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HYPERTENSION

Differential Effects of Antihypertensive Treatment on Left Ventricular Diastolic Function

An ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) Substudy

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Objectives We hypothesized that an amlodipine-based regimen would have more favorable effects on left ventricular (LV) diastolic function.

Background Different antihypertensive therapies may vary in their effect on LV diastolic function.

Methods The HACVD (Hypertension Associated Cardiovascular Disease) substudy of ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) collected detailed cardiovascular phenotypic data on a subset of 1,006 participants recruited from 2 centers (St. Mary's Hospital, London, and Beaumont Hospital, Dublin). Conventional and tissue Doppler echocardiography and measurement of plasma B-type natriuretic peptide (BNP) were performed approximately 1 year after randomization to atenolol-based or amlodipine-based antihypertensive treatment to assess LV diastolic function.

Results On-treatment blood pressure (BP) (mean ± SD) was similar in both groups: atenolol-based regimen, systolic BP of 137 ± 17 mm Hg, diastolic BP of 82 ± 9 mm Hg; amlodipine-based regimen, systolic BP of 136 ± 15 mm Hg, diastolic BP of 80 ± 9 mm Hg. Ejection fraction did not differ between groups, but early diastolic mitral annular velocity (E′), a measure of diastolic relaxation, was lower in patients on the atenolol-based regimen: atenolol-based regimen, 7.9 ± 1.8; amlodipine-based regimen, 8.8 ± 2.0. A measure of left ventricular filling pressure, E/E′, and BNP were significantly higher in patients on the atenolol-based regimen. Differences in E′, E/E′, and BNP remained significant after adjustment for age and sex. Further adjustment for systolic BP, LV mass index, and heart rate had no impact on differences in mean E′ or BNP. The difference in E/E′ was attenuated.

Conclusions Patients receiving treatment with an amlodipine-based regimen had better diastolic function than patients treated with the atenolol-based regimen. Treatment-related differences in diastolic function were independent of BP reduction and other factors that are known to affect diastolic function. (J Am Coll Cardiol 2010;55: 1875–81) © 2010 by the American College of Cardiology Foundation

Heart failure is a common consequence of hypertension (1), and in many patients is related to impaired left ventricular (LV) systolic function. However, heart failure is also commonly associated with diastolic dysfunction and apparently preserved systolic function. This accounts for approximately one-third to one-half of heart failure cases (2,3), and most of these patients have a history of hypertension (1), often with LV hypertrophy and remodeling (4–8).

While many studies have focused on the effectiveness of hypertension treatment in reducing cardiac hypertrophy, less is known about the impact of treatment on LV diastolic function (8,9). Previous studies addressing the impact of different antihypertensive agents on LV diastolic function have largely used conventional echocardiography assessing transmitral filling and isovolumic relaxation. These conventional assessments have limitations as measures of LV diastolic function are load dependent, which makes it

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Abbreviations and Acronyms

BNP = B-type natriuretic peptide

BP = blood pressure

E′ = early diastolic mitral annular velocity

E/A ratio = early transmitral peak velocity

E/E′ = transmitral E-wave/E-wave velocity ratio

LV = left ventricular

LVMI = left ventricular mass index

SBP = systolic blood pressure

TDE = tissue Doppler echocardiography

difficult to separate alterations in loading conditions from intrinsic changes in LV diastolic function due to treatment. Second, the conventional parameters can undergo "pseudonormalization," where the ratio of the early to atrial transmitral peak velocity (E/A ratio) paradoxically increases with progressive diastolic impairment. Tissue Doppler echocardiography (TDE) offers improved assessment of diastolic function (10). TDE measurements of myocardial velocities are significantly less load dependent than conventional echocardiographic measurements; these measurements do not show pseudonormalization and independently predict cardiovascular events and mortality (11–13). Few studies to date have used TDE to assess diastolic function in relation to the effects of different antihypertensive agents.

The ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) study was a large multicenter randomized clinical trial that compared the effects of a beta-blocker plus diuretic (atenolol and bendroflumethiazide-K) regimen with a calcium-antagonist plus angiotensin-converting enzyme (amlodipine and perindopril) regimen on nonfatal myocardial infarction and fatal coronary heart disease (14). The study showed the amlodipine-based regimen was superior to the atenolol-based regimen on all major cardiovascular end points and all-cause mortality. As part of this ASCOT substudy, extensive data on LV diastolic function were collected using both conventional echocardiography and TDE. This provides the ideal setting to determine the impact of different antihypertension treatment regimens on LV diastolic function. We hypothesized that the amlodipine-based regimen would have more favorable effects on LV diastolic function in this large group of well-controlled hypertensive subjects.

Methods

Patients. The population, methods, and response rate for the ASCOT study are described in detail elsewhere (15). In brief, the ASCOT study was a clinical trial of blood pressure (BP)-lowering regimens in 19,342 men and women, age 40 to 79 years, with hypertension. Patients eligible for inclusion had hypertension and ≥3 pre-specified cardiovascular risk factors. Risk factors included male sex, current smoking, age ≥55 years, microalbuminuria/proteinuria, type 2 diabetes mellitus, left ventricular hypertrophy (LVH), electrocardiographic abnormalities, a history of early coronary heart disease in a first-degree relative, ratio of plasma total cholesterol to high-density lipoprotein cholesterol of ≥6, peripheral vascular disease, and a history of cerebrovascular events. All participants were randomly assigned to either atenolol ± bendroflumethiazide-K (atenolol-based regimen) or amlodipine ± perindopril (amlodipine-based regimen). In addition, patients with a nonfasting cholesterol level of ≤6.5 mmol/l not already receiving lipid-lowering therapy were randomly assigned to either atorvastatin 10 mg or placebo. Participants had no history of heart failure, myocardial infarction, angina, uncontrolled arrhythmias, or cerebrovascular event within the past 3 months. They did not have fasting triglycerides >4.5 mmol/l or any important hematological or biochemical abnormality on routine screening.

Detailed cardiovascular phenotypic data were collected in the HACVD (Hypertension-Associated Cardiovascular Disease) substudy after approximately 1 year of treatment from a subset of 1,006 participants recruited from 2 centers (St. Mary's Hospital, London, and the Adapt Center, Beaumont Hospital, Dublin). Echocardiography was performed using an ATL HDI 5000 ultrasound machine equipped with a standard multifrequency transducer 12 months after initiation of treatment. All scans were performed by 3 experienced echocardiographers with the patient semirecumbent in the left lateral position. Interobserver reproducibility data were acquired and showed variations for all echocardiographic parameters between 3.5% and 7.5%. This is within acceptable limits as per previous studies (16). The LV measurements were performed using M-mode from the parasternal long-axis view according to the American Society of Echocardiography conventions (17), and LV mass was calculated according to the formula:

$$\text{LV mass} = 0.8\,[(\text{IVSd} + \text{LVIDd} + \text{PWTd})^3 - (\text{LVIDd})^3] + 0.6\ \text{g}$$

where IVSd = intraventricular septal thickness in diastole, LVIDd = left ventricular diameter in diastole, and PWTd = posterior wall thickness in diastole. This was then indexed for body surface area to give the left ventricular mass index (LVMI). Ejection fraction was calculated using the Teicholz formula from the parasternal long-axis view using M-mode, or if not technically possible, Simpson's rule was used.

Transmitral Doppler was assessed using a 5-mm sample volume placed at the tips of the mitral leaflets in passive end-expiration. A standardized loop of 10 cardiac cycles was downloaded to computer for off-line analysis of the early filling phase (E-wave) and the late filling phase (A-wave). The TDE was performed in the apical 4-, 2-, and 3-chamber views, with the 5-mm sample volume placed over the myocardium on the septal, lateral, and inferior walls at the level of the mitral annulus and the free wall of the right ventricle at the level of the tricuspid annulus. Using minimal gain settings, a series of 10 cardiac cycles were