Opposite Predictive Value of Pulse Pressure and Aortic Pulse Wave Velocity on Heart Failure With Reduced Left Ventricular Ejection Fraction

Insights From an Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) Substudy

Veronique Regnault,* Jérémy Lagrange,* Anne Pizard,* Michel E. Safar, Renaud Fay, Bertram Pitt, Pascal Challande, Patrick Rossignol, Faiez Zannad, Patrick Lacolley

Abstract—Although hypertension contributes significantly to worsen cardiovascular risk, blood pressure increment in subjects with heart failure is paradoxically associated with lower risk. The objective was to determine whether pulse pressure and pulse wave velocity (PWV) remain prognostic markers, independent of treatment in heart failure with reduced left ventricular function. The investigation involved 6632 patients of the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study. All subjects had acute myocardial infarction with left ventricular ejection fraction <40% and signs/symptoms of heart failure. Carotid-femoral PWV was measured in a subpopulation of 306 subjects. In the overall population, baseline mean arterial pressure <90 mm Hg was associated with higher all-cause death (hazard ratio, 1.14 [95% confidence interval, 1.00–1.30]; P<0.05), whereas higher left ventricular ejection fraction or pulse pressure was associated with lower rates of all-cause death, cardiovascular death/hospitalization, and cardiovascular death. In the subpopulation, increased baseline PWV was associated with worse outcomes (all-cause death: 1.16 [1.03–1.30]; P<0.05 and cardiovascular deaths: 1.16 [1.03–1.31]; P<0.05), independent of age and left ventricular ejection fraction. Using multiple regression analysis, systolic blood pressure and age were the main independent factors positively associated with pulse pressure or PWV, both in the entire population or in the PWV substudy. In heart failure and low ejection fraction, our results suggest that pulse pressure, being negatively associated with outcome, is more dependent on left ventricular function and thereby no longer a marker of aortic elasticity. In contrast, increased aortic stiffness, assessed by PWV, contributes significantly to cardiovascular death. *(Hypertension. 2014;63:105-111.)*

Key Words: blood pressure ■ heart failure ■ hypertension ■ pulse wave analysis ■ ventricular ejection fraction ■ vascular stiffness

Cardiovascular physiologists have suggested that blood pressure (BP) may be adequately investigated when divided into 2 components: a steady component, mean arterial pressure (MAP), and a pulsatile component, pulse pressure (PP).¹ At a given left ventricular ejection fraction (LVEF), the steady component, which corresponds to steady flow relates to the status of small arteries, that are total vascular resistances. However, PP, which corresponds to the pulsatile flow really ejected by the heart, is mainly influenced by 2 major and distinct factors: again LVEF and also aortic stiffness. Although MAP is associated with overall cardiovascular risk (involving brain and kidney), PP was an independent predictor of coronary risk and stroke development.² This simple description has the advantage to show that, in subjects with hypertension, it is important to study not only the relationships between MAP and PP but also the respective role of LVEF and aortic stiffness separately, the 2 major determinants of PP. Excessive arterial pulsatility resulting from increased arterial stiffness contributes to abnormal ventricular arterial coupling.

In this context, past epidemiological investigations with baseline assessment of BP and LVEF have considered that hypertension, used as a categorical variable, is one of the most important factors contributing to the progression of overall and cardiovascular risk.³ In patients with heart failure (HF), there is a relatively small number of studies that have been published and recently meta-analyzed.⁴ Mortality is highest when systolic BP (SBP) is <100 mm Hg or >160 mm Hg.⁵ It is critical to identify the BP margin of 100 to 160 mm Hg, higher BP was independently associated with heart failure mortality, and lower BP was associated with higher coronary events.⁶ These studies suggest that SBP between 100 and 160 mm Hg is the critical range for the risk of death from cardiovascular and noncardiovascular causes. In conclusion, SBP between 100 and 160 mm Hg should be considered as the critical range for the risk of death from cardiovascular and noncardiovascular causes.
associated with lower mortality. However, Tartiere et al. and Weber et al. showed that, in middle-aged and old subjects with hypertension, increased arterial stiffness and wave reflections might be independently associated with impaired systolic or diastolic function. These findings suggest that, in patients with HF, to evaluate the relationships between BP and outcome, it is necessary not only to determine the level of LVEF but also to take into account the degree of aortic stiffness.

