The reference level for zero pressure was halfway between the manubrium and the surface of the table. LV cineangiograms were obtained in the 30-40° right anterior oblique position with a 35-mm camera (60 frames/sec) during rapid (2-3-second) injection of 45-60 ml of sodium meglumine diatrizoate through a retrograde arterial catheter. End-diastolic volume (EDV), ESV and ejection fraction were calculated by the area-length method. The total LV stroke volume was obtained by subtracting ESV from the EDV. The product of the total stroke volume and heart rate provided the total cardiac output of the left ventricle. The effective forward cardiac output was determined by the Fick oxygen method. All volumes and flows were indexed to the body surface area. The contractile state of the left ventricle was evaluated by calculating the LV peak systolic pressure/ESV index ratio (LVSP/ESVI). The LV dP/dt and contractility indexes dependent upon this measurement were not used because "catheter whip" of the fluid-filled system introduced substantial artifacts in the recordings of most patients with AR. Regurgitant flow across the aortic valve was calculated by subtracting the effective cardiac output from the total cardiac output, and the regurgitation fraction was calculated as (regurgitant flow/total cardiac output) x 100. In no patient was there a discrepancy between this method and the semiquantitative analysis of the aortic valvulograms.

Data from this study were evaluated with the t test and other appropriate statistical methods for small samples. The level of statistical significance was set at p < 0.05. Values are expressed as mean ± sd.

Results

Clinical and hemodynamic data in the 42 patients with AR are presented in tables 1 and 2. Statistical information for patients with and without an S3 gallop and for the 31 normal subjects are presented in table 3.

Clinical Data

Of the 42 patients with AR, 31 were in NYHA functional class II and the rest were in class III. Twenty-five patients had a systolic BP greater than 140 mm Hg, and 11 had a diastolic BP of 40 mm Hg or lower. Twenty-six patients had an S3 gallop. No patient had clinical evidence of circulatory congestion.

The ECGs of 26 patients fulfilled the criteria for LV enlargement (five or more points), while 14 had four points. The chest roentgenograms revealed a normal (< 0.5) cardiothoracic ratio in 11 patients. In 16 the ratio was 0.51-0.59, and in 15 it was 0.60 or greater.

Exercise stress testing was conducted in 29 patients with AR. The endurance time was within 1 standard deviation of the mean expected normal in 18 patients and more than 2 standard deviations below the expected mean normal in 11 patients.

When the 28 patients with an S3 gallop were compared with 14 patients without an S3, the frequency of LV enlargement by ECG was not significantly different in the two groups. Also, no significant differences were found in the mean NYHA functional class, cardiothoracic ratio by x-ray, age-corrected exercise tolerance on treadmill stress testing, or systolic BP. However, patients with S3 gallops had a significantly lower diastolic and wider pulse pressure than those without an S3 (both p < 0.02).

Hemodynamic Data

The percent regurgitation of total aortic valve flow in 28 patients with an S3 gallop was not significantly different from that of 14 patients without an S3 gallop (56 ± 9% vs 53 ± 4%). Also, there was no significant difference in the mean effective cardiac index (as calculated by the Fick method) between normal subjects and patients with or without an S3 gallop (table 3).

The mean LVEDP in patients without an S3 gallop was not significantly different from that in the normal subjects (11 ± 6 vs 9 ± 3 mm Hg; NS), while the mean LVEDP in patients with an S3 gallop was significantly higher (17 ± 8 vs 11 ± 6 mm Hg; p < 0.005). However, the mean ejection fraction of patients without an S3 gallop was not significantly higher than that in normal subjects (0.70 ± 0.08 vs 0.65 ± 0.05; NS), while that of patients with an S3 gallop was lower (0.53 ± 0.11; p < 0.001).

