Diastolic Heart Sounds during Static (Handgrip) Exercise in Patients with Chest Pain

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SUMMARY
In order to determine the frequency of third and fourth heart sounds during cardiovascular stress, 61 patients with chest pain syndromes and normal resting phonocardiograms underwent phonocardiography both before and during submaximal handgrip exercise. Cardiac catheterization, selective coronary arteriography, and left ventriculography were performed in all patients. Twenty-nine had phonocardiograms simultaneous with hemodynamic studies. Twenty patients had normal coronary arteriograms; 41 had obstructive coronary artery disease. Fifteen percent of the subjects with normal coronary arteriograms and 54% of the patients with coronary artery disease developed diastolic heart sounds after handgrip exercise ($P < 0.05$). Conversely, 88% of the patients developing a diastolic heart sound had coronary artery disease. (If data from the present study are taken together with the previously reported prevalence of diastolic heart sounds at rest, it is estimated that these sounds can be readily demonstrated in approximately 75% of patients with coronary artery disease). Subjects with normal coronary arteriograms who developed postexercise diastolic heart sounds had a greater elevation in LVEDP and a lower EDVI/EHP ratio than did patients without these sounds, although the differences were not statistically significant. However, patients with coronary artery disease who developed abnormal heart sounds had changes which were significantly different from those who did not ($P < 0.001$ and $P < 0.05$, respectively). These findings suggest that (1) the emergence of diastolic heart sounds during handgrip exercise is a useful clinical adjunct in the diagnosis of coronary artery disease and (2) in patients with coronary artery disease, these sounds are associated with significant elevations in LVEDP, which in turn may be related to altered end-diastolic volume-pressure relationships.

Additional Indexing Words:
Third heart sound Coronary arteriography
Fourth heart sound Ventricular compliance

THE PRESENCE of diastolic (third and fourth) heart sounds has proven to be a useful clinical clue in the diagnosis of obstructive coronary artery disease in patients with both acute and chronic chest pain syndromes. However, the absence of these physical findings is a much less reliable sign that coronary anatomy and left ventricular function are normal. In a recent report from this laboratory, 51 of 93 subjects (54%) with coronary artery disease did not exhibit third or fourth heart sounds at rest. The purpose of the present study is to report that the frequency of abnormal sounds can be increased in such patients by means of static (handgrip) exercise. The pertinent clinical, hemodynamic, and angiographic features associated with these phonocardiographic findings will also be discussed.

Materials and Methods
Patient Selection
The study population consisted of 61 patients requiring evaluation of chest pain. None of the patients demonstrated third or fourth heart sounds on phonocardiograms performed in the resting state.

In order to avoid attributing the phonocardiographic findings to the effects of other forms of heart disease, or to the action of drugs, the following criteria were used for selection of patients: all were suspected clinically of having coronary artery disease uncomplicated by other disorders such as hypertension (diastolic blood pressure over 100 mm Hg), or valvular, pericardial, or congenital heart disease; none received propranolol...
within 24 hours of the tests or were taking a digitalis preparation.

Radiologic and Electrocardiographic Criteria

Radiologic evidence of left ventricular enlargement and electrocardiographic evidence of transmural myocardial infarction were both determined by standard diagnostic criteria.3

Catheterization and Angiographic Procedures

Right and left heart catheterizations were performed on all patients using procedures similar to those reported previously.4 Left ventricular end-diastolic pressure (LVEDP) was measured at high sensitivity (normal value ≤ 12 mm Hg). Cardiac index was measured via the indocyanine green dye technic (normal value ≥ 2.5 liters/min/m²). High quality selective cine coronary arteriograms were recorded on 16 mm Ilford Pan F film with either 6-in. dual-field General Electric or Siemens image intensifier X-ray systems. Stenosis of greater than 75% of a vessel lumen was considered significant. Cine left ventriculograms were obtained and evaluated by the method of Herman et al.4 and the term "asynery" was used to define any significant abnormality of left ventricular wall motion. Left ventricular end-diastolic volumes corrected for body surface areas (EDVI) were obtained from angiographic silhouettes using an adaptation of the single-plane method of Greene et al.5 The end-diastolic volume-pressure relationship was expressed as the ratio EDVI/EDP, with the realization that this is not "true" compliance (ΔV/ΔP).

