Asymptomatic Left Ventricular Systolic Dysfunction in Essential Hypertension
Prevalence, Determinants, and Prognostic Value

Paolo Verdecchia, Fabio Angeli, Roberto Gattobigio, Mariagrazia Sardone, Carlo Porcellati

Abstract—Prevalence, determinants, and prognostic value of asymptomatic left ventricular systolic dysfunction (LVSD) in uncomplicated subjects with essential hypertension are still incompletely known. We studied 2384 initially untreated subjects with hypertension, no previous cardiovascular disease, and no symptoms or physical signs of congestive heart failure (CHF). These subjects were studied at entry and followed for up to 17 years (mean 6.0). Asymptomatic LVSD (ALVSD), defined by an echocardiographic ejection fraction <50%, was found in 3.6% of subjects. Cigarette smoking (P=0.013), increased left ventricular (LV) mass (P=0.001), and higher 24-hour heart rate (P=0.014) were independent correlates of ALVSD. During follow-up, a first cardiovascular event occurred in 227 subjects, and 24 of these events were hospitalizations for symptomatic CHF. Incidence of CHF per 100 persons per year was 0.12 in patients without and 1.48 in patients with ALVSD (log-rank test P=0.0001). In a Cox model, after adjustment for age (P=0.0001), LV mass (P=0.0001), and cigarette smoking (P=0.039), LVSD conferred a markedly increased risk for CHF (odds ratio, 9.99; 95% confidence interval, 3.67 to 27.2). Incidence of coronary (0.84 versus 0.62 per 100 person years) and cerebrovascular (0.80 versus 0.62×100 person years) events did not differ (all P=NS) between subjects with and without ALVSD. ALVSD is a potent and early marker of evolution toward severe CHF requiring hospitalization in subjects with essential hypertension. (Hypertension. 2005;45:412-418.)

Key Words: heart failure ■ ventricular function, left ■ echocardiography ■ hypertrophy ■ blood pressure monitoring, ambulatory

Hypertension is a potent risk factor for congestive heart failure (CHF).1,4 According to the American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines for evaluation and management of chronic CHF in the adult, all hypertensive subjects without symptoms of CHF and without structural heart disease should be classified as belonging to stage A, which denotes a high risk for CHF, whereas those without symptoms of CHF but with structural heart involvement denoted, for instance, by left ventricular (LV) hypertrophy, should be classified as belonging to stage B.2 Development of overt CHF may be preceded by a phase of asymptomatic LV systolic dysfunction (ALVSD).3,4 Diagnosis of ALVSD is important because treatment with angiotensin-converting enzyme (ACE) inhibitors may delay progression toward overt CHF in these subjects.5,6 In the general population, prevalence of ALVSD has been estimated at ~2% in most studies, a figure not dissimilar from that of overt CHF.7–12

Many hypertensive subjects without symptoms or physical signs of CHF should thus be considered for screening of ALVSD, an argument that rises cost-effectiveness considerations.12 However, important aspects including prevalence, determinants, and prognostic value of ALVSD in the specific setting of essential hypertension are poorly known because most available studies have been performed in the general population.7–12

Consequently, the present study was undertaken with the aim to address the clinical value of ALVSD determined by echocardiography in a large group of subjects with essential hypertension, including the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) database.13–15 We sought to determine prevalence and determinants of ALVSD and its contribution to the long-term risk of overt CHF and other major cardiovascular adverse events.

Methods

The PIUMA study, initiated in June 1986, is a prospective observational registry in initially untreated subjects with essential hypertension.13–15 Entry criteria include an office blood pressure (BP) ≥140 mm Hg systolic or 90 mm Hg diastolic on at least 3 visits and absence of secondary causes of hypertension, previous cardiovascular disease, including CHF, and life-threatening conditions. During each visit, 3 BP measurements were averaged for analysis. Overall (Figure 1), 3010 subjects consecutively entered the PIUMA registry...
from June 12, 1986, to June 30, 2000, and 174 of these subjects were lost to follow-up. Of the remaining 2836 subjects, 2724 had a complete echocardiographic examination at entry, and in 2384 of these subjects, the echocardiographic tracings were of good technical quality to estimate LV structure and function. Age, sex distribution, frequency of diabetes and cigarette smoking, and office and 24-hour ambulatory BP did not differ (all \(P = \) NS) between the 626 subjects with unavailable echocardiographic tracings and those admitted to the present study.

