Prevalence and Predictors of Audible Physiological Third Heart Sound in a Population Sample Aged 36 to 37 Years

Markku Kupari, MD; Pekka Koskinen, MD; Juha Virolainen, MD; Pauli Hekali, MD; Pekka Keto, MD

Background  A physiological third heart sound (S₃) is common in youth but allegedly very rare after the age of 40 years. The mechanism of its disappearance is not known. The aim of this work was to study the prevalence and predictors of physiological S₃ in a population-based sample of persons approaching 40 years of age.

Methods and Results  A random sample of 120 persons born in 1954 was invited; 93 (42 men) entered the study. Their physical activity, alcohol and tobacco consumption, and salt intake were quantified by diary follow-up. The presence of an S₃ was determined by auscultation and confirmed by phonocardiography. Left ventricular (LV) size, mass, and systolic function were assessed by M-mode echocardiography and LV filling by Doppler velocimetry of transmural flow. An audible S₃ was detected in 22 subjects, 1 of whom had heart disease. The prevalence of physiological S₃ was 23.1%. Subjects with physiological S₃ had a lower body mass index (22.3±2.8 versus 24.6±4.1 kg/m² [mean±SD], P=.005), lower heart rate (63±7 versus 68±10 beats per minute, P=.015), higher peak early diastolic transmitral velocity (67±10 versus 58±8 cm/s, P=.002), and higher acceleration of early diastolic velocity (717±148 versus 622±122 cm/s², P=.012) than those without S₃. No differences were noted in the lifestyle characteristics, blood pressure, or LV mass and systolic function. Body mass index and peak early diastolic transmitral velocity were independent predictors of physiological S₃ in logistic regression analysis.

Conclusions  Nearly one fourth of persons approaching their forties still have an audible physiological S₃. The presence of S₃ is predicted by leanness and a high early diastolic LV inflow velocity; the disappearance of S₃ is unlikely to be secondary to increasing blood pressure and relative LV hypertrophy, as is widely presented, but reflects a more primary age-related alteration of LV early diastolic function. (Circulation. 1994;89:1189-1195.)

Key Words  • heart sounds • left ventricle • diastole • obesity

A physiological third heart sound (S₃) can be heard in practically all healthy children and adolescents but rarely in individuals after the age of 40 years. Although this concept is widely accepted, no population-based data exist to support its validity. Most experts, if not all, attribute physiological S₃ to vibrations of the heart muscle arising from prominent early diastolic left ventricular (LV) filling and the subsequent abrupt inflow deceleration. This why this sound fades away with age has been little studied, and no longitudinal data exist. Comparisons of younger and older study groups have shown, however, that the prevalence of physiological S₃ decreases in parallel with the reduction of the early diastolic LV filling rate. The primary cause is thought to be an age-related increase of blood pressure with the development of relative LV hypertrophy and altered diastolic function. The general applicability of these findings and ideas is unknown, however, because the studies involved selected groups with a majority of male subjects. We have assessed the prevalence and correlates of an audible physiological S₃ in an age-homogeneous but otherwise fully random population sample. The underlying idea was that identifying the correlates of this sound in healthy persons in their late thirties could give insight into its mechanisms and why it ultimately disappears. The factors evaluated included sex, several anthropometric and hemodynamic measurements, echocardiographically determined LV size, mass, systolic and diastolic function, and stiffness of the thoracic aorta measured by magnetic resonance imaging. Certain lifestyle characteristics (physical activity, smoking, alcohol consumption, salt intake) and laboratory measurements (blood lipids, hematocrit, serum insulin) were also included in the analyses; these factors are known to have associations with either the LV structure and function or with the risk of degenerative changes in the cardiovascular system.

Methods

Study Population

This work constitutes part of a comprehensive cardiovascular assessment of a sample of persons born in 1954 and living in Helsinki. The target population consisted of 3730 men and 4250 women. Of them, the Central Population Registry took a random sample of 120 individuals (55 men) whom we invited by a letter explaining the aims and course of our study. A total of 112 persons could be contacted, and 93 (42 men) decided to participate. All were aged 36 to 37 years at the time of our study, and all were white and of Finnish ancestry except for one American and one Italian. Two of them had chronic schizophrenia and one had myasthenia, but no subject had a history of heart disease. Seven subjects had mild allergic

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diseases, but none used sympathomimetics or steroids regularly. Several subjects had been in follow-up for borderline blood pressure elevation, but none used antihypertensive drugs.