Phonocardiographic Studies

In 32 patients (24 with and eight without obstructive coronary disease), phonocardiograms were obtained on the day preceding catheterization. In the other 29 patients (17 with and 12 without coronary artery disease), phonocardiograms were recorded during cardiac catheterization. Phonocardiograms were taken at 50-100 Hz (both at and medial to the apex) with either a Hewlett-Packard piezo-electric crystal microphone and Sanborn heart sound recorder, or an Elema-Schonander Mingograf-51 system. All tracings were recorded with a simultaneous lead II electrocardiogram at a paper speed of 75-100 mm/sec.

Criteria used for identification of abnormal third and fourth heart sounds in the present study have been presented previously.2 In brief, third heart sounds occur 0.10-0.20 sec after the aortic component of the second sound. They are usually considered abnormal if present in subjects over 30 years of age. Fourth heart sounds occur 0.12-0.17 sec after the onset of the P wave of the electrocardiogram, prior to the onset of the QRS complex. Unlike the insignificant and inaudible vibrations often recorded on the phonocardiogram at low frequency ranges, abnormal fourth heart sounds have greater amplitude and pitch, are readily recorded at medium frequency ranges, and are usually audible.

Handgrip Exercise

All patients performed static exercise using a C.H. Stoelting Company hand dynamometer and maintained 50% of maximum tension for 2 min. Heart rate and arterial blood pressure were recorded immediately before the exercise and just prior to release of tension. In 29 patients left ventricular pressures were also obtained.

All patients demonstrated at least a 15mmHg sustained rise in systolic blood pressure and an increase in heart rate of at least 10 beats/min. Normal ventilatory patterns (without Valsalva maneuvers) were observed in all patients during the handgrip exercise.

Results

Clinical Material

Mean age was similar in patients with normal coronary arteriograms and with obstructive coronary atherosclerosis, with a range of 38-63 years and 34-65 years, respectively (table 1). Most patients were less than 55 years of age and only three were over 60 years of age. In patients with normal coronary arteriograms, the distribution of male and female patients was almost equal; males predominated in the group of patients with coronary artery disease. Fifty-eight percent of the patients with coronary artery disease had ECG evidence of a prior transmural myocardial infarction; 24% had radiologic evidence of left ventricular enlargement.

Angiography

Twenty of the 61 patients had normal coronary arteriograms and 41 had coronary artery disease. Twenty-eight (68%) of the 41 had multivessel disease.

Hemodynamics

Seven of the 61 patients (11%) had slightly elevated left ventricular end-diastolic pressures, ranging from 13 to 15 mm Hg; all seven had coronary artery disease. At rest there was no significant difference in LVEDP between patients with and without obstructive coronary artery disease as measured by the unpaired t test. During handgrip exercise, however, patients with coronary artery disease had a significantly higher LVEDP than patients with normal coronary arteriograms (15.6 vs 11.5 mm Hg, P < 0.01).

Phonocardiographic Studies

No third or fourth heart sounds were recorded in the resting phonocardiogram of this series of patients. During handgrip exercise diastolic heart sounds were elicited in 25 of the 61 patients. In these 25 patients the most frequent finding was an isolated fourth heart sound, recorded in three
patients with normal coronary arteriograms and 16 of the 22 with coronary artery disease.

**Phonocardiographic-clinical correlations.** Those patients with coronary artery disease who developed diastolic heart sounds during handgrip exercise exhibited a 64% frequency of prior myocardial infarction and a 27% frequency of left ventricular enlargement, compared to 52 and 21%, respectively, in patients not developing these sounds (P = NS) by the chi-square test.

