EDITORIAL COMMENT

Minding the Gap in Heart Failure

Understanding the Pulse Pressure in Reduced Versus Preserved Ejection Fraction*

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High pulse pressure (PP) is traditionally viewed as a marker of arterial stiffening resulting from the premature arrival of the reflected arterial pressure wave augmenting the central aortic pressure waveform. Indeed, a widened PP is a known risk factor for cardiovascular events, including new-onset heart failure (HF) (1). In established HF, however, the prognostic impact of PP is less straight forward: in asymptomatic and mildly symptomatic patients with HF with reduced ejection fraction (HFrEF) in SOLVD (Studies of Left Ventricular Dysfunction) (2), higher PP was linked to increased mortality; whereas in the advanced HFrEF populations of VMAC (Vasodilation in the Management of Acute Congestive Heart Failure) (3), PRIME-II (Second Perspective Randomized Study of Ibopamine on Mortality and Efficacy) (4), CAPRICORN (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction Study) (5), and EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival) study (6), lower PP was associated with higher mortality. To add to the complexity, left

ventricular (LV) EF has recently been shown to importantly modify the association between PP and mortality in HF (7). In the first investigation of the prognostic value of PP in HF with preserved ejection fraction (HFpEF) from 22 of 31 studies in the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) meta-analysis, there was a highly significant interaction between EF category (HFrEF versus HFpEF, categorized at an EF cut off of 50%) and the relationship between PP and 3-year mortality (7). Lower PP was an independent predictor of mortality in HFrEF, but higher PP was related to higher crude mortality in HFpEF, an association that was attenuated after multivariable adjustment. Intriguingly, in subset analyses of acute (versus chronic) HFpEF, as well as HFpEF without atrial fibrillation, lower PP was related to increased mortality risk (Table 1).

Against this backdrop of diverse findings in HF, the study by Laskey et al.(8) in this issue of *JACC: Heart Failure* is certainly welcome. In the large cohort of hospitalized patients with HF, regardless of EF in the Get With the Guidelines-Heart Failure (GWTG-HF) program, the authors showed that brachial PP at hospital discharge had a U-shaped relationship to 1-year mortality in both HFrEF and HFpEF (defined by an EF cut off of 40%) (**Figure 1**, top panels), with a risk nadir at a PP of 50 mm Hg. In HFrEF, higher PP was independently associated with lower mortality risk when PP was <50 mm Hg but higher mortality risk when PP was ≥50 mm Hg. In HFpEF, the association between PP and mortality risk did not reach statistical significance when PP was <50 mm Hg, but higher PP was independently related to increased mortality when PP was ≥50 mm Hg and systolic blood pressure (SBP)

TABLE 1 Relationship Between Pulse Pressure and Mortality Risk

| | HFrEF | | HFpEF | |
| | GWTG-HF (8) | MAGGIC (7) | GWTG-HF (8,9) | MAGGIC (7) |
HF setting	Hospitalized HF (Multicenter U.S. Registry)	Acute and Chronic HF (22 Observational Studies and Clinical Trials)	Hospitalized HF (Multicenter U.S. Registry)	Acute and Chronic HF (22 Observational Studies and Clinical Trials)
EF cut off	<40%	<50%	≥50%	≥50%
Sample size	15,716	22,038	18,897	5,008
Age, yrs	79	≈65	82	≈69
% of Women	40.0	25	67.3	49
% of Hypertension	73.1	43.5	81.3	63
% of Diabetes	39.3	25.6	40.6	27
% of Atrial fibrillation	36.1	14.8	40.6	23.4
PP, mm Hg	52 (median)	52	60	62
PP measurement	At or closest to discharge	Variable	At or closest to discharge	Variable
SBP, mm Hg	116 (range, 104–131)	≈128 (mean)	126 (range, 112–142)	≈139 (mean)
DBP, mm Hg	64 (range, 57–72)	≈76 (mean)	64 (range, 57–72)	≈79 (mean)
Crude % of mortality	37.5% at 1 yr	22.6% at 3 yrs	35.6% at 1 yr	16.5% at 3 yrs
Association between PP and mortality*	Nonlinear (inverse at PP <50 mm Hg, direct at PP ≥50 mm Hg)	Inverse (HR increased in quintile 3 [46–53 mm Hg], 2 [40–45 mm Hg], and 1 [2–39 mm Hg] relative to quintile 5)	Direct, significant interaction with SBP	Direct in unadjusted analysis; nonsignificant in adjusted models for overall cohort; significant inverse relationship in HFpEF without AF and acute HFpEF

