Editorial

Hypertension, Heart Failure, and Ejection Fraction

William C. Little, MD

More than three quarters of patients with heart failure (HF) have antecedent hypertension. Hypertension appears to play an especially important role in HF associated with a preserved ejection fraction (EF) >0.50 (HFPEF). No proven specific therapy exists for HFPEF, but treatment of systolic hypertension in the elderly (the group at greatest risk for developing HFPEF) reduces the risk of developing HF by about one half. The current issue of Circulation contains an important analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) on the effect of the initial drug used to treat hypertension on the subsequent risk of HF requiring hospitalization stratified by EF.

ALLHAT studied >42 000 hypertensive patients over 55 years of age with at least 1 other coronary artery disease risk factor. The patients were randomized to receive the initial treatment of their hypertension with a calcium channel blocker (amlodipine), an angiotensin-converting enzyme (ACE) inhibitor (lisinopril), an α-adrenergic blocker (doxazosin), or a thiazide diuretic (chlorthalidone). As expected, many of the patients (40% at 5 years) required the addition of other medications to control their hypertension.

Davis et al identified in the ALLHAT patients 1367 hospitalizations classified as being for HF on the basis of a review of the hospital records. Two thirds of these patients had a determination of their EF. This study includes 3 key findings. First, nearly one half of the patients had HFPEF. As expected, these were frequently older women. Second, the patients with HFPEF had a high mortality, but not as high as those who subsequently developed HF with reduced EF <0.50 (HFREF). The third and most important finding was that initial treatment of hypertension with a thiazide diuretic reduced the risk of HFPEF compared with the other therapies. Among patients who subsequently developed HF with a reduced EF, the thiazide and ACE inhibitor were equally effective in reducing the risk of HF.

The EF was not measured at the time of entry into the study. Because patients were enrolled only if they had no history of HF or reduced EF, we can speculate that most had a normal EF on entry. In treating a patient with hypertension who has a low EF, we can safely assume that if HF subsequently develops, it will be associated with a reduced EF. The finding that using an ACE inhibitor or a thiazide as initial therapy was equally effective in patients who developed HF with a reduced EF is consistent with the previous observations that using an ACE inhibitor in patients with an EF <0.35 reduces the risk of subsequently developing HF. Thus, an ACE inhibitor should be included in the initial therapy in patients with hypertension and clearly reduced EF.

In the absence of knowledge of the EF or a normal EF, we do not know if a patient with hypertension will subsequently develop HFPEF or HFREF. In these patients, the initial use of a thiazide would be reasonable. Adding an ACE inhibitor as a second step, if needed, would be reasonable and is supported by the recent Hypertension in Very Elderly Trial (HYVET).

It is possible that the ALLHAT analysis overestimates the frequency of HFREF in hypertensive patients by including many men and patients as young as 55 years. We do not have information on how many of the HFREF patients had intervening myocardial infarctions that could be a reason why the EF was reduced. It is important to note that the presence of another coronary disease risk factor was an entry criterion for the study, and about half of the patients had clinical evidence of atherosclerotic cardiovascular disease. If an older population with more women and without clinical evidence of coronary disease were studied, it is likely that an even higher portion of the HF would be HFPEF.

The analysis of the ALLHAT population was accomplished using the usual EF cut point of 0.50. Those above 0.50 were considered to have HFPEF and those below to have HFREF. The use of 0.50 as the “lower limit” of normal is convenient because it is an easily remembered round number. However, the true lower limit of normal left ventricular EF is higher. For example, when measured by magnetic resonance imaging, the lower 5% confidence limit of normal is 0.59 in men and 0.60 in women. Similarly, Lam et al found that the EF assessed by echocardiography in a large sample (N =617) of healthy adults from the Olmstead County general population was 0.63±0.05 (mean±SD). Thus, if EF >0.50 is used as the definition of HFPEF, it will include some patients whose EF is lower than normal.

Putting a patient with an EF of 0.51 in one group (HFPEF) and a patient with an EF of 0.49 in another group (HFPEF) is making a distinction without a difference. This is especially apparent when one considers the size of the potential error in measuring EF. Furthermore, in the ALLHAT analysis, 201 patients only had a subjective evaluation of EF as normal, borderline, or impaired.

The patients in ALLHAT did not neatly fall into 2 groups divided at an EF of 0.50. Davis et al reported that 44% had EF >0.50, 21% had EF between 0.40 and 0.50, 17% between
0.30 and 0.40, and 21% with EF <0.30. This pattern is consistent with large American and European registries, which demonstrate that patients hospitalized with HF have the entire range of EFs, including normal, mildly reduced, and severely reduced. Thus, HF should no longer be equated with a low EF because HF can occur with any level of EF. Unfortunately, in the past, the large randomized studies that guide therapy of HF used an EF <0.35 or 0.30 as an entry criterion.

Left ventricular EF has been used as the clinical gold standard for systolic function, and patients with EF >0.50 have been considered to have normal systolic function. However, EF is not always a clear-cut measure of systolic contractile function. For example, many patients with HFPEF may have subtle abnormalities of systolic contractile function. Furthermore, the EF can be reduced in a patient with normal systolic function by markedly elevated left ventricular afterload.

The EF is calculated as stroke volume divided by end-diastolic volume. Thus, a reduced EF indicates that the end-diastolic volume is increased relative to the stroke volume. In the absence of shock or marked tachycardia, most stable patients with HF have near normal stroke volumes regardless of EF. Thus, in such patients, the degree of reduction of EF indicates the amount of left ventricular dilation. It is now clear that patients may present with HF having no left ventricular dilation (normal EF and end-diastolic volume) or moderate or severe dilation (normal EF and end-diastolic volume) or severely reduced (markedly increased EF and end-diastolic volume). It is possible that patients who present with HF and who have the entire range of EFs have a fundamentally different disease than patients who do not develop clinically apparent HF until after the left ventricle has dilated and the EF has fallen. This concept is supported by the differing effects of an ACE inhibitor in preventing the development of HFPEF and HREF.

In conclusion, patients with antecedent hypertension may be subsequently hospitalized with HF with the entire range of left ventricular EFs. Treating hypertension is effective in reducing the risk of developing HF. Initiating therapy with a thiazide diuretic in patients with hypertension and a normal EF is further supported by this important analysis of the ALLHAT data by Davis et al.

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References