**Phonocardiographic-angiographic correlations.** Three of the 25 patients (12%) with diastolic heart sounds during handgrip exercise had normal coronary arteriograms. (All three had fourth heart sounds, and all were under 55 years of age). Conversely, the frequency of these sounds was 54% (21 of 41) in patients with coronary disease and 15% (three of 20) in subjects with normal coronary arteries (P < 0.05). There was no significant correlation between number of diseased vessels and frequency of either third or fourth sounds after exercise. Left ventricular asynergy was found more commonly in patients with coronary artery disease who developed diastolic sounds during exercise. This difference was not significant however.

**Phonocardiographic-hemodynamic correlations.** When LVEDP recorded before handgrip exercise was compared with LVEDP recorded during handgrip exercise in 29 patients with simultaneous phonocardiographic-hemodynamic procedures, differences in LVEDP were observed between patients who did and did not develop diastolic heart sounds in both the group with normal coronary arteriograms and the group with coronary disease (table 2). However, only in the latter group was the rise in LVEDP statistically significant (P < 0.001). In these 10 patients, LVEDP increased from 11.4 ± 0.7 to 19.3 ± 0.7 mm Hg.

In the patients with normal coronary arteriograms, the three subjects who exhibited fourth heart sounds during exercise had a mean EDVI of 96 ml/m² while this value was 106 ml/m² in subjects with normal exercise phonocardiograms. The corresponding EDVI/EDP ratios were lower in patients with fourth heart sounds, but this difference was not statistically significant. Similarly, in the group of patients with coronary artery disease, mean EDVI was 108 ml/m² in patients who developed diastolic heart sounds during exercise, and 119 ml/m² in patients with normal phonocardiograms during exercise. The corresponding EDVI/EDP ratios were significantly lower in the patients with induced diastolic heart sounds (P < 0.05).

### Table 1

Interrelationships between Phonocardiographic, Clinical, Angiographic, and Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Phonocardiographic studies</th>
<th>N</th>
<th>Mean age (yrs)</th>
<th>No. of men</th>
<th>No. with MI</th>
<th>No. with LVE</th>
<th>Angiography</th>
<th>Resting hemodynamics*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Patients with normal coronary arteriograms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Diastolic heart sounds during handgrip exercise</td>
<td>20</td>
<td>45</td>
<td>12</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>8.6 ± 0.6</td>
</tr>
<tr>
<td>S₁</td>
<td>3</td>
<td>42</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>9.5 ± 0.4</td>
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<td>S₁ and S₁</td>
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<td></td>
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</tr>
<tr>
<td>S₁</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Normal phonocardiogram during handgrip exercise</td>
<td>17</td>
<td>46</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8.3 ± 0.7</td>
</tr>
<tr>
<td>II. Patients with coronary artery disease</td>
<td>41</td>
<td>47</td>
<td>36</td>
<td>24</td>
<td>10</td>
<td>28</td>
<td>13</td>
</tr>
<tr>
<td>A. Diastolic heart sounds during handgrip exercise</td>
<td>22</td>
<td>47</td>
<td>19</td>
<td>14</td>
<td>6</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>S₁</td>
<td>16</td>
<td>47</td>
<td>19</td>
<td>14</td>
<td>6</td>
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<tr>
<td>S₁ and S₁</td>
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<td>19</td>
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<tr>
<td>B. Normal phonocardiogram during handgrip exercise</td>
<td>19</td>
<td>47</td>
<td>17</td>
<td>10</td>
<td>4</td>
<td>14</td>
<td>6</td>
</tr>
</tbody>
</table>

Abbreviations: MI = myocardial infarction; LVE = left ventricular enlargement (X-ray); MVD = multivessel disease; 1VD = one-vessel disease; LV asyn = left ventricular asynergy; LVEDP = left ventricular end-diastolic pressure; EDVI = end-diastolic volume index; S₁, S₁ = third and fourth heart sounds; N = number of patients.

