Systemic hypertension is well recognized as a potent risk factor for sudden cardiac death. The risk of sudden and nonsudden cardiac death and of nonfatal myocardial infarction is further increased in hypertensive patients by the presence of ECG or echocardiographic evidence of left ventricular (LV) hypertrophy. Reports of frequent and often complex ventricular arrhythmias detected by ambulatory ECG recordings in patients with LV hypertrophy have suggested that an interaction between arrhythmic “triggers” and a vulnerable myocardium might be the cause of sudden death in hypertensive patients. In addition, many hypertensive patients have episodes of asymptomatic ST segment depression during normal activity or various stresses, suggesting the presence of “silent” myocardial ischemia. However, the clinical significance of either ventricular arrhythmias or episodes of ST segment depression in hypertensive patients has been uncertain because of a lack of evidence that they are predictors of complications of hypertension.

See p 1808

This situation has begun to change with the publication in this issue of Circulation of a study by Zehender et al., in which ambulatory ECG evidence of repetitive ventricular arrhythmias and episodes of ST segment depression as well as ECG LV hypertrophy were all found to be univariate predictors of subsequent cardiac death or nonfatal myocardial infarction in patients with essential hypertension. However, before new approaches to risk stratification or clinical management of patients with elevated blood pressure are adopted, careful attention should be paid to critical attributes and limitations of the present study.

Patients whose hypertension had either not been previously treated or who had stopped ineffective treatment were enrolled by Zehender et al. Patients were excluded who had evidence of secondary hypertension, prevalent coronary or other forms of heart disease, or serum potassium levels less than 3.5 mmol/l (an important exclusion in view of the association of diuretic-induced hypokalemia with both ECG repolarization abnormalities and increased morbidity). The 150 eligible patients were predominately male, on the average middle aged, and had a relatively high group mean systolic blood pressure of 174 mm Hg on enrollment. LV hypertrophy was diagnosed by standard ECG criteria in 9% to 17% of the patients, but because ECG sensitivity for detection of anatomic hypertrophy may range from as low as 7% to no more than 50% it is probable that a substantial proportion of patients had elevated LV mass. Because of the strong relations of hypertensive complications to systolic blood pressure and LV mass it is not surprising that the patients of Zehender et al had a high rate (3% per year) of cardiac death or nonfatal myocardial infarction during follow-up. These characteristics differentiate the study population from the majority of hypertensive patients, who have less elevated blood pressure, a lower prevalence of LV hypertrophy, and a lower incidence of morbidity events.

Ambulatory ECG recordings were performed for at least 21 hours in each patient at baseline and were interpreted with human oversight using a computerized system. Criteria for detecting episodes of ST segment depression (a minimum of 1 minute of at least 0.1 mV flat or downward sloping ST depression 80 msec after the J-point in the presence of normal resting repolarization, or further depression by 0.15 mV in addition to repolarization abnormalities of LV hypertrophy) should have favored high specificity. Results obtained with ambulatory ECG systems that do not provide full disclosure of findings or are interpreted with less stringent criteria may not be comparable to those in the present report.

An important methodological contribution of this study is the repetition of ECG recordings after 4 weeks of placebo treatment in a subgroup of 50 patients. ECG LV hypertrophy and the occurrence of ST segment depression were reproducible in 90% to 100% of patients who had these abnormalities on the first recording. In contrast, there was marked intrindividual variability in both the frequency of single premature beats (100% decrease or at least 400% increase in 12 of 50 patients [24%]) and the occurrence of repetitive ventricular arrhythmias (reproducible in only about 50% of patients). This variability of arrhythmias is correctly emphasized by the authors as limiting their usefulness for risk stratification or as a target of treatment.

Of the entire population, about one third had at least one episode of ST depression; 93% of these episodes were asymptomatic. Approximately 90% of patients had at least one ventricular premature contraction, 77% had multiiform ventricular ectopic activity, and 28% had ventricular premature beat couplets or salvos of from
three to 13 beats. Striking interactions were observed among ambulatory and resting ECG abnormalities. Repetitive ventricular arrhythmias were more common in patients with ECG LV hypertrophy. The frequency of ventricular premature contractions was nearly fivefold higher during periods of ST segment depression, and the likelihood of repetitive ventricular arrhythmias was increased by more than sixfold in patients with ST segment depression as opposed to those without episodes of ST segment depression.