*Adjusted for age, sex, ischemic cause, atrial fibrillation, hypertension, and diabetes (both studies), as well as race, insurance status, anemia, stroke/transient ischemic attack, hyperlipidemia, chronic obstructive pulmonary disease or asthma, peripheral artery disease, renal insufficiency, smoking, SBP on admission, heart rate, SBP on discharge, serum sodium, blood urea nitrogen, hospital characteristics (region, type, number of beds, rural vs. nonrural), and defect-free compliance score (GWTG-HF only).

AF = atrial fibrillation; DBP = diastolic blood pressure; EF = ejection fraction; GWTG-HF = Get With the Guidelines-Heart Failure; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; MAGGIC = Meta-Analysis Global Group in Chronic Heart Failure; PP = pulse pressure; SBP = systolic blood pressure.

was ≥140 mm Hg. Furthermore, the effect of PP on mortality increased with increasing SBP. Thus the study by Laskey et al.(8) adds the following novel concepts in thinking about the PP gap in HF: 1) the existence of a nonlinear relationship with increased mortality risk at both ends of the PP distribution; 2) the independent prognostic value of PP in HFpEF; and 3) the important influence of SBP on the latter relationship. Of note, effect sizes were small (albeit with strong statistical significance due to large numbers), and results were not robustly achieved when PP was modeled as a categorical variable.

At face value, it may be difficult to reconcile the current GWTG-HF results with those of the prior MAGGIC meta-analysis. However close inspection of the 2 studies, using a similar EF cut off of 50% to define the HFpEF groups and based on prior published data from GWTG-HF (9), provides further insights (Table 1, Figure 1). Immediately obvious are the differences in patient populations studied. On average, the GWTG-HF cohort was older and sicker (with greater comorbidity burden and higher crude mortality) than the MAGGIC cohort regardless of EF group, consistent with real-world patients in the former and significant proportion of clinical trial patients in the latter. Other differences include variable timing of PP measurement, as well as differences in analytical methods and statistical modeling. However, side-by-side comparisons of the hazard plots from both studies revealed some consistencies (Figure 1): in HFrEF, the mortality risk starts to increase at a PP of <54 mm Hg in MAGGIC, consistent with the increased mortality with PP of <50 mm Hg in GWTG-HF. Above the risk nadir of ~50 mm Hg, the up-sloping limb of the U-shaped relationship observed in GWTG-HF, but not in MAGGIC, may be related to enrichment by much older patients with the highest PP in GWTG-HF. Age-related increases in PP are well described and portend a poor prognosis in the elderly (10). In HFpEF, inspection of the hazards plots show similar patterns in both studies, where the HFpEF plots are of similar shape but shallower (lower gradients of risk) than the respective HFrEF hazards plots in each study. The independent prognostic impact of PP in GWTG-HF, but not in MAGGIC following multivariable adjustment, may be related to larger numbers of HFpEF in GWTG-HF (more than triple the number in MAGGIC). To address the issue of timing of PP measurement, it would have been useful to know whether consistent results were obtained using the PP on admission rather than at discharge in GWTG-HF.