**Study Design**

The study started with a prospective collection of lifestyle data. Each participant was given a pocket diary for recording of daily physical activity and consumption of alcohol and tobacco. Another diary was given for a 7-day food record to assess salt intake. The subjects were asked not to change their lifestyle or diet because of participation. After about 2 months, they returned the diaries and underwent measurement of height and weight, physical examination including cardiac auscultation and confirmatory phonocardiography, blood tests, 12-lead ECG, and a complete two-dimensional, M-mode, and Doppler echocardiographic study. Fifty-five individuals (31 men) also underwent magnetic resonance imaging of the thoracic aorta to assess aortic stiffness; all participants could not be studied by this technique because of the limited laboratory time allocated to our use. For the purposes of the present report, the data were subjected to analyses targeted to identify the correlates of physiological $S_1$ in the population of interest. The protocol was approved by the institutional ethics committee.

**Lifestyle Diary and Data Analysis**

**Physical Activity**

Each day, the subjects recorded the type of physical activity they had practiced (eg, walking, jogging, swimming, gardening, etc) and its exact duration. Only leisure-time activities were noted. The energy expended was calculated by multiplying the metabolic equivalent value (MET, 1 MET equals the energy expended by a person at rest, $ie, 1 \text{kcal} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) of each activity by the time (hours) spent in it. The MET values of different activities were adopted from previously published tables. The average energy expenditure per day of follow-up was used as a physical activity index. Supporting its utility, the physical activity index (MET $\cdot$ h/d) correlated inversely with body mass index ($r = -0.27, P = 0.010$) and resting heart rate ($r = -0.23, P = 0.039$) and directly with the average daily energy intake calculated from the food records (see below) ($r = 0.24, P = 0.028$).

**Alcohol and Tobacco Consumption**

The subjects entered in the diary the types and exact amounts of alcoholic beverages consumed and the number of cigarettes smoked each day. The alcoholic drinks were converted to grams of absolute ethanol. The average daily use of ethanol and tobacco was determined by dividing the respective total consumptions by the number of follow-up days. Supporting the utility of the data, the calculated daily ethanol consumption correlated directly with serum gammaglutamyltransferase measured at the end of the diary follow-up period ($r = 0.40, P = 0.001$).

**Diet Records and Assessment of Sodium Intake**

The data on diet were collected by means of a 7-day food record. The recording days were distributed evenly over the 2-month follow-up period. Each day of the week was included once. The subjects were given written and illustrated instructions prepared by a nutritionist to ensure accurate completion of the records. They returned the records personally to the nutritionist, who checked the food entries for adequacy and analyzed the records for energy, nutrient, and mineral intake using commercial software (UNILEVER DIETARY ANALYSIS PROGRAM, Unilever, Inc, Rotterdam, The Netherlands) and a database on nutrient and mineral composition of Finnish foods. The average daily intake of sodium (mEq) was calculated. Earlier research in our country has shown that sodium intake calculated from food records can be used to estimate dietary salt intake.10

**Laboratory Tests**

Venous blood was sampled after an overnight fast. Peripheral blood count, hemoglobin, blood glucose, serum electrolytes, serum creatinine, and liver enzymes were determined immediately, and the remaining serum was stored at $-20^\circ$C. Serum total cholesterol was measured using a commercial kit (Boehringer, Mannheim, Germany) and serum triglycerides using a Technicon Autoanalyzer II (Technicon Instruments, Tarrytown, NY). The high-density lipoprotein cholesterol fraction was separated from the serum by precipitation of the other lipoproteins with heparin-manganese-chloride. Low-density lipoprotein cholesterol was calculated using the Friedewald equation.11 Serum insulin was measured using a commercial radioimmunoassay kit (Pharmacia, Uppsala, Sweden).

