Physicians make the diagnosis of heart failure when patients present with exercise intolerance that is limited by dyspnea, fatigue, or both and that can be attributed to an identifiable abnormality of cardiac function. Patients with exertional symptoms attributable to severe primary valvular disease respond symptomatically and prognostically to surgical valve repair or replacement. Patients with exertional dyspnea attributable to left ventricular systolic dysfunction exhibit fluid retention and neurohormonal activation and respond both symptomatically and prognostically to the administration of diuretics, inhibitors of the renin-angiotensin system, \( \beta \)-blockers, and aldosterone antagonists. Although circulating levels of brain natriuretic peptide (BNP) can be measured in these 2 groups of patients, there is no reliable or persuasive evidence that such measurement provides a useful guide to the selection of patients to be treated, the medical or surgical interventions to be prescribed, or the timing of surgery or the doses of drugs to be achieved.\(^1\)

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Many elderly patients experience symptoms of exertional dyspnea or fatigue but have no evidence of valvular disease or left ventricular systolic dysfunction. The majority are elderly women who are physiologically deconditioned and frequently have hypertension, obesity, atrial fibrillation, anemia, coronary artery disease, chronic obstructive pulmonary disease, and chronic renal insufficiency.\(^2\) Which of these abnormalities is responsible for these patients’ exercise intolerance? Although their symptoms and survival are largely determined by their comorbid conditions,\(^3,4\) physicians frequently focus on the heart in their pursuit of a cause of exertional symptoms and poor prognosis. Noninvasive cardiac imaging typically reveals a preserved left ventricular ejection fraction, occasionally shows left ventricular hypertrophy and left atrial enlargement, and often demonstrates changes in echocardiographic variables that suggest an increase in left ventricular filling pressure and a reduced rate of blood flow into the left ventricle during diastole.\(^5\) The finding that left ventricular filling pressures may be increased in these patients leads the physician to assign the diagnosis of heart failure—but with a preserved left ventricular ejection fraction.

What is the nature of the cardiac disorder in patients who are given the diagnosis of heart failure with a preserved ejection fraction (HFPEF)? Conventional wisdom holds that patients with HFPEF have an abnormality of relaxation that impairs the ability of the left ventricle to passively fill with blood during diastole, leading some to apply the term diastolic dysfunction to describe the clinical syndrome in these patients.\(^6\) Certainly, young and middle-aged patients with certain hypertrophic cardiomyopathies fulfill the conventional criteria for diastolic dysfunction in that they have small left ventricles that cannot fill, have low blood pressures, are intolerant of diuretics, and show an upward and leftward shift in the left ventricular diastolic pressure-volume relation.\(^7\) However, most elderly women with exertional dyspnea and fatigue have increased age-adjusted left ventricular dimensions, have high blood pressures, respond favorably to diuretics, and do not exhibit an abnormal shift in the left ventricular diastolic pressure-volume relation.\(^7,8\) Although the rapidity of ventricular inflow and indices of ventricular relaxation may be slowed and myocardial stiffness may be increased, such abnormalities are likely to be the result (rather than the cause) of the elevation of ventricular filling pressures. Left ventricular filling pressures in patients with HFPEF are elevated not because the left ventricle cannot fill, but because it is overfilled, most likely as a result of the interplay of numerous comorbid conditions that can affect the level and distribution of circulating blood volume and ventricular-vascular coupling.\(^9\)

How can a physician know whether exertional dyspnea or fatigue in an elderly woman is related to a cardiac disorder or to a combination of obesity, physical deconditioning, atrial fibrillation, and chronic renal insufficiency? Because increased left ventricular filling pressures may be associated with increased levels of BNP in patients with impaired left ventricular systolic function,\(^1\) some have suggested that increased levels of BNP also could be used to identify patients with cardiac-related dyspnea who have preserved left ventricular systolic function.\(^10,11\) Unfortunately, levels of BNP are strongly influenced by both age and sex as well as by the presence of obesity, atrial fibrillation, anemia, hypertrophy, pulmonary disease, and renal insufficiency and, thus, are likely to be extremely difficult to interpret in elderly women with exertional symptoms and multiple comorbid conditions.\(^12,13\)

Plasma levels of BNP may be strikingly increased in elderly...
women with hypertension and renal insufficiency who do not have exertional symptoms or clinical evidence of heart failure.\textsuperscript{13,14} No study has established a threshold level of BNP or N-terminal pro-BNP that is reliably indicative of the presence of heart failure in these patients. Nevertheless, it is generally believed that the higher the level of BNP or N-terminal pro-BNP, the more likely it is that exertional dyspnea or fatigue in an elderly woman is related to heart failure rather than to other comorbid conditions.

Because of this belief, recently launched clinical trials of pharmacological interventions that target diastolic function in patients with HFPEF have required patients to have markedly increased plasma levels of BNP or N-terminal pro-BNP as a criterion for enrollment.\textsuperscript{15} The requirement that eligible patients have unequivocally increased levels of BNP serves 3 potentially useful purposes: (1) markedly increased levels of BNP may reflect increased left ventricular filling pressures, even in women with advanced age and renal insufficiency; (2) increased levels of BNP may identify patients at increased risk of experiencing a major cardiac event, thus reducing the sample size needed to detect a clinically relevant treatment effect; and (3) increased levels of BNP may identify patients most likely to respond favorably to drugs that act by interfering with the renin-angiotensin system. Unfortunately, only a small proportion of elderly patients who have received a diagnosis of HFPEF have plasma levels of BNP high enough to qualify for entry into many current trials; the rarity of these patients has made recruitment for these studies very difficult.