Electrocardiography

Standard 12-lead ECG was recorded at 25 mm/s and 1 mV/cm calibration. Subjects with complete right or left bundle branch block, previous myocardial infarction, Wolff-Parkinson–White syndrome, or atrial fibrillation were excluded from the analyses which tested the relation of ECG LV hypertrophy to ALVSD and outcome. LV hypertrophy was defined by using the Cornell/Strain index, a modification of the Perugia score, to be considered positive for LV hypertrophy in the presence of a modified Cornell voltage (sum of S wave in lead V3 and R wave in lead aVL) >2.4 mV in men or >2.0 mV in women or a typical strain pattern.

Echocardiography

Details about reading procedures and reproducibility of linear measures of LV mass in our laboratory have been reported previously. Linear measurements were made according to the American Society of Echocardiography. LV volumes used to estimate ejection fraction (EF) were determined by using the Teichholz method. The EF threshold used for defining ALVSD was arbitrarily set to 40% to 49% in 87% of subjects. Compared with the subjects without ALVSD, those with ALVSD were more frequently men and current smokers. Office and 24-hour ambulatory BP did not differ (all \(P = \) NS) between the 626 subjects with unavailable echocardiographic tracings and those admitted to the present study.

End Points

For assessment of end points, hospital record forms and other source documents of patients who died or experienced a cardiovascular event were collected and reviewed in conference by the authors of this study. Details about the international standard criteria used to diagnose outcome events in the PIUMA study have been reported previously. CHF has been defined as a documented hospitalization, or attendance in an acute care setting, for treatment of CHF.

Data Analysis

Statistical analysis was performed using SPSS (SPSS) and SAS-Stat (SAS Institute). In addition to standard descriptive and comparative analyses, a multivariate logistic regression model was used to estimate the independent correlates of ALVSD. All the variables reported in Table 1 were tested in the model. For the subjects who experienced multiple events, survival analysis was restricted to the first event. Survival curves were estimated using the Kaplan–Meier product-limit method and compared with the Mantel (log-rank) test. The effect of prognostic factors was evaluated by stepwise Cox model. The following covariates were tested: age (years), sex (women or men), systolic and diastolic BP (mm Hg), heart rate (bpm), family history of cardiovascular disease at age <55 in the father or <65 in the mother (no or yes), diabetes (no or yes), serum cholesterol (mmol/L), triglycerides (mmol/L), smoking habits (nonsmokers or current smokers), body mass index (kg/m²), antihypertensive treatment at the first follow-up visit before terminating event or censoring (lifestyle measures, diuretics, \( \beta \)-blockers, ACE inhibitors, calcium channel blockers, angiotensin II antagonists), LV mass (g/height[m]².3), LV mass (g/height[m]².3), ALVSD (no or yes), and year of entry into the study (2-year intervals from 1986). To limit the impact of collinearity between the office and ambulatory values of BP and heart rate, these covariates were included into the model either as office or ambulatory values. The antihypertensive drug classes at follow-up entered the model coded as 1 for present and 0 for absent. Diabetes was defined by a fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) or antidiabetic drugs. Two-sided \( P \) values <0.05 were considered statistically significant.

Results

The clinical characteristics of subjects with and without ALVSD are shown in Table 1. None of the subjects had evidence of alcoholic, postpartum, or viral or restrictive cardiomyopathy. Also, none of the subjects had segmental wall motion abnormalities. A total of 75% of the subjects had never been treated for hypertension, whereas previous treatment had been discontinued for \( \approx 4 \) weeks before entry because of side effects, diagnostic tests, or unwillingness to continue by the subjects in the remaining 25%. Diabetes was found in 4.9% of participants, and 52% of these subjects were receiving antidiabetic drugs.

Features of Subjects With LVSD

Prevalence of ALVSD was 3.6%. EF was 40% to 49% in 87% of subjects, 30% to 39% in 9% of subjects and <30% in 4% of subjects. Compared with the subjects without ALVSD, those with ALVSD were more frequently men and current smokers. Office and 24-hour ambulatory BP levels were increased in the subset with than in that without ALVSD. The 24-hour ambulatory heart rate was slightly but significantly
higher in the subset with than without ALVSD. Age, body mass index, diabetes, and known duration of hypertension did not differ between the 2 groups. The greater LV mass in the subjects with than in those without ALVSD resulted from a greater wall thickness and internal diameter, without changes in the relative wall thickness between the 2 groups. Prevalence of LV hypertrophy in the total sample was 15.4% at ECG and 37.2% at echocardiography. All 56 subjects with septum or posterior wall thickness ≥1.5 cm showed elevated levels of BP (average office BP 170/105 mm Hg; average 24-hour BP 153/97 mm Hg), thus ruling out the possibility of hypertrophic cardiomyopathy.

