versus dyspnea on exertion because, as detailed in the limitations section, symptoms besides bendopnea were ascertained by patient recall over the preceding week, whereas bendopnea was assessed on the day of the right heart catheterization. We agree that it will be important to determine the prevalence and significance of bendopnea in other patient populations including those who do not have heart failure. However, we do not concur that the nomenclature “pseudobendopnea” should be used for this symptom in patients without heart failure. As a rationale for our opinion, we give the example of an obese patient without heart failure who gets short of breath in the supine position. In such a setting, the symptom would still be termed orthopnea rather than pseudoorthopnea. In terms of where to go from here, we hope future studies will determine whether ascertainment of bendopnea can improve clinical decision making.

We are aware of the case series of 3 patients with heart failure referenced by Dr. Brandon. Although it is not particularly useful to debate primacy of ideas, it is worth reiterating, as denoted in our publication, that our study had been presented at the Samuel A. Levine Young Clinical Investigator Award competition at the American Heart Association Scientific Sessions in November 2012 (2), well before Brandon’s publication in August 2013. Additionally, we are concerned that he may have reached an inaccurate conclusion as to the hemodynamic basis of bendopnea. Specifically, he reported that the estimated pulmonary capillary wedge pressure (PCWP) increased substantially more with bending in patients with bendopnea than in those without bendopnea. In fact, based on our study of invasively measured hemodynamics, the PCWP increased the same in patients with or without bendopnea; rather, the hemodynamic feature that distinguished those with the symptom was that patients with bendopnea had a higher baseline PCWP before bending forward. We believe he may have been led astray by an extremely small sample size, as well as by the use of low-resolution physiological techniques. Others have shown that E/E’ in the supine position may not accurately reflect left ventricular filling pressures in patients with advanced heart failure (3), and its utility in the bent position is entirely unknown. Additionally, its use in assessing changes in PCWP is even more imprecise (4). A larger series that utilized echocardiographic assessment of filling pressures in patients with or without bendopnea, published in preliminary form, also reached a different conclusion from Brandon (5).

We are intrigued by Dr. Brandon’s observation that watery post-nasal drip may be a marker of volume overload and look forward to a carefully performed hemodynamic study that characterizes this symptom.

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What Is Normal in HFpEF?

The Case for HFpEF

We have come a long way in the diastolic heart failure (HF)–HF with normal systolic function—HF with normal ejection fraction (EF)–HF with preserved EF world (1). Just 2 decades ago, we couldn’t agree whether this syndrome existed. This skepticism has been replaced by general recognition that it not only exists, but that it constitutes a sizeable proportion of the HF population and is a deadly disease. However, this is where the consensus seems to end—we can’t agree on what to call it, nor if it is a distinct syndrome or part of the same continuous spectrum as HF with reduced EF (HFrEF).

Perhaps the purest description of this syndrome was the first by Topol et al. (2) in 1985, where the term hypertensive hypertrophic cardiomyopathy of
the elderly was used to describe 21 elderly, predominantly female hypertensive patients with HF symptoms, left ventricular (LV) hypertrophy, high EF, and diastolic dysfunction. Robust epidemiological evidence has confirmed that this is a condition predominantly affecting elderly hypertensive women.

The term diastolic HF was coined to underscore the hallmark of LV diastolic dysfunction seen in most, if not all, patients. The diastolic/systolic HF distinction became popular because it was easy to use, neatly divided the HF world into 2 halves, and reflected the leading pathophysiological factor believed to cause each syndrome. However, population-based studies showed that LV diastolic dysfunction was present in a large proportion of adults without HF, and that patients with “systolic HF” were even more likely to have diastolic dysfunction compared to patients with so-called “diastolic HF.”

Thus entered the term HF with normal systolic function (HFNSF)—a term that did not make assumptions regarding underlying disease mechanisms and could therefore accommodate emerging evidence of pathophysiological processes extending beyond diastolic dysfunction to vascular, atrial, pulmonary, right-sided, and noncardiovascular organ (e.g., renal) dysfunction. However, HFNSF was deemed suboptimal when it became apparent that systolic function was not necessarily normal in these patients, and that myocardial contractile dysfunction existed despite normal overall chamber pump function.

