previously reported\(^3\), \(^5\) and they also had no evidence of end-organ disease. These data raise the possibility that suppressed kallikrein observed by others occurs as a result rather than cause of hypertension.

Our data show that young mildly hypertensive male patients with normal plasma renin activity levels have normal urinary kallikrein levels, and that their kallikrein levels respond normally to sodium restriction. This suggests that classification of patients with regard to plasma renin activity, as well as to other factors, is essential in trying to determine the role of the kallikrein-kinin system in hypertension. This study does not demonstrate that the renin-angiotensin system directly influences the kallikrein-kinin system but further investigation of the interrelationships between the two systems is needed.

Acknowledgment

The authors wish to express their appreciation to the nurses, dietitians, and staff of the Clinical Research Center for their dedicated and conscientious assistance. In addition, the authors thank Mr. Stephen Wyatt, Mr. Ronald Erickson, and Mr. Jeremy Shellhase for their technical assistance and Mrs. Sue Bair for her secretarial assistance.

References


The Aortic Closure Sound in Pure Aortic Insufficiency

HANI N. SABBAH, FAREED KHAJA, M.D., DANIEL T. ANBE, M.D., AND PAUL D. STEIN, M.D.

SUMMARY The second sound in aortic insufficiency has been described as accentuated, normal, or moderately diminished. A study of intracardiac phonocardiograms was performed to evaluate its intensity and to eliminate extracardiac factors. Pressure and intracardiac sound measurements were made in 28 patients undergoing diagnostic cardiac catheterization. Recordings were obtained above the aortic valve and within the left ventricle in 14 patients with normal aortic valves and 11 patients with aortic insufficiency uncomplicated by aortic stenosis. The amplitude of the aortic closure sound in the patients with pure aortic insufficiency, 1000 ± 100 dynes/cm\(^2\), was significantly lower than in those patients with normal aortic valves, 3100 ± 200 dynes/cm\(^2\) (P < 0.001).

The results indicate, therefore, that the presence of aortic insufficiency causes a diminished amplitude of the aortic closure sound. These results are supportive of the theory that the second heart sound is caused by diastolic vibrations of the closed aortic cusps. Diminished valvular vibrations and sound would occur in pure aortic insufficiency if the valve is unable to properly tense during diastole, or if the rate of development of the driving pressure is diminished.

ALTHOUGH it is well known that the aortic component of the second sound is diminished or absent in acquired aortic stenosis, little attention has been given to the intensity of the second sound in aortic insufficiency. The intensity of the second sound has previously been described as accentuated,\(^1\) \(^4\) normal,\(^1\) \(^9\) \(^4\) moderately diminished,\(^4\) or faint.\(^1\) It should be noted, however, that such descriptions of the intensity of the second heart sound are based upon the results of physical examination or uncalibrated phonocardiograms, a fact which may account for the wide variations observed. Previous work in this laboratory related to ejection murmurs has shown a diminished second sound in one patient with pure aortic insufficiency.\(^5\) In order to minimize such factors which depend on personal judgment and rule out extracardiac factors which may affect the apparent intensity of the second heart sound, an intracardiac phonocardiographic study of
the closure sound in aortic insufficiency was performed. The purpose of the study was to measure the amplitude of the aortic closure sound in patients with pure aortic insufficiency, and to attempt to formulate a possible mechanism to explain its deviation from normal.

Methods

Measurements of intracardiac pressure and intracardiac sound were made in 28 patients during diagnostic cardiac catheterization. Fourteen patients had normal aortic valves based upon the absence of a pressure gradient across the aortic valve, the absence of aortic regurgitation on aortography, and the absence of a systolic or diastolic murmur on physical examination. All of these patients were catheterized because of angina. Eleven patients had pure aortic insufficiency of grade 1+ to 4+ severity as judged by aortography.6 None of these patients showed a pressure gradient across the aortic valve or calcification of the valve on cineradiography. Six of the patients with pure aortic insufficiency had a history of rheumatic fever, one had a history of syphilis, one patient had a bicuspid aortic valve, and three patients had aortic insufficiency of undetermined origin.