FIGURE 1 Association Between Pulse Pressure and Mortality in HFrEF and HFpEF
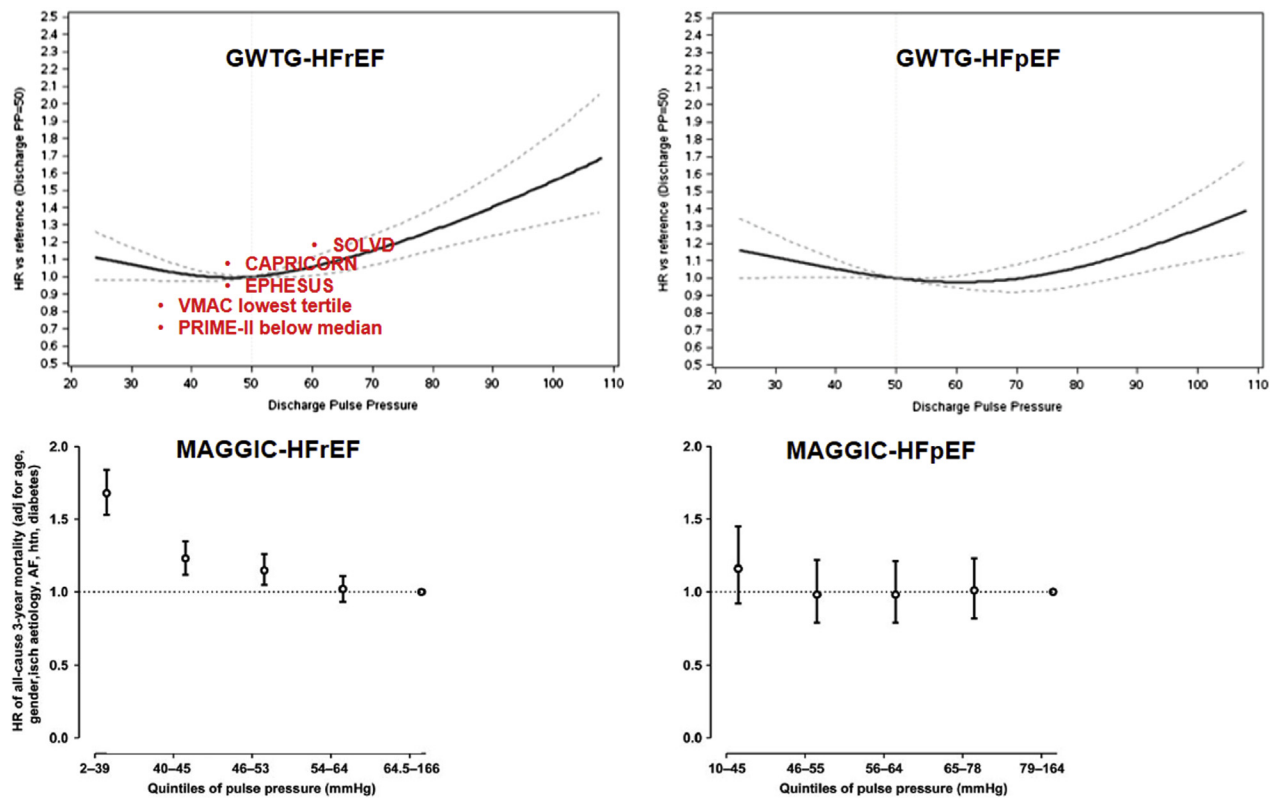
AF = atrial fibrillation; CAPRICORN = Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction Study; EPHESUS = Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival; GWTG = Get With the Guidelines-Heart Failure program; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; htn = hypertension; isch = ischemia; MAGGIC = Meta-Analysis Global Group in Chronic Heart Failure; PP = pulse pressure; PRIME II = Second Perspective Randomized Study of Ibopamine on Mortality and Efficacy;SOLVD = Studies of Left Ventricular Dysfunction; VMAC = Vasodilation in the Management of Acute Congestive Heart Failure. Adapted with permission from Laskey et al. (8) and Jackson et al. (7).

The U-shaped relationship of PP with mortality in GWTG-HFrEF helps to fill gaps in understanding divergent results from other previous studies. Beyond considerations of acuity of HF presentation, severity of disease, and LVEF, the absolute PP in previous studies (and hence their positions on the curve in **Figure 1**) may explain some differences in results. For instance, higher mean PP in the upper 2 quartiles of SOLVD (~52.5 mm Hg) places these patients in the ascending limb of the U (above the nadir of 50 mm Hg in **Figure 1**). Indeed a direct association between higher PP and increased mortality was observed in SOLVD, driven by the worse survival in the upper 2 PP quartiles (with no survival difference in the lower 2 quartiles as shown in the hazards plot) (2). In contrast, the inverse association of lower PP with higher mortality in VMAC was seen only in the lowest PP tertile (mean PP of 34 mm Hg), consistent with the descending limb of the U-shaped curve

below the nadir of ~50 mm Hg. Similarly, in PRIME-II, the inverse association between lower PP and higher mortality was most pronounced in those with PP <45 mm Hg, where mean PP was 34.5 mm Hg. In both CAPRICORN and EPHESUS, the mean PP was ~47 mm Hg in patients with advanced HFrEF, and inverse relationships between PP and mortality were observed.