The term HF with normal EF (HFNEF) was then embraced and adopted in guidelines. However, EF is a continuous variable with a normal distribution within the population, and the threshold value to define “normal” versus “reduced” EF is arbitrary. Indeed, Framingham Heart Study participants with an EF of 40% to 50% were at greater risk of HF and death compared with those with an EF >50% (3), and distinct physiological differences were described among Chinese with HF and EF >55% versus EF of 40% to 55% (4).

Furthermore, the “normal” distribution shifts in the very population most affected by this syndrome: data from MESA (the Multi-Ethnic Study of Atherosclerosis) showed that...

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![Figure 1: Age- and Sex- Related Differences in “Normal” LVEF](image-url)

Data from 5,004 participants undergoing cardiac magnetic resonance imaging in MESA (the Multi-Ethnic Study of Atherosclerosis), showing how ejection fraction (EF) increases with age as left ventricular (LV) end-diastolic volume (LVEDV) (in the denominator) decreases out of proportion to stroke volume (numerator). Figure reproduced from Cheng et al. (5). LVESV — left ventricular end-systolic volume.
Atherosclerosis) (5) has shown that EF “normally” rises with age and is higher in women than men in the general population (Figure 1). The key issue is that EF is a fraction, which will increase as the heart remodels and the LV end-diastolic volume (denominator) shrinks out of proportion to the stroke volume (numerator). This prompts the question, what is the normal EF in an elderly female patient who has HF? If “normal” is a higher EF in these patients, then by using an age- and sex-neutral cutoff of 50% to define HFNEF, we are effectively selecting for elderly women who actually have “relatively abnormal” EF for their age and sex. By extrapolation, this concept may apply to all subjects with smaller heart sizes (smaller LV end-diastolic volumes)—not just women (versus men) or those with concentrically remodeled ventricles (elderly, hypertensive), but also subjects of smaller body size in general.

One may stop here and argue that we should not be looking at EF in the first place (1). However, the most significant counterargument to this is that clinical trials using EF to stratify HF have revealed 2 phenotypes that respond differently to the same therapy: renin-angiotensin-aldosterone system blockade improves survival in HFpEF, but not in HFNEF. Any classification that can guide treatment would be useful in clinical practice: a well-accepted example being the classification of myocardial infarction into ST-segment elevation versus non-ST-segment elevation myocardial infarction, as opposed to the outdated terminology Q-wave versus non-Q-wave myocardial infarction. Although we still have a long way to go before we understand the pathophysiological differences between HFpEF and HFNEF as deeply as we do for ST-segment elevation versus non-ST-segment elevation myocardial infarction, recent studies have been revealing and continue to demonstrate differences at the cardiac chamber and ultrastructural levels, as well as the hemodynamic response to therapeutic interventions. Until we can effectively tease apart pathophysiological subtypes in HF using a different classification system of proven utility for clinical management and targeted therapy, we are left with our current system of using EF.

Hence, the case for the term HF with preserved EF (HFpEF), which makes no assumptions regarding what a normal EF is, and arguably rolls off the tongue more easily than “HF with relatively normal EF depending on age, sex, and body size” (HFRNEF-DASBS). Furthermore, the humble small p allows us to acknowledge the tongue-in-cheek nature of our arguments on semantics, with hidden emoticons as in HF:pEF. After all, regardless of favored nomenclature, we are united in our efforts to better understand, prevent, and treat this syndrome.

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REPLY: What Is Normal in HFNEF?
The Case for HFpEF

Dr. Lam makes many sensible and reasonable comments in response to my viewpoint, and it appears we are in agreement on most aspects. Of course, one can quibble about the definition of what is a truly “normal” ejection fraction (above 45%, 50%, or 55%), but it is curious that this objection is never raised when discussing the definition of heart failure with a “reduced” ejection fraction, although it can have equally important implications (1). Presumably, if one can define a reduced ejection fraction, then everything above that is fairly acceptable, and the generally recognized cutoff would appear to be 50%. However, “preserved” is definitely not the correct word to use because it is clear that in the condition some call “HFNEF,” the ejection fraction is not unchanging, but rather gradually falls; and whatever else is debatable, the definition of the word preserved is not arguable: it is generally accepted to mean something that is unchanged or “maintain (something) in its original or existing state” (OED) (2). It may appear to be nitpicking, but precision in the use of words is important, especially in science as well as politics (as George Orwell said if “thought corrupts language, language can also corrupt thought” [3]).