At the last follow-up visit before the terminating event or censoring, diuretics were taken more frequently by subjects with LVSD at entry than by those without (43% versus 32%; \( P = 0.03 \)), whereas distribution of ACE inhibitors (38% versus 42%), \( \beta \)-blockers (17% versus 22%), calcium channel blockers (23% versus 20%), and angiotensin II antagonists (8.2% versus 8.2%) did not differ between the 2 groups (all \( P = \text{NS} \)).

**Correlates of ALVSD**

In a logistic regression analysis, cigarette smoking (\( P = 0.013 \)), echocardiographic LV mass (\( P = 0.001 \)), and 24-hour heart rate (\( P = 0.014 \)) showed a direct and independent relationship with ALVSD. Office heart rate did not achieve significance. Figure 2, which reports the results of analysis, allows visualization of the expected probability of ALVSD for any given level of the significant covariates.

**Incident Cardiovascular Events**

The mean duration of follow-up was 6.0 years (range 0 to 17), and the 2384 subjects contributed 14,204 person years of follow-up. At the last follow-up contact, 35.2% of the subjects were receiving lifestyle measures alone, 11.1% diuretics or \( \beta \)-blockers alone or combined, 20.2% ACE inhibitors or calcium channel blockers alone or combined, and 33.5% other drug combinations. Overall, there were 227 first cardiovascular events, and the crude rate of events was 1.59 per 100 subjects per year. Of these first events, 24 were hospitalizations for symptomatic CHF, and their crude rate was 0.17 per 100 subjects per year (0.12 in the subjects without and 1.48 in those with ALVSD). Three of these subjects died shortly after hospitalization because of severe CHF. Figure 3 displays the cumulative hazard and the crude rate of overt CHF during follow-up in subjects with and without ALVSD at entry. As shown in Figure 4, the crude rate of total cardiovascular events was 3.16 and 1.55 per 100 subjects per year, respectively (log-rank test \( P = 0.003 \)), in the subjects with and without ALVSD at entry. However, such a difference was entirely explained by the difference between

**TABLE 1. Clinical Characteristics of Subjects With and Without ALVSD at Entry**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal LV Systolic Function (n=2299)</th>
<th>LVSD (n=85)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>50 (12)</td>
<td>49 (12)</td>
<td>0.68</td>
</tr>
<tr>
<td>Men, %</td>
<td>53.5</td>
<td>67.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Body mass index, kg×m(^{-2})</td>
<td>26.7 (4)</td>
<td>26.9 (4)</td>
<td>0.59</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>23.9</td>
<td>40.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>5.0</td>
<td>3.5</td>
<td>0.54</td>
</tr>
<tr>
<td>Duration of hypertension, years</td>
<td>4.0 (6)</td>
<td>4.3 (6)</td>
<td>0.63</td>
</tr>
<tr>
<td>Office BP, mm Hg</td>
<td>156/97 (19/10)</td>
<td>160/101 (20/11)</td>
<td>0.04/0.001</td>
</tr>
<tr>
<td>Office HR, bpm</td>
<td>75 (11)</td>
<td>76 (13)</td>
<td>0.47</td>
</tr>
<tr>
<td>24-Hour BP, mm Hg</td>
<td>137/87 (15/10)</td>
<td>142/90 (19/11)</td>
<td>0.002/0.009</td>
</tr>
<tr>
<td>24-Hour HR, bpm</td>
<td>75 (9)</td>
<td>77 (11)</td>
<td>0.03</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.50 (1.1)</td>
<td>5.52 (1.4)</td>
<td>0.86</td>
</tr>
<tr>
<td>Creatinine, mol/L</td>
<td>85.6 (20)</td>
<td>88.6 (25)</td>
<td>0.22</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.56 (1.2)</td>
<td>5.42 (1.2)</td>
<td>0.21</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.28 (0.3)</td>
<td>1.23 (0.4)</td>
<td>0.22</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.58 (0.9)</td>
<td>3.65 (1.1)</td>
<td>0.56</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.64 (1.1)</td>
<td>1.57 (0.7)</td>
<td>0.58</td>
</tr>
<tr>
<td>Uric acid, mmol/L</td>
<td>280 (82)</td>
<td>283 (85)</td>
<td>0.80</td>
</tr>
<tr>
<td>Interventricular septum (cm)</td>
<td>1.11 (0.2)</td>
<td>1.19 (0.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>LV internal dimension (cm)</td>
<td>4.93 (0.5)</td>
<td>5.29 (0.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Posterior wall (cm)</td>
<td>1.00 (0.2)</td>
<td>1.07 (0.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>LV mass (g/height×m(^{2}))</td>
<td>48.3 (13)</td>
<td>59.0 (20)</td>
<td>0.001</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.41 (0.9)</td>
<td>0.41 (0.9)</td>
<td>0.91</td>
</tr>
<tr>
<td>EF (%)</td>
<td>67.8 (8)</td>
<td>44.7 (6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Electrocardiographic LVH (%)</td>
<td>15.0</td>
<td>26.3</td>
<td>0.008</td>
</tr>
<tr>
<td>Echocardiographic LVH (%)</td>
<td>36.3</td>
<td>61.2</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