During follow-up, cardiac death occurred in five patients (three within 1 hour of the onset of symptoms), nonfatal myocardial infarction in eight patients, and other manifestations of coronary artery disease developed in seven others; six died of noncardiac or unknown causes. Those patients who suffered cardiac death or myocardial infarction had higher initial systolic pressures but did not differ from the remaining patients in age, sex, diastolic pressure, or the occurrence or frequency of ventricular premature beats. In contrast, baseline ECG LV hypertrophy and episodes of ST depression and of repetitive ventricular arrhythmia detected by ambulatory recordings were all strong predictors of complications. Relative risks of adverse outcomes associated with these ECG findings ranged from about 6 to 10. In multivariate analyses, ECG LV hypertrophy and episodes of ST segment depression remained statistically independent predictors of morbid events, whereas repetitive ventricular arrhythmias, age, and other variables did not add significantly to predictive models.

Several additional limitations of the study by Zehender et al deserve consideration. First, the potential selection biases influencing referral of patients to the authors cannot be ascertained, making it impossible to determine how generalizable the results may be to other patient groups. As an example, major complications occurred at a rate twofold to threefold higher than expected in individuals with mild to moderate hypertension, suggesting that the results may be most applicable to other high-risk groups. Second, because patients were treated by multiple physicians and with varied antihypertensive regimens during follow-up, it cannot be determined whether clinical outcomes were influenced by either the adequacy of blood pressure control or side effects of treatment, such as diuretic-induced hypokalemia. Finally, the number of mortal or morbid events on which the prognostic conclusions of this study are based is too small (n = 13) to assure stability of the results. Additional research in larger, more representative patient groups who are given standardized antihypertensive treatment during follow-up will be needed to resolve these uncertainties.

Interpretation of the results of the present study is facilitated by advances in understanding the relations of apparent myocardial ischemia and arrhythmogenesis to myocardial hypertrophy and coronary artery abnormalities in the hypertensive heart. Although ST segment depression in hypertensive patients may reflect abnormalities of hypertrophied myocytes, available evidence suggests that ST depression usually reflects myocardial ischemia because of excessive oxygen demand, inadequate supply, or both. The fact that most episodes of ST segment depression in the present study were preceded by increases in heart rate and the similarity of their distribution over 24 hours to the known diurnal pattern of blood pressure is consistent with their being caused by a myocardial supply–demand imbalance. Available data indicate that such an imbalance in hypertensive patients may be caused by the effects of myocardial hypertrophy, by abnormalities of the smaller resistance vessels in the coronary circulation, or by large-vessel coronary disease similar to that seen in normotensive individuals.

The need to supply oxygen and other nutrients to the greater myocardial mass of the hypertrophied left ventricle increases resting myocardial blood flow and blunts the coronary flow reserve in response to stress. In this setting, the ability to maintain normal blood flow by autoregulation when perfusion pressure is decreased may be impaired, adding a potential hazard of overzealous blood pressure reduction. However, hypertensive patients with normal LV mass may also experience symptomatic or asymptomatic myocardial ischemia associated with abnormal coronary flow reserve, possibly caused by hypertrophy of myocardial arteries. Additionally, evidence is now emerging of a relation between hypertensive LV hypertrophy and atherosclerosis, drawing attention back to the role of large-vessel coronary disease. Although the mechanism of the ECG abnormalities in the patients of Zehender et al cannot be determined, their prediction of morbid events is consistent with the increased mortality associated with LV hypertrophy in hypertensive patients with normal or obstructed coronary arteries.

Ventricular arrhythmias were also found by Zehender et al to be associated with both ECG LV hypertrophy and episodes of silent ischemia. In this setting, the arrhythmias may reflect not only the proarrhythmic effects of myocardial ischemia but also those of myocardial hypertrophy, including altered dispersion of repolarization, prolonged intraventricular conduction, and myocardial fibrosis.

The potential mechanisms of myocardial ischemia and arrhythmogenesis outlined above and the prognostic observations reported by Zehender et al both suggest that therapeutic approaches to high-risk hypertensive patients should at present be directed toward preventing or reversing myocardial ischemia and hypertrophy instead of focusing on antiarrhythmic interventions. The lack of angina during most episodes of ST segment depression in this study and the known high proportion of silent myocardial infarctions in hypertensive patients means that recognition of an individual hypertensive patient’s high-risk status often must depend on ECG or other test results. Further research is urgently needed to determine whether reversal of hypertensive LV hypertrophy, prevention of recurrent myocardial ischemia, and the control of associated arrhythmias is best accomplished with any specific class of antihypertensive agents, and whether such effects will translate into prevention of morbid events.

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