Pressure and sound were measured above the aortic valve in all patients and they were measured within the left ventricle in all but two patients. In the aorta, the tip of the catheter was advanced until contact with the aortic cusps was made. It was then withdrawn one or two centimeters from the valve. Within the ventricle, sound was recorded in the outflow tract as close to the valve as possible, yet with the tip free and not in contact with the leaflets. Pulmonary arterial pressure and sound were obtained above the pulmonary valve in 9 of 14 patients with normal aortic valves and in 3 of 11 patients with pure aortic insufficiency. In order to achieve a uniform position near the valve, the catheter was withdrawn to the right ventricular outflow tract, and then advanced one or two centimeters past the valve. None of the patients had disease of the pulmonary valve, as indicated by the absence of a pressure gradient across the pulmonary valve and the absence of an intracardiac murmur in the region of the pulmonary valve. The sound recordings were made using the same catheter and amplifier as aortic sound measurements. This was done to facilitate comparisons of the amplitude of both pulmonary and aortic closure sounds.

Pressures and sound pressure (referred to as intracardiac sound) were measured with a catheter-tip micromanometer (Millar Instruments, Inc.) with a frequency response of 0 to 10 kHz. Both intracardiac pressure and sound were measured through the same transducer. This was achieved by filtering the low frequency components of the pressure signal and amplifying the upper frequency range. The low frequency cut-off in the sound mode, when used with 10 megohm loading was 6 dB at 40 Hz, 3 dB at 50 Hz and flat above 90 Hz.

The peak sound pressure for any specified time interval is the maximum absolute value of the instantaneous pressure in that interval.7 The unit is dynes/cm². We therefore calibrated intracardiac sound in these units. The sound mode with the system we used amplifies sound pressure 11 times greater than pressure signals. This amplification of the sound-pressure relative to the pressure was determined by the manufacturer. To obtain a calibration of sound, we attached the output of the pressure mode to the sound amplifier and inserted an electrical signal which was equivalent to 20 mm Hg on the pressure mode. This same signal, therefore, would be equal to 1.82 mm Hg if it were recorded directly from the sound mode. Recordings of pressure and sound were obtained on a VR-6 photographic recorder (Electronics for Medicine) at speeds of 25 to 200 mm/sec. The frequency response of the recording system was flat to 700 Hz with a 3 dB drop at 2100 Hz. Sound and pressure recordings were filtered at 250 Hz. When sound and pressure were filtered at 2500 Hz, no noticeable difference of the amplitude of sound and pressure were noted.

Results

The amplitude of the aortic closure sound in patients with pure aortic insufficiency (figs. 1, 2) was consistently lower than the amplitude of the closure sound in patients with normal aortic valves (fig. 3). In patients with normal aortic valves, it ranged from 1900 to 4800 dynes/cm², with a mean and standard error of 3200 ± 200 dynes/cm² (table 1); whereas in patients with pure aortic insufficiency the amplitude of the closure sound ranged from 400 dynes/cm² to 1600 dynes/cm², with a mean and standard error of 1000 ± 100 dynes/cm² (P < 0.001)* (table 2) (fig. 4). In the patients with aortic insufficiency, the amplitude of the closure sound in each instance was lower than the amplitude of the closure sound in any of the patients with normal valves. The aortic diastolic pressure in patients with pure aortic insufficiency, 71 ± 2 mm Hg, was slightly lower than that in patients with normal aortic valves, 79 ± 3 mm Hg (P < 0.05).

*Unpaired t-test.

![Figure 1. Intracardiac sound and pressure in a patient with pure aortic insufficiency (patient 4) shown during pullback of the catheter-tip micromanometer from the left ventricle (LV) to the aorta (AO). Within the left ventricle, a diastolic murmur (DM) was recorded. The aortic closure sound (S₃), recorded just above the aortic valve, was diminished (400 dynes/cm²).](image)
The pulmonary closure sound in patients with normal aortic valves in whom right-sided sound measurements were recorded, 900 ± 200 dynes/cm², was significantly lower than the aortic closure sound, 3100 ± 200 (P < 0.001) (fig. 4). On the other hand, the three patients with pure aortic insufficiency in whom the pulmonary closure sound was measured showed a higher amplitude of the pulmonary closure sound than the aortic closure sound (tables 1, 2).