The mean LVEDV index (EDVI 158 ± 36 ml/m²) and ESVI (48 ± 14 ml/m²) in patients without an S3 gallop were significantly larger than the respective mean normal values of 82 ± 16 and 28 ± 7 ml/m² (both p < 0.005); but the mean EDVI and ESVI in patients with an S3 gallop were even larger, 206 ± 48 and 97 ± 36 ml/m², respectively (p < 0.005).
Figure 1 demonstrates the exponential curvilinear relationship between EDVI and ESVI in normal subjects and patients with AR. Patients with AR expanded both volumes to a proportionate degree until EDVI approximated and exceeded 200 ml/m². Further expansion of the EDVI resulted in a disproportionate increase in ESVI. Figure 2 shows that patients without an S₃ gallop emptied their left ventricles more completely than normal subjects and thus had a smaller residual fraction (31 ± 8% vs 35 ± 7%; p < 0.025). In contrast, patients with an S₃ gallop had significantly less emptying and a larger residual fraction (46 ± 11%; p < 0.005). When the LVSP/ESVI ratio was used as an index of contractility, patients with an S₃ gallop had a significantly lower mean value (1.57 ± 0.71 mm Hg/ml/m²; p < 0.001) compared with normal subjects (4.04 ± 0.55) and other patients with AR (3.24 ± 0.82).

### Sensitivity, Specificity and Predictive Accuracy of an S₃ Gallop

To test the sensitivity and specificity of the S₃ gallop in regard to abnormal LV performance characteristics, we compared the hemodynamic data of patients with AR and data of 31 normal subjects. An abnormal ESVI was defined as a value greater than 2 standard deviations above the normal mean. An abnormal ejection fraction and LVSP/ESVI index were defined as values less than 2 standard deviations below the respective normal mean (table 4). The association between S₃ galloping and abnormal values of ESVI, ejection fraction and LVSP/ESVI index were tabulated and calculated separately to obtain the following indexes for patients with chronic AR:

Sensitivity = true positive/(true positive + false negative) × 100. Expressed as a percentage this is the

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**Table 1. Hemodynamic Data in 28 Patients with Aortic Regurgitation and S₃ Gallop**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>EDVI (ml/m²)</th>
<th>ESVI (ml/m²)</th>
<th>RF (%)</th>
<th>EF (%)</th>
<th>LVSP/ESVI (mm Hg/ml/m²)</th>
<th>LVEDP (mm Hg)</th>
<th>Cardiac index (L/min/m²)</th>
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± SD ± 14 ± 48 ± 36 ± 9 ± 0.11 ± 0.71 ± 8 ± 0.79

**Abbreviations:** EDVI = end-diastolic volume index; ESVI = end-systolic volume index; RF = regurgitant fraction of total aortic valve flow; EF = ejection fraction; LVSP/ESVI = ratio of left ventricular peak systolic pressure to end-systolic volume index; LVEDP = left ventricular end-diastolic pressure.
Table 2. Hemodynamic Data in 14 Patients with Aortic Regurgitation Who Did Not Have an S₃ Gallop

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<th>Pt</th>
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<th>ESVI (ml/m²)</th>
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<th>EF (%)</th>
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<td>± SD</td>
<td>± 15</td>
<td>± 36</td>
<td>± 14</td>
<td>± 4</td>
<td>± 0.08</td>
<td>± 0.82</td>
<td>± 6</td>
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Abbreviations: See table 1.

Table 3. Statistical Data in 31 Normal Subjects, 14 Patients with Aortic Regurgitation and No S₃, and 38 Patients with Aortic Regurgitation and an S₃ Gallop