HR indicates heart rate; LVH, left ventricular hypertrophy.
the groups in the incidence of overt CHF. In fact, neither the cerebrovascular (58 cases of stroke and 26 cases of transient ischemic attacks) nor the coronary (44 cases of acute myocardial infarction, 42 cases of unstable angina, and 6 cases of sudden cardiac death) events showed any statistical differences between the 2 groups (Figure 3). The other 27 patients developed occlusive arterial disease (n=19) or severe renal failure requiring dialysis (n=8) as their first cardiovascular event.

Multivariate Analysis

Table 2 shows the list of variables that achieved significance in the multivariate analysis according to the Cox model. Age (P=0.0001), LV mass (P=0.001), and ALVSD (P=0.0001) were the sole independent predictors of overt CHF, and none of the other variables (see data analysis) achieved statistical significance in modeling the multivariate hazard function. Table 2 shows the final multivariate model with 3 covariates. End-diastolic LV internal diameter was a significant predictor of CHF when it entered the equation alone (P=0.0001) and after simultaneous adjustment for age and ALVSD (P=0.014). However, its predictive value did not remain significant (P=0.40) when LV mass entered the equation. LV hypertrophy at ECG showed an independent association with overt CHF after adjustment for age and ALVSD (hazard ratio, 3.03; 95% confidence intervals, 1.26 to 7.29; P=0.013), but its predictive value did not remain significant (P=0.27) after correction for LV mass.

Discussion

The present study provides the first assessment of prevalence, determinants, and prognosis of ALVSD in a large population of subjects with essential hypertension. In these subjects,
prevalence of ALVSD, defined by an echocardiographic EF <50%, was 3.6%, and the subjects with ALVSD showed a 9-fold higher risk of hospital admission for CHF over a mean follow-up period of 6 years compared with those with normal EF. The excess risk associated with ALVSD persisted after simultaneous adjustment for age and LV mass, although these results are supported by a relatively low number of outcome events.

Previous Studies
As discussed by Wang and et al., most of the available studies that examined prevalence and clinical correlates of ALVSD have been conducted in general population samples. In these studies, prevalence of ALVSD ranged between 0.9% and 12.9%, depending on the clinical characteristics of the population and the EF values used to define ALVSD. The only available report in patients with essential hypertension is a cross-sectional analysis of the Genetic Epidemiology Network (HyperGEN) study, performed on 2086 hypertensive subjects. In these subjects, EF was normal (54%) in 86% of participants and depressed in the remaining 14%. The inclusion of subjects with previous myocardial infarction or overt CHF may contribute to explain the greater prevalence of systolic dysfunction when compared with the present study. Importantly, increased LV mass at echocardiography was a strong and independent predictor of systolic dysfunction in the HyperGEN and in our study.