The findings of Anand et al.,\textsuperscript{16} published in this issue of Circulation: Heart Failure, challenge the current assumption that patients with HFPEF must have high circulating levels of BNP or N-terminal pro-BNP to respond favorably to treatment. The authors carried out an unplanned subgroup analysis of the Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial, which evaluated the effect of the angiotensin receptor blocker irbesartan in patients with HFPEF. Patients with N-terminal pro-BNP levels greater than the median had a high risk of dying of or being hospitalized for heart failure, and this risk was not affected by irbesartan (placebo, 23.7%; irbesartan, 27.0%). In contrast, patients with lower levels of N-terminal pro-BNP were at low risk (11.0%) of dying of or being hospitalized for heart failure if treated with placebo and experienced a further reduction in risk (to 6.6%) if treated with irbesartan. Amazingly, >90% of the patients in the low N-terminal pro-BNP subgroup did not experience a clinically important heart failure event during >4 years of follow-up, even though at entry into the trial all patients had reportedly been recently hospitalized for heart failure or had class III or IV symptoms. Thus, irbesartan reduced the risk of heart failure events only in patients already unlikely to experience heart failure events.

How can the findings reported by Anand et al be explained? The observation that irbesartan was effective in patients unlikely to experience a heart failure event during long-term follow-up suggests that most of the patients in the irbesartan-responsive subgroup did not truly have heart failure at the time of their entry into the I-PRESERVE trial. Such a conclusion is supported by the finding that the mean plasma level of N-terminal pro-BNP in this subgroup was <150 pg/mL, a value that is well within the range of values seen in elderly women with comorbid conditions who do not have heart failure.\textsuperscript{8–10} This conclusion also is consistent with the observation that at the time of entry into the study, only a minority of the patients in the irbesartan-responsive subgroup had pulmonary congestion on chest radiograph or a recent history of hospitalization for heart failure. Interestingly, in the HOPE (Heart Outcomes Prevention Evaluation) trial, inhibition of the renin-angiotensin system for 4 years in patients with vascular disease and a preserved left ventricular ejection fraction but without heart failure or known diastolic dysfunction was shown to reduce the risk of new-onset heart failure.\textsuperscript{17} Such an effect was attributed to antagonism of the deleterious effects of angiotensin on vascular function and not to any direct effect of treatment on ventricular relaxation. Could irbesartan have exerted a similar benefit in patients with vascular disease and a preserved left ventricular ejection fraction at low risk of heart failure in the I-PRESERVE trial? Possibly, but this hypothesis cannot explain why the analyses presented by Anand et al\textsuperscript{16} the presumed benefits of irbesartan were totally abolished in patients with markedly elevated levels of N-terminal pro-BNP, most of whom had had a recent hospitalization for heart failure and pulmonary congestion at the time of entry into the trial. Does the presence of heart failure blunt the vascular benefits of irbesartan?

The difficulty in reconciling the results presented by Anand et al with the known effects of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers suggests another explanation for their findings; specifically, their subgroup analyses may represent a statistical fluke resulting from the play of chance. Post hoc subgroup analyses that identify a responder group among patients enrolled in a clinical trial are notorious for yielding spurious results, particularly when they are carried out in large-scale studies whose overall results show no benefit of treatment.\textsuperscript{18} The likelihood of replication is particularly low when the favorable effect is seen in the subgroup with the fewest number of events, as was the case with Anand et al.\textsuperscript{16} Advocates of the Anand hypothesis might dispute arguments about the play of chance by pointing out that the \(P\) value for the interaction between N-terminal pro-BNP and treatment was statistically significant across several clinically relevant end points. However, the statistical test for interaction has not been reliable in identifying valid subgroup effects in previous heart failure trials. A highly significant interaction between ischemic etiology and treatment reported in a large-scale heart failure trial with amlodipine could not be confirmed in a subsequent study.\textsuperscript{19} Similarly, a highly significant interaction between geographical location and treatment reported in a large-scale heart failure trial with metoprolol also has been discounted as a statistical fluke.\textsuperscript{18} Indeed, the findings of Anand et al are already known to be inconsistent with the observations of the PEP-CHF (Perindopril in Elderly People with Chronic Heart Failure) trial,\textsuperscript{20} which reported that patients with HFPEF who had higher levels of N-terminal pro-BNP had a somewhat more (not less) favorable response to perindopril than those with lower levels of N-terminal pro-BNP.

How should physicians respond to the subgroup findings from the I-PRESERVE trial? Physicians who are impressed
by small P values regardless of their context or reliability may actually believe in the apparent benefit of irbesartan proposed by Anand et al. As a result, they may start to routinely measure levels of N-terminal proBNP in elderly women with exertional symptoms in the hope of finding those with relatively normal values and treating them with irbesartan. Following such a strategy would constitute a horrific and irresponsible interpretation of the data presented by Anand et al, who admirably do not suggest that their peculiar findings merit routine measurement.

Instead, the findings of I-PRESERVE should raise serious questions about the utility of measuring N-terminal proBNP in elderly patients with exertional symptoms and a preserved left ventricular ejection fraction. Because interpretation of levels of N-terminal proBNP in these elderly women is hopelessly confounded, measurement of the peptide is likely to provide a convenient, but misleading, explanation for their symptoms, which will forever encumber these patients with a diagnosis they do not have and their physicians cannot treat.

Disclosures

None.

References


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