In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial, baseline LVEF was available in the total population and was <40%. Eplerenone reduced significantly the rate of death resulting from progressive HF and sudden death, as well as the rate of hospitalization for HF. In a post hoc analysis, it was found that in patients without history of hypertension, eplerenone reduced HF hospitalization but had no effect on mortality or the composite end point, whereas in patients with a history of hypertension, all outcome end points were influenced favorably by eplerenone.

The objective of the study was to determine whether hemodynamic factors related to arterial stiffness (PP and pulse wave velocity [PWV]) remain prognostic markers, independent of treatment in HF with reduced LVEF.

**Methods**

**Study Design and Patient Populations**

The design and main results of the EPHESUS trial have been reported previously. EPHESUS enrolled patients with HF in the setting of acute myocardial infarction complicated by left ventricular systolic dysfunction (ejection fraction ≤40%). HF had to be documented by ≥1 of the following: presence of pulmonary rales, chest radiography showing pulmonary venous congestion, or the presence of a third heart sound. Patients were entered into the study at any point from 3 to 14 days after myocardial infarction. Patients with diabetes mellitus were not required to have evidence of HF. All patients were randomly assigned to treatment with eplerenone 25 mg daily or placebo depending on serum potassium levels. Treatment with eplerenone was given in addition to standard medical therapy, which would include angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, diuretics, aspirin, statins, and coronary reperfusion therapy. EPHESUS was an event-driven study, and the mean duration of follow-up was 16 months.

Among the 6632 patients enrolled in the EPHESUS study, 19 were excluded from the present analysis because of unavailable BP data at baseline. Standard brachial routine clinical sphygmomanometer BP measurements were performed during each patient visit. In the present study, we defined 2 patient subgroups, in which the terms normotension and hypertension were used exclusively as qualitative variables. Patients with normotension were defined as those having no history of hypertension and baseline SBP <140 mm Hg and diastolic BP <90 mm Hg. All the remaining patients were those with hypertension, either controlled or uncontrolled with drug treatment. Furthermore, in a substudy, 306 patients had a baseline PWV assessment. These patients were enrolled from 41 centers from 12 countries (Belgium, Belarus, Poland, Romania, Russia, United States, Brazil, Columbia, Mexico, Venezuela, Israel, and New Zealand). These centers were selected on their ability to measure PWV using the same Complior device as previously described.

**Statistical Analysis**

Analyses were performed using SAS V9.22 (SAS Institute, Cary, NC). The 2-tailed significance level was set to P<0.05. Univariate analyses were performed using the Mann–Whitney and χ² tests. Summary statistics were presented as mean±SD for continuous variables and frequency (percent) for categorical variables. In multivariable analyses, 18 baseline covariates were tested: study drug, hypertension, diabetes mellitus, sex, age, BP measurements (SBP, diastolic BP, MAP, PP, each separately), heart rate, LVEF, blood potassium, estimated glomerular filtration rate, reperfusion therapy, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, diuretics (loop or others), and nitrates. PWV was additionally tested in the subgroup of patients with available data. Only significant factors were kept in the final models if not otherwise specified. Association of these covariables with all-cause mortality, cardiovascular death/hospitalization, and cardiovascular death was analyzed using Cox regression. Results are presented as hazard ratios and 95% confidence interval. Factors associated with PP and PWV were identified using multivariable linear regression. Results are reported as regression coefficients±SEE. Variance explained independently by the significant factors was estimated as squared semipartial correlation coefficients computed using type II sums of squares. Adjustment of mean PWV on age and MAP was performed using ANOVA. The validity of the multivariate models was thoroughly checked: proportionality of hazards (Cox regression), normality of the residual distribution and homoscedasticity (linear regression and ANOVA), linearity of the associations, and absence of collinearity and interaction.

