

EDITORIAL COMMENT

In Search of New Targets and Endpoints in Heart Failure With Preserved Ejection Fraction*



Barry A. Borlaug, MD

In *Search Of...* was an American television series broadcast in the early 1980s that tackled various unsolved mysteries and paranormal phenomena. The show's stated goal was to "suggest some possible explanations, but not necessarily the only ones, to the mysteries" examined in each episode. Around this very time in the world of medicine, cardiologists began to appreciate that many patients presenting with heart failure (HF) had a relatively preserved ejection fraction (HFpEF) (1). Seminal studies over the past 3 decades have shown us that diastolic dysfunction plays a central role in HFpEF, at least partially "de-mystifying" things, but we continue to search for and suggest other possible explanations. In this light, it has recently been established that many patients with HFpEF develop pulmonary hypertension (PH) and right ventricular dysfunction, and that these abnormalities independently contribute to adverse outcomes in this cohort (2-4). Perhaps novel therapies that target these abnormalities may hold promise in HFpEF.

SEE PAGES 459 AND 467

In this issue of *JACC: Heart Failure*, Al-Naamani et al. (5) present intriguing new data that supports this idea. The authors prospectively characterized 73 patients with HFpEF and PH undergoing invasive hemodynamic assessment between 2004 and 2012. According to recent consensus guidelines (6), the authors defined participants as having significant

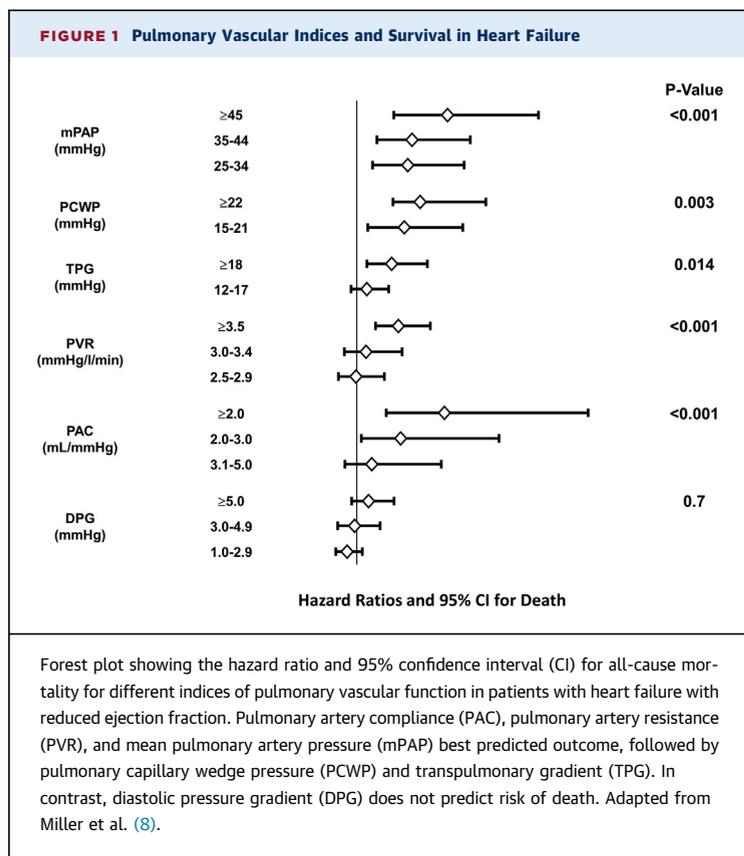
pulmonary vascular disease (PVD) if their diastolic pressure gradient (DPG) (pulmonary artery [PA] diastolic minus PA wedge pressure) was ≥ 7 mm Hg. The main goal was to determine if the presence of PVD in HFpEF was associated with adverse outcome. In addition, the authors evaluated other indices of PVD, including PA compliance (PAC) (stroke volume divided by PA pulse pressure), which better integrates pulsatile vascular load as well as downstream left heart filling pressures (7-9).

Over a median follow up of 3.6 years, there were 25 deaths (34%) (5). Notably, patients with elevated DPG (36% of the total) had similar outcome to those with normal DPG ($p = 0.7$), arguing against the importance of PVD in HFpEF. Receiver-operating characteristic analysis revealed DPG to be no better than flipping a coin to predict mortality (area under the curve: 0.5). In contrast, patients with low PAC (<1.1 ml/mm Hg) were found to have nearly 5-fold greater risk of death compared with those with higher compliance values ($p < 0.001$). Thus, it isn't that PVD is irrelevant in HFpEF, it simply appears that DPG is not the best way to define PVD in this cohort. The majority of participants also underwent vasodilator challenge. There were no adverse events, despite elevation in left heart pressures in many patients. A minority of subjects met criteria as responders, but their outcome was indistinguishable from nonresponders (5).