**Physical Examination**

All subjects were studied by the same clinical cardiologist. Auscultation was performed in a quiet room with the subject in the supine and left lateral positions. To study diastolic heart sounds, the bell of the stethoscope was positioned at several sites around the apex beat. The subjects were breathing normally, and no provocative maneuvers were attempted. $S_1$ was graded as present or absent. It was considered present even if heard only intermittently. The presence of $S_2$ was confirmed by displaying the heart sounds through the phonocardiography channel of the echocardiograph used in the study (see below). The microphone was attached to the skin at the apical area or at the site of the peak auscultatory intensity of $S_2$. $S_1$ was considered present if the phonocardiogram showed distinct low-frequency vibrations 100 to 200 milliseconds after the second heart sound. The brachial artery blood pressure (Korotkoff phases I and V) was measured after a 15- to 30-minute rest using a sphygmomanometer with the subject in a sitting position. The measurement was made at the subject's first visit to our unit and repeated twice at the echocardiographic study about 2 months later. The three measurements of systolic and diastolic blood pressures were averaged for results.

**Echocardiography**

All studies were made with a commercial ultrasonograph (Aloka SSD 830) equipped with a 2.5-MHz, phased-array transducer and a strip-chart recorder. The subjects were in a postabsorptive state and rested supine for 10 to 15 minutes before the examination. Throughout the study, they were lying in the left lateral position. After twodimensional and color Doppler assessment for valve diseases and abnormalities of LV function, the following measurements were performed.

**M-Mode Measurements**

A standard M-mode LV study was recorded through the sector scan as detailed elsewhere.12 The recordings were taken at a speed of 50 mm/s together with an ECG and a phonocardiogram. The tracings were analyzed later on an x-y digitizer to determine, as previously described,12 the LV end-diastolic and end-systolic dimensions, fractional shortening, and peak diastolic lengthening rate of the LV dimension. Septal and posterior wall thicknesses were measured at end diastole. The LV mass was calculated with the cube formula14 and the correction equation of Devereux et al.15 The left atrial dimension was measured at end systole on an M-mode recording taken through the aortic root and the left atrium. All measurements were made by the leading edge—to—leading edge technique and averaged over five cycles. The analyzer was blinded to the subject's other data including the presence of $S_1$. The reproducibility of the M-mode measurements has been validated previously in our laboratory.12
Doppler Indexes of LV Filling

The pulsed Doppler studies of transmitial flow were made from an apical transducer position by aligning the beam with the flow direction at color Doppler imaging; no angle corrections were made. The sample volume was positioned at the mitral annulus and adjusted to obtain sharp velocity envelopes. An ECG and a phonocardiogram were recorded simultaneously with the Doppler signal; the speed was 50 mm/s. The recordings were analyzed without knowledge of the subject's other data by tracing the modal velocities on the x-y digitizer. The following indexes were determined as detailed earlier: peak early and atrial (late) transmitral velocities, early-to-atrial peak velocity ratio, time from the second heart sound to the early diastolic velocity peak (that is, the relaxation time), acceleration and deceleration of the early diastolic velocity, and atrial filling fraction. The data were averaged over five cardiac cycles. The reproducibility of these measurements in our laboratory has been validated and reported earlier.

Stroke Volume and Peripheral Arterial Resistance

Stroke volume was determined in the LV outflow tract by the Doppler method described by Lewis et al. The diameter of the outflow tract was first determined in parasternal two-dimensional views as the average of three measurements. The area was calculated assuming circular geometry. Pulsed-wave Doppler then was used to record the systolic flow velocity at three adjacent sites across the LV outflow tract immediately below the aortic annulus. Velocity recordings were made from an apical window by aligning the beam with the flow direction in the color Doppler modality; angle corrections were avoided. Modal velocities were traced on an x-y digitizing table, and the velocity-time integral was averaged over 15 measured cycles (five cycles at each measurement site). The velocity-time integral was multiplied by the cross-sectional area of the outflow tract to give the stroke volume. To assess the reproducibility of stroke volume, 6 subjects were re-examined by Doppler echocardiography after 3 weeks. The absolute difference of the paired stroke volume data was 12.7±8.7% of their average (mean±SD).