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<th>Age (years)</th>
<th>BP (mm Hg)</th>
<th>EDVI (ml/m²)</th>
<th>ESVI (ml/m²)</th>
<th>(ESV/EDV) x 100 (%)</th>
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<td>28 ± 7</td>
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<td>43 ± 15 p &lt; 0.05</td>
<td>137/65 ± 18/15</td>
<td>158 ± 36</td>
<td>48 ± 14</td>
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<tr>
<td>AR and S₃ gallop</td>
<td>32 ± 14 p &lt; 0.05</td>
<td>145/53 ± 23/14</td>
<td>206 ± 48</td>
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<table>
<thead>
<tr>
<th>EF (%)</th>
<th>RF (%)</th>
<th>LVEDP (mm Hg)</th>
<th>Fick CI (l/min/m²²)</th>
<th>LVSP/ESVI index</th>
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<tr>
<td>AR and no S₃ gallop</td>
<td>0.70 ± 0.08 p &lt; 0.05</td>
<td>53 ± 4</td>
<td>11 ± 6</td>
<td>3.60 ± 0.86</td>
</tr>
<tr>
<td>AR and S₃ gallop</td>
<td>0.53 ± 0.11 p &lt; 0.05</td>
<td>56 ± 9</td>
<td>17 ± 8</td>
<td>3.45 ± 0.79</td>
</tr>
</tbody>
</table>

Values are mean ± sd.

Abbreviations: AR = aortic regurgitation; BP = blood pressure; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; ESV/EDV x 100 = left ventricular residual volume expressed as a fraction of the end-diastolic volume; EF = ejection fraction; RF = regurgitant fraction of the total aortic valve flow; LVEDP = left ventricular end-diastolic pressure; CI = cardiac index; LVSP/ESVI index = ratio of left ventricular systolic pressure to end-systolic volume index.

likelihood that an S₃ gallop will be present in patients with an abnormally large ESVI (74%), an abnormally depressed ejection fraction (93%) or LVSP/ESVI index (82%).

Specificity = true negative/(true negative + false positive) × 100. Expressed as a percentage, this is the likelihood that an S₃ gallop will be absent in patients with a normal ESVI (100%), ejection fraction (48%), or LVSP/ESVI index (100%).

Predictive accuracy = true positive/(true positive + false positive) × 100. Expressed as a percentage, this is the percent of all S₃ gallops that are true markers of LV dysfunction in patients with chronic AR. It is equal to the product of prevalence and sensitivity divided by the denominator of the same product plus the false positive, which also depends on prevalence. The predictive value depends on the prevalence of the disorder in the population under study. The predictive accuracy was 100% for an abnormally increased ESVI or depressed LVSP/ESVI index, but only 50% for an abnormally reduced ejection fraction.

In summary, an S₃ gallop is sensitive but not satisfactorily specific for a depressed ejection fraction, whereas it is both sensitive and specific for an abnormally expanded residual volume and depressed contractility as measured by the LVSP/ESVI index. Also, the S₃ gallop has 100% predictive accuracy in identifying an abnormally expanded ESVI and a depressed contractility index.
Exponential curvilinear relationship between the end-diastolic and end-systolic volume indexes (EDVI and ESVI) in 31 normal subjects and 42 patients with aortic regurgitation (AR). The latter group consists of 28 patients with and 14 without an S₃ gallop.

Hemodynamic Data Before and After Development of an S₃ Gallop

Patients 32 and 36 (table 2) did not have an S₃ gallop at the time of their first cardiac catheterization but developed one after 2 and 6.8 years of follow-up, respectively. Cardiac catheterization was repeated because of the onset of S₃ gallop in both and worsening of symptoms in patient 36. The clinical and hemodynamic data, before and after the development of an S₃ gallop, are presented in table 5. Although the severity of regurgitation and LVEDP was unchanged, both patients had reduced ejection fraction and LVSP/ESVI and a large increase in the LV residual volume after the onset of the S₃ gallop.