On the basis of a small number of studies, the 5th World Symposium on PH recommended that the DPG should be used to identify the presence or absence of PVD in people with HF (6). The data from Al-Naamani and colleagues, along with several other recent studies (5,10,11), raise serious questions with this approach. Indeed, analyzing previously published data from our group reveals that PAC greatly outperforms DPG to predict outcome in HF with reduced

*Editorials published in *JACC: Heart Failure* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Division of Cardiovascular Diseases, Department of Medicine, Mayo Clinic, Rochester, Minnesota. Dr. Borlaug has reported that he has no relationships relevant to the contents of this paper to disclose.



EF (Figure 1) (8). In everyday practice, the optimal approach to prognosticate and determine therapy likely requires integration of all pulmonary vascular function indices, as recently reviewed (11). However, entry criteria for trials need to be binary and easy to apply. Because PAC predicts outcome and because it improves with HF treatment, it represents both a target and entry criterion for trials to identify HFpEF patients at greater risk for events (5,8,9). Further study confirming these findings will be important moving forward.

In addition to the search for new targets in HFpEF, there is also a need to identify trial endpoints that are both clinically meaningful and deliverable in a Phase 2 trial. Pivotal trials evaluating the time-tested endpoint of cardiovascular death or HF hospitalization have consistently produced neutral results in HFpEF (1). There are many reasons why this may be, but at least part of the explanation resides in the fact that many of deaths and hospitalizations in HFpEF are not cardiovascular in origin. What alternative endpoints might be considered that would reflect the disease and be meaningful to patients? People with HFpEF complain of dyspnea and fatigue during activity, and improvement in the pathophysiologic

derangements causing exercise intolerance should improve aerobic capacity, but what is known regarding the prognostic importance of exercise capacity in patients with HFpEF?

Zotter-Tufaro et al. (12) tackled this important question in another interesting paper in this issue of *JACC: Heart Failure*. The authors enrolled 142 patients with HFpEF and PH in a registry over 2.5 years. Participants underwent right heart catheterization, 6-min walk test, and echocardiography and were followed prospectively for the combined endpoint of HF hospitalization or all-cause mortality. Over a mean follow-up of 14 months there were 43 events (30%). Lower 6-min walk distance (6MWD) predicted increased event rates, consistent with another recent study (13), but subjects with lower 6MWD also displayed characteristics known to be associated with adverse outcome in HFpEF, including older age, diabetes, higher New York Heart Association functional class, and more prior HF hospitalizations, which confounds interpretation of this finding (12). Intriguingly, patient-reported dyspnea severity during the walk test predicted higher event rates as well (hazard ratio: 1.4; $p < 0.001$). These results support the use of objective exercise performance (6-min walk) and subjective symptoms during exercise (Borg dyspnea scores) as markers of risk and perhaps more importantly valued patient-centric endpoints for trials.

Zotter-Tufaro et al. (12) also examined the correlates of 6MWD (12). The authors refer to these correlates as determinants, but of course causality cannot be discerned in a cross-sectional study such as this. Lower 6MWD was associated with increasing age, higher body mass, beta-blocker and diuretic use, and prior HF hospitalization. Resting hemodynamics were also correlated with exercise capacity: with inverse relationships between 6MWD and PA pressure, right and left heart filling pressures, transpulmonary gradient, and pulmonary vascular resistance. Complementing the outcome findings of Al-Naamani et al. (5), PAC was found to be directly correlated with 6MWD by Zotter-Tufaro et al. (12). Resting cardiac output was not associated with 6MWD, but, as recently demonstrated, exercise rather than baseline cardiac output is the more relevant factor to consider in this setting (14). Left ventricular biopsy was obtained in a subset of subjects, and the extent of tissue fibrosis was also correlated with 6MWD, though the extent of fibrosis observed seems higher than other reports in HFpEF (15).

The main limitation of both studies is sample size and consequently a relatively small number of events. This increases the risk of Type II error and

limits the ability to determine whether the outcome predictors tested are independent of other variables. Thus, one could posit that DPG might have been predictive with a much larger sample, but the fact that PAC was predictive of mortality in a relatively small sample, particularly in light of other congruent studies, is important. Similarly, in the Zotter-Tufaro et al. (12) study, one cannot exclude some contribution from the many baseline differences in patients with low 6MWD. However, the patient-centric aspect of this endpoint largely allays this concern. If one were to ask a person if he or she would want to take a drug that allowed him or her to walk 40 m farther in 6 min, the individual would not bat an eye. However if one shared that this improvement might translate to greater ability to participate in the activities of daily

life, in addition to prolonging survival, that person might jump at the chance.

Just as *In Search Of...* didn't fully resolve the mysteries surrounding the Loch Ness monster and Bigfoot, we have yet to fully comprehend the mechanisms and treatment of HFpEF. However, the studies of Al-Naamani et al. (5) and Zotter-Tufaro et al. (12) have taken us another step forward in this search, by identifying new targets for intervention and new ways to test the efficacy of these interventions in this growing population of patients.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Barry A. Borlaug, Mayo Clinic and Foundation, 200 First Street Southwest, Rochester, Minnesota 55905. E-mail: borlaug.barry@mayo.edu.

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KEY WORDS diastole, exercise, heart failure, outcomes, pulmonary hypertension