Discussion

The results of this study indicate that a diminished aortic closure sound occurs in patients with pure aortic insufficiency. We believe that these observations can be explained by considering the semilunar valves to act, in early diastole, analogously to a stretched circular membrane. Such a membrane, when set into motion, generates compression and rarefaction of the blood within the arterial and ventricular cavities. These compressions and rarefactions cause instantaneous pressure changes producing audible sounds. Valvular vibrations that produce these compressions and rarefactions were shown to occur in vitro. The driving force which causes the vibrations of the semilunar valve in early diastole is the diastolic pressure gradient (Δp) between the aorta and ventricle.

Using membrane analysis studies as well as studies in dogs, the rate of change of the diastolic pressure gradient, d(Δp)/dt, has been shown to relate to the amplitude of the second sound. Others have demonstrated this empirically.

In view of the above mechanism of the second heart sound, two factors now can be attributed to the observed diminished second sound. 1) The diminished aortic diastolic pressure, which in general is associated with aortic insufficiency, may cause a diminished rate of development of the driving pressure, d(Δp)/dt; 2) The presence of aortic insufficiency may reduce the ability of the valve to tense upon closure, and this diminishes valve vibration; 3) The cross-sectional area of the valve that is capable of diastolic vibration may be diminished, thereby producing a smaller effective vibrating membrane; 4) Physical changes within the valves may also participate in its diminished ability to vibrate.

If acquired calcific aortic stenosis were present in combination with the aortic insufficiency, as usually occurs, then an additional mechanism for the reduction of the closure sound would be present. This additional effect would not be present in young individuals with pliable congenitally stenotic valves. In calcific aortic stenosis, the increased stiffness and increased mass of the valve inhibit the capability of the valve to vibrate during diastole (unpublished observations). In the present study, patients with aortic stenosis
were excluded in order to assess the effects of insufficiency alone upon the closure sound. Obviously, the effects of calcific stenosis combined with insufficiency would be additive, causing a closure sound of even lower amplitude.

Previous studies which describe the intensity of the second sound in aortic insufficiency were based upon auscultation and external phonocardiograms. Such techniques are of tenuous value for accurately quantifying sound intensity. Various descriptions of the intensity of the second heart sound in aortic regurgitation have been given, but results were based upon nonquantitative methods and judgments. In patients with traumatic aortic regurgitation caused by rupture of the aortic valve, the second sound has been described as faint by some and accentuated by others. Levine and Harvey described the second sound in rheumatic aortic insufficiency as accentuated, while Friedberg described it as being of a normal intensity and Fowler described the second sound as normal or moderately diminished. We observed an increased amplitude of the pulmonary closure sound in comparison to the aortic closure sound in three of the patients with pure aortic insufficiency, and two of three had pulmonary hypertension. Since heart