*Mean = standard error of the mean.
Table 2
Changes in LVEDP during Handgrip Exercise in 29 Patients Studied with Simultaneous Phonocardiography

<table>
<thead>
<tr>
<th>Pt</th>
<th>N</th>
<th>Normal PCG</th>
<th>N</th>
<th>P</th>
<th>S4 and/or S4</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal coronary arteriograms</td>
<td>12</td>
<td>2.5</td>
<td>9</td>
<td>NS</td>
<td>3.5</td>
<td>3</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>17</td>
<td>2.3</td>
<td>7</td>
<td>&lt;0.001</td>
<td>7.9</td>
<td>10</td>
</tr>
</tbody>
</table>

Abbreviations: LVEDP = left ventricular end-diastolic pressure; PCG = phonocardiogram; S4 = third and fourth heart sounds; NS = P value not significant by unpaired t test; N = number of patients.

Complications

Angina pectoris was observed in four patients, all with coronary disease. All four patients developed fourth heart sounds and elevations of LVEDP of at least 5 mm Hg.

Occasional ventricular premature beats were common, but there were no instances of ventricular fibrillation.

Discussion

Static (handgrip) exercise often elicits evidence of left ventricular dysfunction in patients with cardiac disease, while having little adverse effect on ventricular hemodynamics in normal subjects.\(^6\)\(^-\)\(^8\) In this respect it is comparable to dynamic (total body) exercise, although its mechanism of action is not dependent on increased venous return but rather on an acute increase in the afterload against which the ventricle must contract.\(^9\)\(^-\)\(^10\) It is also a much easier type of test to perform than dynamic exercise, it rarely precipitates angina, and it does not have the attendant feature of exercise-related tachypnea. The latter is an especially important factor in phonocardiographic studies. Marked tachypnea can distort the phonocardiographic recording and interfere with an accurate interpretation of heart sounds and murmurs. It was for these reasons that handgrip exercise was chosen as the stress test for the present study.

Diastolic heart sounds are commonly observed in patients with obstructive coronary artery disease but are found in less than 15% of (1) asymptomatic middle-aged subjects\(^11\) and (2) subjects with chest pain syndromes and normal coronary anatomy.\(^2\) During the submaximal and maximal dynamic\(^11\)\(^-\)\(^12\) and maximal static\(^12\) exercise the frequency of these sounds in patients with angina pectoris or documented myocardial infarction has been reported to be significantly increased compared to individuals free of heart disease. The purpose of the present study was to correlate the frequency of these sounds during submaximal static exercise with clinical, hemodynamic, and angiographic findings in a group of patients suspected of having obstructive coronary artery disease of whom the majority were under 55 years of age. Thus, this study forms an extension of a previous series\(^2\) in which diastolic heart sounds were studied in a similar group of patients in the resting state. The results of these two studies suggest that in a patient population meeting the previously cited selection criteria (1) approximately 75% of patients with coronary artery disease will exhibit abnormal third and/or fourth heart sounds either at rest or after submaximal static exercise, compared to approximately 25% of subjects with a chest pain syndrome and normal coronary arteriogram, and conversely (2) approximately 90% of patients with chest pain and a diastolic heart sound will have angiographically documented coronary artery disease.

Any conclusions regarding the clinical usefulness of these sounds (either by themselves or in conjunction with other findings\(^13\) ) must be qualified by several factors, however. The most important of these is that abnormal diastolic heart sounds are not specific for coronary artery disease and may also be present in patients with other forms of myocardial disease. Why middle-aged individuals apparently free of heart disease should produce these sounds, either at rest or after exercise, is unclear. That these individuals have an occult cardiomyopathy is a distinct possibility. Only with long-term follow-up (as recently undertaken by Aranow et al.\(^14\) ) can this point be clarified. The lower EDVI/EDP ratio and higher exercise LVEDP in these patients (although not statistically significant in this small group) suggest but do not prove the presence of latent hemodynamic abnormalities. Certainly in the patients with coronary artery disease, alterations in end-diastolic volume-pressure relationships appear to be the basis for the abnormal phonocardiographic and hemodynamic findings during the exercise state. Whether this probable alteration in ventricular compliance is due to prior ventricular scarring is
unconfirmed. The frequency of transmural myocardial infarction in this study was similar whether or not the patients exhibited third and fourth heart sounds on static exercise.

References
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