**Results**

**Baseline Characteristics of Patients**

The whole study was composed of 4702 men (59.5% had hypertension) and 1911 women (75% had hypertension). The substudy population with available PWV included 225 men (59% had hypertension) and 81 women (74% had hypertension). Table 1 shows the characteristics of the whole population and substudy with patients of measurement of PWV. PP and LVEF were similar in both populations. PWV values were significantly higher in patients with hypertension than in patients with normotension.

**Opposite Effects of Baseline PP and PWV on Outcomes**

Increasing age, diabetes mellitus, and reduction of estimated glomerular filtration rate (<60 mL/min per 1.73 m³) were independent determinants of all-cause death, cardiovascular death/hospitalization, and cardiovascular death in the whole study population (Table 2). Furthermore, MAP <90 mm Hg was also associated with increased all-cause death. In contrast, higher levels of LVEF, PP, and eplerenone treatment were associated with lower rates of outcomes. Replacing PP by SBP in the model provided similar results for all-cause death (0.96 [0.94–0.99]; P=0.01), cardiovascular death/hospitalization (0.96 [0.94–0.98]; P=0.001), and cardiovascular death (0.96 [0.93–0.98]; P<0.01). Finally, notwithstanding the collinearity among SBP, PP, and MAP, we performed a sensitivity analysis including all 3 parameters in the multivariate models and observed that neither MAP nor SBP was found to be associated with the tested outcomes, whereas PP remained significantly associated with lower rate of all-cause death (P=0.034) and cardiovascular death (P=0.048).

In the PWV substudy population, increased PWV was found to be associated with worse outcomes (all-cause death, which almost exclusively corresponded to cardiovascular deaths), independent of age and ejection fraction. PP was no longer found to be significantly associated with outcomes, which might be because of the loss of power resulting from the reduction in sample size.
Factors Associated With Baseline PP and PWV
Using multiple regression analysis in the entire population, we showed that SBP was the main positively and independently associated factor, accounting for 53.8% of the PP variance in a model explaining 61.0% of the PP variance (Table 3). This analysis also showed that age was positively associated with PP, whereas hematocrit, heart rate, and LVEF were negatively associated with PP.

In the PWV study, SBP also accounted for 55.3% of PP variance, and age remained independently associated with PP.
in a model explaining 68.2% of the PP variance. The factors SBP and age were also positively associated with PWV and explained 2.4% and 13.0% of a total of 20.1% of the PWV variations. In this population, 2.6% and 11.2% of a total of 20.2% of the PWV variations were explained by a multiple regression in which PP and age were included as covariates.