The peripheral arterial resistance was calculated as 101·MBP/HR·SV, where MBP is mean blood pressure (mm Hg), HR is heart rate (beats per minute), and SV is stroke volume (milliliters). To determine blood pressure at the time of echocardiography, noninvasive finger arterial pressure was recorded continuously for 5 to 10 minutes using an Ommeda 2300 Finapres device, an analog-to-digital converter, and commercial software (Cafits, Medikro, Inc, Kuopio, Finland). A stationary 5-minute segment of this recording was selected and used to compute the average mean blood pressure used in the above formula. The details and validation of our finger blood pressure measurements are reported elsewhere.

Assessment of Aortic Stiffness

Stiffness of the thoracic aorta was studied by magnetic resonance imaging with a previously described technique. We used a 1.0-T, superconducting Siemens imager (Magnetom 42 SP), a body coil, and ECG triggering. To examine the pulsatile changes in the cross-sectional areas of the ascending and descending thoracic aorta, a cine examination was acquired in a plane transsecting the aorta axially at the level of pulmonary artery bifurcation. A two-dimensional gradient echo sequence was used with a repetition time of 50 milliseconds and an echo time of 12 milliseconds; the flip angle was 30°, matrix size was 128×256, and slice thickness was 7 mm. Brachial artery systolic, diastolic, and pulse pressures were averaged over measurements made with a sphygmomanometer just before and after the imaging period. The aortic studies were analyzed without knowledge of the subject under assessment. The smallest diastolic and the largest systolic circumferences of the ascending and descending thoracic aorta were traced with a mouse-driven cursor in an off-line image analysis system (RADGON/WIZ, Contextvision, Struers Vision AB). The cross-sectional aortic luminal areas were determined by multiplying the number of pixels by the pixel size. Aortic strain was determined as the systolic change of the luminal area divided by the end-diastolic area. Aortic elastic modulus was calculated as 1332·pulse pressure/aortic strain; the coefficient converts mm Hg to dyne/cm². The mean of values of elastic modulus in the ascending and descending aorta was taken to represent the stiffness of the thoracic aorta for each individual. To assess the reproducibility of this technique, 8 subjects were reimaged after 1 week. The reproducibility (calculated as for stroke volume, see above) of the smallest diastolic aortic luminal area was 7.1±14% (median, 3.5%), and the reproducibility of the elastic modulus was 24.9±7.5% (median, 23%).

Statistics

Continuous variables were tested for normal distribution by Kolmogorov-Smirnov one-sample test. Comparisons between subjects with and without physiological S, were made with the Student’s independent t test and ANCOVA (normally distributed continuous variables), Mann-Whitney U test (asymmetrically distributed continuous variables), and y² test (frequency data). Multiple logistic regression was used to identify the factors independently associated with the presence of physiological S. Odds ratios were calculated from logistic coefficients. Bivariate correlation was assessed by the Pearson’s product-moment method. The results are given as mean±SD for normally distributed variables and as median (range) for asymmetrically distributed data. For selected data, the 95% confidence intervals were also calculated. Values of P<.05 were considered statistically significant. All analyses were performed on a microcomputer using a commercially available statistical package (Systat version 5.2, Systat, Inc, Evanston, Ill).

Results

All 93 participants except for two women completed the study. The lifestyle follow-up period averaged 64 days (range, 13 to 74 days). Acceptable echocardiographic recordings were obtained in 89 of 91 studied participants, and the diet records were sufficiently exact for analysis of sodium intake in 85 subjects (40 men). The subjects (n=55) who underwent magnetic resonance imaging of the thoracic aorta did not differ statistically significantly from those who could not be studied regarding sex distribution, body mass index, blood pressure, or any lifestyle or laboratory characteristic (data not shown). All subjects had normal blood counts, fasting blood glucose, and serum creatinine concentrations.