### Table 1. Intracardiac Pressure and Sound in Patients with Normal Aortic Valves

<table>
<thead>
<tr>
<th>Pt #</th>
<th>AoP (mm Hg)</th>
<th>LVP (mm Hg)</th>
<th>PAP (mm Hg)</th>
<th>Ampl aortic closure sound (dynes/cm²)</th>
<th>Ampl pulmonary closure sound (dynes/cm²)</th>
<th>Dx</th>
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<tr>
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<td>155/11</td>
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<td>400</td>
<td>CHD</td>
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<tr>
<td>2</td>
<td>121/66</td>
<td>121/9</td>
<td>—</td>
<td>2200</td>
<td>—</td>
<td>CHD</td>
</tr>
<tr>
<td>3</td>
<td>100/73</td>
<td>100/20</td>
<td>24/13</td>
<td>3200</td>
<td>1600</td>
<td>CHD</td>
</tr>
<tr>
<td>4</td>
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<td>144/16</td>
<td>22/11</td>
<td>2600</td>
<td>500</td>
<td>CHD</td>
</tr>
<tr>
<td>5</td>
<td>141/91</td>
<td>141/15</td>
<td>—</td>
<td>2600</td>
<td>—</td>
<td>Normal</td>
</tr>
<tr>
<td>6</td>
<td>121/79</td>
<td>121/4</td>
<td>—</td>
<td>1900</td>
<td>—</td>
<td>CHD</td>
</tr>
<tr>
<td>7</td>
<td>108/76</td>
<td>108/9</td>
<td>14/3</td>
<td>3800</td>
<td>600</td>
<td>Normal</td>
</tr>
<tr>
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</tr>
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<td>125/72</td>
<td>125/14</td>
<td>28/8</td>
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</tr>
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<td>800</td>
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<td>CHD</td>
</tr>
<tr>
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<tr>
<td>13</td>
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<td>3000</td>
<td>—</td>
<td>CHD</td>
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<tr>
<td>14</td>
<td>125/81</td>
<td>125/12</td>
<td>38/20</td>
<td>3800</td>
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<td>Prolapsed MV</td>
</tr>
<tr>
<td>Mean</td>
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<td>131/12</td>
<td>26/11</td>
<td>3100</td>
<td>900</td>
<td></td>
</tr>
<tr>
<td>± se</td>
<td>5/3</td>
<td>5/1</td>
<td>3/2</td>
<td>200</td>
<td>200</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CHD = coronary heart disease; MV = mitral valve; AoP = aortic pressure; LVP = left ventricular pressure; PAP = pulmonary artery pressure; Ampl = amplitude.

### Table 2. Intracardiac Pressure and Sound in Patients with Pure Aortic Insufficiency

<table>
<thead>
<tr>
<th>Pt #</th>
<th>AoP (mm Hg)</th>
<th>LVP (mm Hg)</th>
<th>PAP (mm Hg)</th>
<th>Ampl aortic closure sound (dynes/cm²)</th>
<th>Ampl pulmonary closure sound (dynes/cm²)</th>
<th>AI</th>
<th>Dx</th>
</tr>
</thead>
<tbody>
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<td>48/30</td>
<td>1600</td>
<td>4200</td>
<td>3+</td>
<td>RHD</td>
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<tr>
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<td>150/22</td>
<td>—</td>
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<td>—</td>
<td>3+</td>
<td>RHD</td>
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<tr>
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<td>115/4</td>
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<td>2300</td>
<td>2+</td>
<td>Bicuspid</td>
</tr>
<tr>
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<td>145/25</td>
<td>—</td>
<td>400</td>
<td>—</td>
<td>3+</td>
<td>RHD</td>
</tr>
<tr>
<td>5</td>
<td>109/60</td>
<td>109/-</td>
<td>—</td>
<td>1000</td>
<td>—</td>
<td>2+</td>
<td>RHD</td>
</tr>
<tr>
<td>6</td>
<td>145/76</td>
<td>145/11</td>
<td>—</td>
<td>1300</td>
<td>—</td>
<td>2+</td>
<td>RHD</td>
</tr>
<tr>
<td>7</td>
<td>126/72</td>
<td>126/7</td>
<td>39/19</td>
<td>700</td>
<td>3000</td>
<td>1+</td>
<td>RHD</td>
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<tr>
<td>8</td>
<td>174/72</td>
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<td>—</td>
<td>1300</td>
<td>—</td>
<td>3+</td>
<td>?</td>
</tr>
<tr>
<td>9</td>
<td>135/75</td>
<td>135/7</td>
<td>—</td>
<td>1500</td>
<td>—</td>
<td>1+</td>
<td>?</td>
</tr>
<tr>
<td>10</td>
<td>120/60</td>
<td>120/24</td>
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<tr>
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<td>140/9</td>
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<td>1100</td>
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<td>4+</td>
<td>Lues</td>
</tr>
<tr>
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<td>136/15</td>
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<td>1000</td>
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<td></td>
<td></td>
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<tr>
<td>± se</td>
<td>6/2</td>
<td>6/1</td>
<td>13/16</td>
<td>100</td>
<td>600</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: RHD = rheumatic heart disease; AI = aortic insufficiency; for others see table 1.