### Table 2. Association of Pulse Pressure With Outcomes

<table>
<thead>
<tr>
<th>Variables</th>
<th>All-Cause Death</th>
<th>Cardiovascular Death/Hospitalization</th>
<th>Cardiovascular Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole population (events/patients)</td>
<td>1017/6551</td>
<td>1824/6454</td>
<td>876/6551</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>0.86 (0.76–0.97)*</td>
<td>0.87 (0.79–0.96)†</td>
<td>0.84 (0.74–0.96)*</td>
</tr>
<tr>
<td>Age per 5-y increment</td>
<td>1.20 (1.17–1.24)‡</td>
<td>1.15 (1.12–1.18)‡</td>
<td>1.21 (1.16–1.25)‡</td>
</tr>
<tr>
<td>PP per 5-mm Hg increment</td>
<td>0.95 (0.93–0.98)‡</td>
<td>0.96 (0.94–0.98)‡</td>
<td>0.94 (0.91–0.97)‡</td>
</tr>
<tr>
<td>MAP &lt;90 mm Hg</td>
<td>1.14 (1.00–1.30)*</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Hematocrit per 5% increment</td>
<td>NS</td>
<td>0.94 (0.90–0.99)†</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF per 2% increment</td>
<td>0.92 (0.90–0.94)‡</td>
<td>0.93 (0.91–0.94)‡</td>
<td>0.91 (0.90–0.93)‡</td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min per 1.73 m²</td>
<td>1.52 (1.33–1.73)‡</td>
<td>1.40 (1.27–1.55)‡</td>
<td>1.49 (1.29–1.72)‡</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.36 (1.20–1.55)‡</td>
<td>1.39 (1.27–1.53)‡</td>
<td>1.36 (1.19–1.56)‡</td>
</tr>
<tr>
<td>PWV substudy (events/patients)</td>
<td>28/306</td>
<td>64/306</td>
<td>26/306</td>
</tr>
<tr>
<td>Age per 5-y increment</td>
<td>NS</td>
<td>1.16 (1.03–1.30)*</td>
<td>NS</td>
</tr>
<tr>
<td>PWV per m/s increment</td>
<td>1.16 (1.03–1.30)*</td>
<td>NS</td>
<td>1.16 (1.03–1.31)*</td>
</tr>
<tr>
<td>LVEF per 2% increment</td>
<td>0.84 (0.75–0.95)†</td>
<td>0.87 (0.81–0.94)‡</td>
<td>0.84 (0.74–0.95)†</td>
</tr>
</tbody>
</table>

Results are presented as events/patients and hazard ratios (95% confidence interval) from Cox multivariable analysis. eGFR indicates estimated glomerular filtration rate; LVEF, left ventricle ejection fraction; MAP, mean arterial pressure; NS, nonsignificant; PP, pulse pressure; and PWV, pulse wave velocity.

*P<0.05.
†P<0.01.
‡P<0.001.

### Table 3. Baseline Factors Associated With Pulse Pressure and Pulse Wave Velocity

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pulse Pressure, mm Hg</th>
<th>Pulse Wave Velocity, m/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (per 5-mm Hg increment)</td>
<td>2.92±0.03‡</td>
<td>53.8</td>
</tr>
<tr>
<td>Age (per 5-y increment)</td>
<td>0.64±0.05‡</td>
<td>1.2</td>
</tr>
<tr>
<td>Hematocrit (per 5% increment)</td>
<td>−1.05±0.10‡</td>
<td>0.7</td>
</tr>
<tr>
<td>Heart rate (per 5-bpm increment)</td>
<td>−0.29±0.04‡</td>
<td>0.3</td>
</tr>
<tr>
<td>LVEF (per 5% increment)</td>
<td>−0.50±0.08‡</td>
<td>0.2</td>
</tr>
<tr>
<td>Total variance explained (unadjusted)</td>
<td>61.0</td>
<td></td>
</tr>
</tbody>
</table>

PWV substudy

Model with SBP

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pulse Pressure, mm Hg</th>
<th>Pulse Wave Velocity, m/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (per 5-mm Hg increment)</td>
<td>2.96±0.13‡</td>
<td>55.3</td>
</tr>
<tr>
<td>Age (per 5-y increment)</td>
<td>0.80±0.19‡</td>
<td>1.9</td>
</tr>
<tr>
<td>Total variance explained (unadjusted)</td>
<td>68.2</td>
<td>20.1</td>
</tr>
</tbody>
</table>

Model with PP

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pulse Pressure, mm Hg</th>
<th>Pulse Wave Velocity, m/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP (per 5-mm Hg increment)</td>
<td>...</td>
<td>0.23±0.07‡</td>
</tr>
<tr>
<td>Age (per 5-y increment)</td>
<td>...</td>
<td>0.52±0.08‡</td>
</tr>
<tr>
<td>Total variance explained (unadjusted)</td>
<td>20.2</td>
<td></td>
</tr>
</tbody>
</table>

Variance explained by each factor: independent of each other. Baseline covariables tested in the models were age, sex, SBP, mean arterial pressure, PP, heart rate, LVEF, blood potassium, estimated glomerular fraction rate (from Modification of Diet in Renal Disease formula), angiotensin-converting enzyme inhibitors/angiotensin II receptor blocker, β-blockers, nitrates, diuretics (loop or others), and PWV in the substudy. Only significant covariables were kept in the above models. LVEF indicates left ventricular ejection fraction; PP, pulse pressure; PWV, pulse wave velocity; and SBP, systolic blood pressure.