Prevalence of Heart Disease and Physiological S

Clinical examination did not suggest heart disease in any participant. One man reported occasional effort-related chest pain, but his exercise ECG was normal. No subject had significant aortic or mitral valve disease at combined two-dimensional and color Doppler echocardiography, but minor mitral valve leakage was not uncommon. One man had a dilated and slightly hypokinetic left ventricle at echocardiography and ST-segment and T-wave alterations on 12-lead ECG; incipient dilated cardiomyopathy was considered very likely. One woman had moderate tricuspid regurgitation (probably congenital in origin) at color Doppler echocardiography. These two subjects were thought to have heart disease; both were asymptomatic.
TABLE 1. Sex, Anthropometric Measurements, Lifestyle Factors, and Laboratory Data in Relation to the Presence of Audible Physiological S₃ in a Population Sample Aged 36 to 37 Years

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Present (n=21)</th>
<th>Absent (n=66)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (men/women)</td>
<td>9/12</td>
<td>32/34</td>
<td>.629</td>
</tr>
<tr>
<td>Height, cm</td>
<td>172±11</td>
<td>172±9</td>
<td>.625</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>67±13</td>
<td>72±14</td>
<td>.116</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22.3±2.8</td>
<td>24.6±4.1</td>
<td>.005</td>
</tr>
<tr>
<td>Physical activity index, MET·h/d</td>
<td>2.2 (0-6.5)</td>
<td>2.1 (0-13.8)</td>
<td>.550</td>
</tr>
<tr>
<td>Smoking, n (subjects in categories 0/1/2)*</td>
<td>13/3/5</td>
<td>34/19/13</td>
<td>.390</td>
</tr>
<tr>
<td>Habitual ethanol consumption, g/d</td>
<td>7.3 (0-75)</td>
<td>16.5 (0-84)</td>
<td>.269</td>
</tr>
<tr>
<td>Sodium intake, mEq/dt</td>
<td>157±52</td>
<td>159±50</td>
<td>.893</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>41.2±3.4</td>
<td>42.0±3.8</td>
<td>.362</td>
</tr>
<tr>
<td>Serum LDL cholesterol, mmol/L</td>
<td>2.68±0.74</td>
<td>2.95±0.90</td>
<td>.169</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mmol/L</td>
<td>1.76±0.55</td>
<td>1.78±0.48</td>
<td>.889</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td>0.68 (0.4-2.6)</td>
<td>0.82 (0.4-4.2)</td>
<td>.258</td>
</tr>
<tr>
<td>Serum insulin, mU/L</td>
<td>3.9 (1.8-19.4)</td>
<td>4.9 (1.5-30.4)</td>
<td>.066</td>
</tr>
</tbody>
</table>

MET indicates metabolic equivalent value (energy consumption of a person at rest, which equals about 1 kcal·kg⁻¹·h⁻¹); HDL, high-density lipoprotein; and LDL, low-density lipoprotein. Data are given as the number of subjects for categorical variables, as mean±SD for normally distributed continuous variables, and as median (range) for continuous variables with asymmetrical data distribution.

*Categories of smoking: 0, nonsmoker; 1, 1-10 cigarettes/d; 2, >10 cigarettes/d.
†Sodium intake could be analyzed in 83 subjects, 19 with and 64 without physiological S₃.

An auscultatory S₃ was identified in 22 subjects (9 men) and confirmed by phonocardiography in all. One of them was the woman with tricuspid regurgitation, but the rest were free of heart disease. The prevalence of physiological S₃ was thus 23.1% (95% confidence interval, 14.4 to 31.6).

Predictors of Physiological S₃

Comparisons of subjects free of heart disease with and without physiological S₃ are summarized in Tables 1 through 3. Table 1 shows that the body mass index was lower in the presence of S₃, but there were no statistically significant differences in sex distribution, lifestyle characteristics, sodium intake, or laboratory data. Regarding hemodynamics (Table 2), the only statistically significant difference was a lower heart rate in subjects with physiological S₃. The aortic elastic modulus showed a trend toward less stiff aorta with physiological S₃, but the LV diameters, mass, and fractional shortening were nearly identical in the two groups (Table 2). The Doppler indexes of LV filling, by contrast, showed conspicuous differences between the groups (Table 3). The presence of S₃ was associated with a higher peak value and acceleration of the early diastolic velocity, a higher early-to-atrial peak velocity ratio, and a lower atrial filling fraction. Since the LV filling indexes are sensitive to heart rate, the groups were compared also after adjustment for the heart rate difference with ANCOVA. These analyses confirmed statistically significant rate-independent differences in the peak early diastolic velocity (F=12.4, P=.001) and in the acceleration of the early velocity (F=8.5, P=.005) but not in the peak velocity ratio (F=1.7, P=.195) or in the atrial filling fraction (F=1.2, P=.282). It was also analyzed whether the Doppler indexes of LV filling were related to body mass index in our study population. Statistically significant correlations with body mass index were found for the early-to-atrial peak velocity ratio (r=-.27, P=.011) and the atrial filling fraction (r=-.32, P=.002) but not for the peak early diastolic velocity (r=-.14, P=.187) or the acceleration of velocity (r=.18, P=.101).