![Figure 4](http://circ.ahajournals.org/Downloaded from http://circ.ahajournals.org/)

**FIGURE 4.** Amplitude of aortic closure sound in patients with normal (NL) aortic valves and patients with pure aortic insufficiency (AI). In the presence of a normal valve, the closure sound was 3200 ± 200 dynes/cm² and with AI it was 1000 ± 100 dynes/cm².
sounds may radiate widely on the chest wall, and some patients with aortic insufficiency may have elevated pulmonary arterial pressures, it may be that in some instances in which the sound was single, an accentuated pulmonary closure sound was interpreted as a normal aortic closure sound.

In conclusion, intracardiac phonocardiographic measurements of the aortic closure sound in patients with pure arterial insufficiency showed that the amplitude of the aortic closure sound in such patients was significantly lower than the amplitude of the closure sound in patients with normal aortic valves. The reduced closure sound can be attributed in part to a lower diastolic pressure which results in a diminished rate of change of the driving pressure, and in part to a diminished ability of the valve to tense and vibrate after closure.

References
10. Sabbah HN, Stein PD, Blick EF: Dependence of the intensity of aortic closure sound upon the rate of ventricular relaxation and ventricular performance. Am J Cardiol 39: 285, 1977

Cardiac Size and Function in Acromegaly

JAMES B. MARTINS, M.D., RICHARD E. KERBER, M.D., BARRY M. SHERMAN, M.D., MELVIN L. MARCUS, M.D., AND JAMES C. EHRHARDT, PH.D.

With the Technical Assistance of Phillys Shellady, Linda Rath and Marcia Miller

SUMMARY Sixteen acromegalic patients underwent echocardiography, phonocardiography, stress electrocardiography with Thallium perfusion scanning and gated radioisotope left ventricular angiograms. Abnormalities consisting of increased echo left ventricular mass index, low velocity of circumferential fiber shortening or elevated pre-ejection period to left ventricular ejection time ratio were found in six patients with coexistent hypertension or coronary disease. Concentric left ventricular hypertrophy was also found in three patients with no known etiology other than acromegaly of greater than 13 years' duration or with fasting growth hormone concentrations greater than 100 ng/ml. One of these three also had left ventricular dysfunction. Neither hypertrophy nor ventricular dysfunction was found in other acromegalics with shorter duration of disease or lower growth hormone concentrations, or with normal growth hormone concentrations after therapy.

A high prevalence of coronary artery and hypertensive heart disease is associated with acromegaly. A few patients with acromegaly have a specific, potentially reversible cardiomyopathy probably related to prolonged acromegaly or very high growth hormone concentrations.

CARDIAC HYPERTROPHY and congestive heart failure have been described in as many as one-third of acromegaly patients. This has been attributed to coexistent hypertension which is found in 23–42% of acromegaly patients, or to coronary disease. However, sporadic reports have described patients who, in the absence of hypertension or coronary disease, have cardic hypertrophy and diminished ventricular function. These reports suggest that cardiac abnormalities may be produced as an effect of elevated growth hormone concentration. The purpose of this study was to determine whether a specific acromegalic heart disease could be detected using recently developed non-invasive methods for assessing cardiac size and function.

Methods

Patients
All patients with documented acromegaly by clinical criteria and elevated growth hormone concentration followed by the Endocrinology Division of the University of Iowa Hospital were invited to participate in this study. Of 30 contacted, 22 who responded were admitted to the Clinical Research Center for study. Informed consent was obtained using a format approved by the Committee on Research In-
The aortic closure sound in pure aortic insufficiency.
H N Sabbah, F Khaja, D T Anbe and P D Stein

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