*P<0.05.
†P<0.01.
‡P<0.001.
Discussion

We demonstrated that PP and PWV are independent opposite prognostic markers. In such population, the increase in PP associated with improved outcome cannot be considered as an index of arterial stiffness.

An important result of the study was that PP, measured at admission in patients mostly with symptomatic HF and low ejection fraction, was a strong independent predictor of overall and cardiovascular risk prognosis. High PP is associated with a significant decrement in the overall and cardiovascular risk in patients with HF contrary to the general population. This finding was shown even after adjustment for hypertension and MAP and established clinical predictors of adverse outcome. This first observation is reinforced by 2 main results. First, drugs administered during hospitalization do not affect the prognosis value of PP measured at admission. In our study, all patients were treated with or without eplerenone in addition to standard medical therapy, but it was not the aim of the study to focus on the effects of treatment. Second, in this study, MAP is a parameter associated with occurrence of poor overall outcomes for all-cause death.

PP is thought to be determined by cardiac function and arterial stiffness through wave reflections. Increased central arterial stiffening is a hallmark of the aging process and the consequence of many disease states such as diabetes mellitus, atherosclerosis, and chronic renal compromise. Large-artery stiffness is the main determinant of PP. Aortic stiffness has independent predictive value for total and cardiovascular mortality, coronary morbidity and mortality, and fatal stroke in patients with essential hypertension, end-stage renal failure, or diabetes mellitus. However, several studies have reported controversial results on the relationship between PP and all-cause death in patients with HF. In the present study, PP was significantly associated with lower rate of all-cause death and cardiovascular death. In contrast to our data, several studies Studies of Left Ventricular Dysfunction (SOLVD), the Survival and Ventricular Enlargement trial (SAVE), and the Cavedilol Post-Infarct Survival Control in LV Dysfunction study (CAPRICORN) showed a positive relationship between PP and overall and cardiovascular mortality. Because a significant proportion of patients in these trials were asymptomatic or qualified as Killip class I, this observation that prognosis worsens with increased PP has been attributed to increased large-vessel stiffness. In line with this, PP was associated with known risk factors for arterial stiffness, such as advanced age, diabetes mellitus, and renal failure, indicating that elevated PP reflects, in part, increased arterial stiffness. However, our study in agreement with the Vasodilation in the Management of Acute Congestive HF study (VMAC), Comorbidities and Outcome in patients with chronic heart Failure: a study in Internal mEdicine units in Italy (CONFINE), the Prospective Randomized study of Iobapine on Mortality and Efficacy (PRIME), Heart Institute of Japan-Department of Cardiology-HF (HIJC-HF) studies, and Italian Network of Congestive Heart Failure (IN-CHF) registry showed that high PP independently predicts decreased mortality.

As shown in VMAC study in which LVEF increased with tertiles of PP, there was evidence that a relatively preserved left ventricular systolic function is required to maintain an elevated PP. Our results probably reflect that in patients with HF, PP is more dependent on left ventricular function and stroke volume than aortic elasticity. The lack of measurement of stroke volume as an index of cardiac performance is a limitation of our study. Only LVEF was measured, according to the devised protocol, to establish left ventricular dysfunction.