To identify the independent predictors of physiological S₃, logistic regression analysis was performed with body mass index, heart rate, peak early diastolic velocity, acceleration of the early diastolic velocity, peak velocity ratio, and atrial filling fraction as explanatory variables in the model. The statistically significant independent predictors were the peak early diastolic velocity with a logistic coefficient (±standard error) of 0.14±0.06 (P=.027) and body mass index with a coefficient of −0.23±0.11 (P=.037). Given, for instance, a 10-cm/s difference upward in the peak early diastolic velocity, the odds ratio (95% confidence interval) for the presence of physiological S₃ was 4.1 (1.2 to 13.5), and given an increment of 5 kg/m² in body mass index, the odds ratio was 0.32 (0.19 to 0.93).

Discussion

We assessed the prevalence and predictors of an audible physiological S₃ in a population-based, cross-sectional study of persons born in 1954 and aged 36 to 37 years at the time of our work. The study group can be considered representative of the target population because the sample was random and the participation rate was nearly 80%. The age homogeneity of the popula-
TABLE 2. Hemodynamic Data, Aortic Stiffness, and Left Ventricular and Left Atrial Measurements by M-Mode Echocardiography in Relation to the Presence of Audible Physiological S3 in a Population Sample Aged 36 to 37 Years

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Physiological S3</th>
<th>Present (n=21)</th>
<th>Absent (n=66)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats per minute</td>
<td></td>
<td>63±7</td>
<td>68±10</td>
<td>.015</td>
</tr>
<tr>
<td>Brachial artery systolic blood pressure, mm Hg</td>
<td></td>
<td>127±18</td>
<td>125±13</td>
<td>.587</td>
</tr>
<tr>
<td>Brachial artery diastolic blood pressure, mm Hg</td>
<td></td>
<td>80±12</td>
<td>81±9</td>
<td>.800</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td></td>
<td>58.1±11.2</td>
<td>55.5±11.6</td>
<td>.371</td>
</tr>
<tr>
<td>Peripheral arterial resistance, mm Hg · min⁻¹ · L⁻¹</td>
<td></td>
<td>25.7±7.0</td>
<td>26.1±5.7</td>
<td>.779</td>
</tr>
<tr>
<td>Aortic elastic modulus, 10⁸ dyne/cm²*</td>
<td></td>
<td>284 (122-1289)</td>
<td>407 (100-2191)</td>
<td>.110</td>
</tr>
<tr>
<td>Left ventricular measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-diastolic diameter, mm</td>
<td></td>
<td>49.7±4.2</td>
<td>49.5±3.9</td>
<td>.826</td>
</tr>
<tr>
<td>End-systolic diameter, mm</td>
<td></td>
<td>33.1±4.4</td>
<td>33.4±4.4</td>
<td>.809</td>
</tr>
<tr>
<td>Fractional shortening, %</td>
<td></td>
<td>33.4±4.4</td>
<td>32.7±5.1</td>
<td>.522</td>
</tr>
<tr>
<td>Peak rate of diameter lengthening, mm/s</td>
<td></td>
<td>138±31</td>
<td>126±30</td>
<td>.159</td>
</tr>
<tr>
<td>Septal thickness, mm</td>
<td></td>
<td>9.0±1.7</td>
<td>9.2±1.8</td>
<td>.629</td>
</tr>
<tr>
<td>Posterior wall thickness, mm</td>
<td></td>
<td>9.6±1.9</td>
<td>9.6±1.8</td>
<td>.887</td>
</tr>
<tr>
<td>Mass, g</td>
<td></td>
<td>167±52</td>
<td>168±46</td>
<td>.972</td>
</tr>
<tr>
<td>Left atrial systolic diameter</td>
<td></td>
<td>36.0±5.9</td>
<td>35.5±4.4</td>
<td>.724</td>
</tr>
</tbody>
</table>

Results are given as mean±SD or as median (range) in case of asymmetrical data distribution.
*Aortic elastic modulus was measured in 55 subjects, 13 with and 42 without a physiological S₃.