Discussion

Our study offers a solution to the controversy concerning the significance of an S₃ gallop in patients with chronic AR. In support of the clinical impressions of some,¹⁸-²² and in contrast to those of others,¹¹,²²-²⁵ our hemodynamic data demonstrate that the S₃ gallop related not to the degree of regurgitation per se, but rather to the presence of LV dysfunction. Although many of our patients with AR and an S₃ gallop had normal cardiac output, LVEDP and ejection fraction, none had normal contractility as measured by the LVSP/EDVI.⁴⁷-⁴⁹ The cardiac output and LVEDP are relatively insensitive measures of LV performance because they depend on many factors in addition to contractility.⁴⁸-⁵⁵ It has also been suggested that the ejection fraction may be an unreliable index of LV function because it is substantially altered by changes in preload or afterload.⁵⁵-⁶⁰ Indeed, some patients with AR and a normal resting ejection fraction have been shown to develop distinctly abnormal ventricular function curves, diminished stroke volume and a reduced ejection fraction when stressed.⁵⁷-⁶⁰ The residual LV volume has been proposed as a more sensitive means of distinguishing changes in the contractile state of the left ventricle.⁵,⁴⁷ because expansion of this volume is a consequence of LV failure and inade-
quate systolic emptying. It appears that the Frank-Starling law (and the ejection fraction) defines the potential of the left ventricle to do work while the residual volume is the true result. For this reason, a contractility index derived from the LVSP and ESV is capable of detecting cardiac decompensation, even in patients who can maintain a normal ejection fraction at rest. Both of our patients who developed an S3 gallop during the study period expanded their ESV and decreased their contractility index to an abnormal degree while maintaining a normal ejection fraction.

The ideal timing of prosthetic valve replacement is controversial. Despite significantly improved operative techniques, durability, and flow characteristics, the long-term morbidity and mortality after surgery remains high enough to discourage routine valve replacement in asymptomatic patients with significant AR. On the other hand, the onset of symptoms often signifies overt and irreversible ventricular dysfunction, reducing the potential benefits of surgery. Also, the 3-year mortality after valve replacement in patients with AR and a depressed ejection fraction is more than 35%, which is over three times greater than that in patients with normal LV function. Serial cardiac catheterizations cannot be justified for asymptomatic patients; therefore, noninvasive assessment is required to detect early signs of LV dysfunction. Recent studies have shown that an increased ESV serves as an important indicator of postoperative mortality and LV function in patients with AR. All of our patients with an S3 gallop had an abnormal increase in their LVESV. The detection of an S3 gallop may play an important role in the selection of patients for cardiac catheterization and possible prosthetic valve replacement if LV dysfunction is confirmed.

Apparent limitations of the present study need clarification. First, the separation of patients on the basis of auscultation alone is dependent upon the clinical skills of the examiner, with an unmeasurable element of subjectivity. Second, the lack of hard data in the form of phonocardiography may be distressing. We justify the absence of phonocardiograms in our study because appropriate filter settings permit the recording of an S3 in all patients with significant AR, and in many normal subjects, even in the absence of an audible S3. Audibility of the S3 gallop, in the proper context, invariably implies organic heart disease. We therefore decided to sacrifice sensitivity to preserve specificity. Another apparent limitation is the younger mean age of our patients with S3 gallops. Young subjects would be more apt to have a physiologic S3, so one might encounter young patients with AR, an S3, and normal LV size and function. However, this combination was not seen in any of our patients. Moreover, the failure of the pathologic S3 to be reduced in intensity or disappear when the patient assumes an upright position is a useful screening procedure.

Our study shows that the S3 gallop is a highly specific and sensitive marker of LV dysfunction in patients with chronic AR, with 100% predictive accuracy, and that the sound correlates well with LV cineangiographic parameters of impaired LV performance. Moreover, we feel that careful auscultation for, and detection of, an S3 gallop may have an important role in selecting patients for cardiac catheterization and possible aortic valve replacement. This role is particularly important because serial cardiac catheterization is impractical, and single echocardiographic measurements of LV dimensions and function indexes are clinically unsatisfactory and may be misleading in patients with AR. Also, the validity of serial echocardiographic studies has not been satisfactorily documented by comparison with LV cineangiography, the standard for evaluating cardiac performance. The long-term prognosis of patients with an S3 gallop needs further evaluation.
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Clinical significance and hemodynamic correlates of the third heart sound gallop in aortic regurgitation. A guide to optimal timing of cardiac catheterization.
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