In fact, PP reflects a complex interaction of the heart and the arterial and venous systems. Cardiac parameters, such as distal flow filling and contractility, affect PP. The dependence of PP on hemodynamic factors (eg, stroke volume and peak aortic blood flow) other than aortic and peripheral conduit vessel stiffness per se makes it an imperfect indicator of conduit vessel function. In line with this, several groups have reported that patients with HF and preserved LVEF have increased central aortic stiffness relative to age-matched healthy and hypertensive subjects without HF. Only 1 study in HF and LVEF <45% revealed that PWV predicts adverse clinical outcomes. Such alterations suggest that abnormal ventricular–vascular coupling may contribute to the pathophysiology of HF with preserved ejection fraction and even may become especially important in the setting of severe decompensated HF, in which significant correlations between PWV and LVEF have not been observed. Because PP results from cardiac and arterial factors, the relationship that we observed in this study between reduced PP and mortality might be a consequence of LVEF impairment, leading to a decrease in stroke volume and rate of ejection. However, the adverse prognosis associated with reduced PP was independent of baseline LVEF, indicating that a low PP is not simply a marker of a low LVEF at rest. We speculate that a low PP in the setting of clinical decompensation represents more advanced cardiovascular alterations, probably with most profound LV and peripheral hemodynamic changes.

As a result of ventricular–vascular interaction in HF, aortic PWV, a key measure of arterial stiffness, is altered in this disease. A limitation of our PWV substudy population is an insufficient power to highlight the role of PP as an independent predictor of clinical events in the substudy patient subset. Nevertheless, the number of patients was sufficient to show that increased PWV was associated with worse outcomes, independent of age and ejection fraction. This result is even more reliable because there are no significant changes in longitudinal measurements of PWV during a 9-month period. Arterial stiffness exerts deleterious effects on the heart, including increased afterload and myocardial oxygen demand, impaired ventricular relaxation, and subendocardial ischemia.

We next investigated which were the determinants of PP and PWV. We found that SBP was the main determinant of PP but not of PWV in the PWV substudy population. Despite a strong positive association using an univariate analysis, multivariate analysis showed that LVEF and hematocrit were negative determinants of PP but explained only 0.2% and 0.7% of variance of PP. There was no significant correlation between LVEF and PWV, suggesting that, during the course of HF, both factors participated independently to PP level. The significant determinants of PWV were age, SBP, or PP, but its main factors, such as geometry and structure of the aortic wall, have not been measured in this study.
Perspectives
In this study, PP is no longer a surrogate marker of arterial stiffness in patients with HF, whereas PWV remains a valid measure of arterial stiffness and is associated with increased cardiovascular risk in this setting. PP and PWV are non-redundant parameters exploring complementary evaluation of cardiac and vascular functions in patients with HF. These observations suggest that the prognostic significance of elevated PP may not be similar in the full spectrum of patients with HF. In compensated HF, elevated PP may reflect, in part, increased large-vessel stiffness and, therefore, may be associated with increased risk. In contrast, in the setting of severe decompensated systolic HF, survival was shortened in patients with decreased PP or improved in those with increased PP. Here, 2 factors are important to consider. First, SBP plays a major contribution to prognosis, and future investigations are required to determine whether this acts through its peak level or through its role as a major pathway for reflectance properties. Second, the 2 major factors predicting mortality are LVEF and PWV. Finally, measure of PWV may allow a better assessment of the effect of beneficial existing therapeutic agents such as eplerenone on arterial stiffness for future longitudinal studies.

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Disclosures
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**Novelty and Significance**

**What Is New?**
- Pulse pressure and pulse wave velocity are independent opposite prognostic markers in heart failure with reduced ejection fraction: in the setting of severe decompensated systolic heart failure, survival was improved in patients with increased pulse pressure and shortened in those with increased pulse wave velocity.

**What Is Relevant?**
- In heart failure with reduced ejection fraction, pulse pressure cannot be considered as an index of arterial stiffness, whereas pulse wave velocity remains a valid measure.

**Summary**
High pulse pressure, measured at admission, is negatively associated with outcome in heart failure with reduced left ventricular ejection fraction, whereas aortic stiffness, assessed by pulse wave velocity, contributes significantly to cardiovascular death, independent of treatment. Pulse pressure is more dependent on left ventricular function and thereby no longer a marker of aortic elasticity.
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