TABLE 3. Doppler Indexes of Left Ventricular Filling in Relation to the Presence of Audible Physiological S₃ in a Population Sample Aged 36 to 37 Years

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Physiological S₃</th>
<th>Present (n=21)</th>
<th>Absent (n=66)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak early diastolic velocity, cm/s</td>
<td></td>
<td>67±10</td>
<td>58±8</td>
<td>.002</td>
</tr>
<tr>
<td>Peak atrial velocity, cm/s</td>
<td></td>
<td>39±5</td>
<td>39±7</td>
<td>.885</td>
</tr>
<tr>
<td>Early-to-atrial peak velocity ratio</td>
<td></td>
<td>1.72±0.29</td>
<td>1.54±0.32</td>
<td>.021</td>
</tr>
<tr>
<td>Acceleration of early diastolic velocity, cm/s²</td>
<td></td>
<td>717±148</td>
<td>622±122</td>
<td>.012</td>
</tr>
<tr>
<td>Deceleration of early diastolic velocity, cm/s²</td>
<td></td>
<td>522±98</td>
<td>486±106</td>
<td>.158</td>
</tr>
<tr>
<td>Relaxation time, ms</td>
<td></td>
<td>175±15</td>
<td>180±17</td>
<td>.502</td>
</tr>
<tr>
<td>Atrial filling fraction, %</td>
<td></td>
<td>23±4</td>
<td>26±6</td>
<td>.006</td>
</tr>
</tbody>
</table>

Data are mean±SD.

Adapted and reorganized from the original document to improve clarity and coherence.
nately, the sex distribution of the study group was not reported, and the population from which the subjects were derived was not specified. In a phonocardiographic study of 165 selected individuals, Van de Werf et al reported a physiological S₃, in practically every subject (97%) younger than 36 years and in no less than 39% of those beyond 40 years (no auscultatory data were given). Their subjects were mostly school children and hospital workers, with a majority of male subjects. Although the data of Wilken et al support the axiom of physiological S₃ being audible always in childhood but rarely beyond 40 years of age, it is clear that the scientific foundation of this concept should be studied further.

The Mechanism of Physiological S₃

In our study, subjects with physiological S₃ had higher acceleration and peak amplitude of the early diastolic LV inflow velocity, higher early-to-atrial peak velocity ratio, and lower atrial filling fraction than their healthy age mates without S₃. These results agree well with earlier findings of a higher LV posterior wall thinning rate⁴ and an increased early diastolic transmural velocity and peak velocity ratio⁶ in the presence of physiological S₃. Altogether, these data indicate that the presence of audible or recordable physiological S₃ is associated with a conspicuously rapid and complete early diastolic LV filling.

There are understandably no invasive studies on the mechanical correlates of physiological S₃ in humans. An S₃ associated with experimental LV volume load in healthy animals has been attributed to a prominent rapid filling wave of the intraventricular pressure reversing the transmural gradient and causing abrupt deceleration of LV inflow.⁵ The released kinetic energy is thought to set the heart muscle vibrating, and sonomicrometric recordings have indeed demonstrated oscillations of the LV wall coincident with an S₃.⁶ Interestingly, the early diastolic transmural velocity peak—which was the single most important predictor of physiological S₃ in our subjects—has been shown to mark the reversal of the transmural pressure gradient⁷ and to coincide exactly with the onset of S₃.⁸ Although certainly not identical, the mechanism of physiological S₃ in humans may resemble the genesis of an S₃ in transiently volume-overloaded healthy animals. Both states are characterized by a high early diastolic LV inflow velocity, and a prominent rapid filling wave also can be seen in association with physiological S₃ in humans (on the apex cardiogram).⁴