Importantly, EPHESUS also showed that, whereas PP was inversely related to mortality, carotid-femoral pulse wave velocity (CPWV), a more direct measure of arterial stiffness, was directly related to mortality. The opposing effects of PP and CPWV demonstrate that the PP encompasses more than pure arterial stiffening, and is also influenced by LV function. The latter effect is obvious in severe HFrEF where the inability of the LV to generate adequate stroke volume results in a lower PP. In decompensated HFrEF, both low PP reflecting poor cardiac output and high

PP related to increased arterial stiffness (increased LV afterload) may be expected to predict worse outcomes. The novel U-shaped relationship of PP and outcomes in HFrEF reported by Laskey et al.(8) may reflect these opposing factors at play in hospitalized HFrEF patients, in whom the threshold PP of 50 mm Hg may be the "breakpoint" above which arterial stiffening plays a predominant role and below which reduction in cardiac output predominates. Of course, the limitations of a single time point measurement, suboptimal standardization in a registry setting, and lack of central PP measurements must be acknowledged in the interpretation of these results. Nonetheless, central and peripheral pressures have been shown to be highly correlated (11).

In the setting of normal cardiac output, one would expect PP to predominantly reflect arterial stiffening and therefore relate directly to outcomes. This is indeed the case in the general population and individuals with hypertension (6), as well as in HFpEF, as now shown by Laskey et al.(8). Arterial stiffening contributes to the pathophysiology of HFpEF via arterial-ventricular mismatching, particularly with exertion (12,13), afterload-induced diastolic dysfunction, and subendocardial ischemia. Exceptions to the direct relationship between PP and mortality include acute (versus chronic) HFpEF and HFpEF without atrial fibrillation in MAGGIC, caveats of subgroup analyses notwithstanding, both subgroups were postulated by the authors to have lower stroke volumes despite preservation of global LV chamber function, thus explaining the indirect association between PP and outcomes. In GWTG-HF, the nonlinear association between PP and outcomes may be related to inclusion of patients with midrange EF (40% to 50%); these patients constituted an appreciable proportion of GWTG-HF (n = 5,626 [14%]), were included in the hazards plot of HFpEF (**Figure 1**), and are expected to have mild reductions in stroke volumes that may have impacted PP (9). Unfortunately hazards graphs were not available for HFpEF restricted to those with EF ≥50%.

The prominent modifying effect of SBP in HFpEF deserves mention. SBP relates directly to effective arterial elastance [∼0.9 · SBP/stroke volume], a measure of total arterial load consisting of pulsatile load (PP) and mean resistive/steady flow load (mean arterial pressure). Increased effective arterial elastance in patients with HFpEF is matched by increased LV systolic elastance at rest (14); however, increases in arterial elastance out of proportion to that of LV elastance leads to arterial-LV mismatch during exertion (12,13). Although PP and SBP are highly correlated, Laskey et al.(8) demonstrated the independent contribution of PP to mortality (in models adjusted for discharge SBP), as well as the dependence of the magnitude of this contribution on SBP. The lack of stroke volume measurements or direct analyses of mean arterial pressure limit the interpretation of these results. However, by inference, the contribution of aortic stiffening/pulsatile load (PP) to mortality appears to be independent of peripheral resistance/steady load but enhanced in the presence of increased total load. The extent to which arterial-LV mismatch contributes to this risk augmentation, and the implications for afterload reduction as a therapeutic strategy, warrant further study.

These data fuel the debate regarding whether HFpEF and HFrEF are overlapping syndromes in a continuous spectrum versus 2 distinct syndromes. Proponents of the former concept will point to the similarly shaped hazards splines in HFpEF and HFrEF, both of which are U-shaped with a nadir at PP of ∼50 mm Hg. Opponents will highlight the independent direct association between PP and death in HFpEF in contrast to the nonlinear relationship in HFrEF. Of note, Laskey et al.(8) did not assess whether LVEF was a significant effect modifier of the association between PP and outcomes. Thus, it remains arguable whether the prognostic value of PP is more similar to or different from HFpEF and HFrEF in GWTG-HF.

In aggregate, these real-world data from the large GWTG-HF cohort serve as a call to mind the PP gap in HF, to carefully consider its hemodynamic significance (beyond arterial stiffening and including LV function), as well as to recognize its prognostic implications in both HFrEF and HFpEF.

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