Correlates of ALVSD
BP did not show any independent association with ALVSD. However, increased LV mass could have mediated part of the effects of pressure overload and other potential pathogenetic factors on ALVSD. In a previous study, 24-hour ambulatory systolic BP, gender, body mass index, postload insulin, and insulin-growth factor-1 were independent determinants of LV mass, and their combination explained 64% of the variability of LV mass. In addition to LV mass, ambulatory heart rate emerged as an independent correlate of ALVSD. Our findings do not allow us to establish whether the association of heart rate with ASVSD is a cause or effect relationship. In experimental studies, pacing-induced tachycardia is a well-established technique to induce CHF. However, the impact of tachycardia as a potential determinant of ALVSD is scarcely known from epidemiological studies. In the Echocardiographic Heart of England Screening Study, resting heart rate was 71 bpm in the total sample of 3960 subjects and 77 bpm in the subset of individuals with ALVSD, but the statistical significance of such a difference was not reported. In the present study, the availability of ambulatory heart rate values may have facilitated the disclosure of the burden attributable to heart rate over the 24 hours as a potential determinant of ALVSD. Cigarette smoking was another independent correlate of ALVSD. In the HyperGEN study, no significant association was found between cigarette smoking and LVSD. In the Framingham study, the risk of developing overt CHF was higher in smokers than in never smokers by 65% in men and 56% in women. In the National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study, the risk of overt CHF was 59% higher in smokers than in nonsmokers. The basic mechanisms of the deleterious effect of smoking on systolic function are scarcely known. Cigarette smoking affects microvascular function, which may be impaired in subjects with ALVSD.

Natural History of ALVSD
The present study examined the relationship between ALVSD and subsequent cardiovascular events in the specific setting of uncomplicated subjects with essential hypertension. In a previous study in hypertensive subjects, mean pulmonary wedge pressure recorded invasively was an independent predictor of mortality and of cardiovascular events. In the present study, ALVSD was associated with a greater risk of overt CHF, but not of coronary and cerebrovascular events. Although the results of the echocardiographic study performed at entry were open to the treating physicians, awareness of echocardiographic EF did not lead to more frequent use of ACE inhibitors in the subset with ALVSD. It should be noted that the PIUMA study began in 1986, before the widespread acceptance of ACE inhibitors in subjects with ALVSD. In previous general population studies, ALVSD was associated with an increased risk of cardiovascular mortality, all-cause mortality, and nonfatal cardiovascular events. Several potential explanations, including different definitions of ALVSD and the inclusion of subjects with previous myocardial infarction and other comorbid conditions, may contribute to explain the variable prognostic impact exerted by ALVSD on the different outcome events. Indeed, overt CHF may be expected as a frequent complication in the natural history of ALVSD. In a cohort of elderly participants to the Cardiovascular Health Study (mean age 72 years), 5.5% of subjects showed ALVSD, and the subsequent incidence of CHF events approximated 3% per year. The less stringent definition for overt CHF, which did not require hospitalization, and the older age of the population may contribute to explain the higher incidence of CHF in the Cardiovascular Health Study than in the present study.

Study Limitations
We could not evaluate the prognostic impact of severe systolic dysfunction because EF was <30% only in 4% of subjects with ALVSD. In a general population study, only 3% of subjects without previous cardiovascular disease had an EF ≤30%. In a report from the Framingham Heart Study, prevalence of subjects with EF <30% was 6%, but individuals with previous myocardial infarction and valvular disease were not excluded. Furthermore, because our population is exclusively composed of white subjects, extrapolation of results to different ethnic groups may be problematic. In addition, because only about one third of the subjects had periodical echocardiographic examinations during follow-up,
the prognostic impact of serial changes in LV anatomy and function could not be determined. Two further limitations of the present study are the lack of assessment of diastolic dysfunction, which may be combined with a normal or abnormal LV pump function,35 and the assessment of systolic function at midwall level, which may also be impaired in subjects with endocardial EF >50%.36 Finally, because diagnosis of CHF had to be corroborated by hospitalization or attendance for treatment in an acute care setting, we might have missed subjects with acute heart failure who died before attending the hospital and less severe subjects who were treated by their family doctors at home. The present standard definition of CHF is endorsed in large intervention trials in the field of cardiovascular prevention.37,38

Perspectives
ALVSD, defined by an echocardiographic EF <50%, is clinically important in asymptomatic subjects with essential hypertension without overt CHF. In our study, its frequency was 3.6%, and these subjects showed a 9-fold higher risk of hospital admission for CHF when compared with the subjects with normal EF. Once diagnosed, ALVSD should prompt implementation of aggressive lifestyle and pharmacological strategies to delay or prevent evolution toward symptomatic CHF. Such strategies may be rewarding because treatment of hypertension decreases the risk of CHF by ≈50%,39 and ACE inhibitors reduce the risk of overt CHF in patients with ALVSD.40–42 Appropriate strategies for ALVSD prevention in hypertensive subjects with normal systolic function should be investigated in future trials.

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References


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