What could underlie the high early diastolic LV filling rate that apparently produces physiological S₃? The amplitude of the early diastolic transmural velocity peak depends on four factors: the pressure in the left atrium and the relaxation, chamber compliance, and end-systolic volume of the left ventricle.⁹ There were no differences in LV volumes in relation to S₃ in our subjects, and differences in left atrial pressure also are highly unlikely because all persons were asymptomatic and had similar left atrial size. Thus, the higher early transmural velocity peak in persons with S₃ is likely to reflect a difference (relative increase) in either LV relaxation or chamber compliance or both; the enhanced acceleration of flow supports the role of relaxation.⁹ It has been presented earlier that physiological S₃ could result from enhanced LV relaxation caused by a relatively high sympathetic tone.⁴ Our findings, however, do not support this idea because subjects with physiological S₃ had lower heart rate than those without S₃.

Disappearance of Physiological S₃ With Age

Van de Werf et al⁴ reported that the prevalence of recordable physiological S₃ decreased in relation to an increase of LV wall thickness and mass with age. They thought that the basic mechanism was an age-related increase of blood pressure resulting in LV hypertrophy and reduced early diastolic filling rate. Wilken et al⁵ also concluded that the development of relative LV hypertrophy may be the primary cause of the disappearance of physiological S₃ with age. In our study, which was population-based and in which the effect of age was deliberately excluded, both blood pressure and LV mass were practically identical in the presence and absence of physiological S₃. This suggests that the disappearance of this sound may not be related primarily to blood pressure or LV mass but reflects a more primary alteration (aging) in LV diastolic properties. Other recent works support this idea in showing that age-related changes in the Doppler indexes of LV filling are independent of blood pressure and LV wall thickness and mass.⁶⁷ Animal and human data indicate that aging of the heart muscle results in a delayed onset and reduced rate of LV relaxation.⁸ Although changes in the passive myocardial elastic properties and LV compliance are also possible, they are less prominent and clearly less consistent.⁹ Considering LV relaxation and its triple control,¹⁰ age-related changes could occur in the biochemical actomyosin inactivation but also in the relaxation rate and in the synchrony of LV filling. The stiffness of the thoracic aorta contributes to the LV relaxation load¹⁰¹¹ and is strongly age dependent,¹² and we thought that increasing aortic rigidity, which delays relaxation,¹³ could promote the disappearance of physiological S₃ with age. Although the absence of physiological S₃ was associated with a somewhat higher aortic stiffness in our subjects, supporting our idea, the association was not statistically significant.

Since physical activity¹⁴ and alcohol consumption¹⁵ are known predictors of LV diastolic function, we thought that these and other lifestyle characteristics might also predict the presence (persistence) of physiological S₃ in our subjects. This could not be proven, however. Indirectly, these negative findings are compatible with recent data suggesting that LV diastolic function may be associated with lifestyle in middle or old age but not in young adulthood.¹⁶ A limitation of our analyses is, however, that we did not ascertain how well the subjects’ current habits and activities represent their lifestyle over the past years.

Leaness and Physiological S₃

Subjects with physiological S₃ had a lower body mass index (were more lean) than the healthy subjects without an S₃. This relation was independent of LV diastolic function. A simple explanation is that the thick insulating layer between the vibrating heart muscle and the stethoscope weakens the audibility of S₃ in obese persons. However, obesity may also impair LV early diastolic filling¹⁷¹⁸ and it could thereby promote the disappearance of physiological S₃ in otherwise healthy subjects. In the present study, the early-to-atrial peak
velocity ratio but not the early peak velocity per se correlated inversely with body mass index.

Conclusions
Our population-based study shows that nearly one fourth of healthy persons aged 36 to 37 years have an audible physiological S3. The presence of this sound is associated independently with leanness and with a relatively high peak early diastolic transmitral velocity. Our data give some support to the idea of physiological S3 resulting from a high rate of early diastolic LV filling caused by swift relaxation. The concept of why this sound disappears with age probably needs a revision, however. The immediate reason may well be a reduction of early diastolic LV filling, but the basic mechanism probably is not LV hypertrophy caused by increased blood pressure, as is widely thought, but a more primary alteration (aging) of the LV diastolic properties. Clinicians will want to know that in persons approaching their forties, an audible physiological S3 is likely to imply delayed functional aging of the heart.

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