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Heart rate, pulse pressure and mortality in patients with myocardial infarction complicated by heart failure

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ABSTRACT

Objective: To assess the relationship between heart rate (HR), pulse pressure (PP), and their association with mortality in a population of high-risk patients following acute myocardial infarction (MI).
Methods: We performed an analysis in 22,398 patients included in "The High-Risk Myocardial Infarction Database Initiative", a database of clinical trials evaluating pharmacologic interventions in patients with MI complicated by signs of heart failure (HF) or left ventricular dysfunction. We found an interaction between HR and PP. Based on median HR and median PP, patients were divided in four categories: (1) HR < 75 bpm and PP ≥ 50 mm Hg (reference), (2) HR < 75 bpm and PP < 50 mm Hg, (3) HR ≥ 75 bpm and PP ≥ 50 mm Hg, and (4) HR ≥ 75 bpm and PP < 50 mm Hg. The association between these categories and outcomes was studied using a Cox proportional hazard model.
Results: After a median follow-up of 24 (18–33) months, 3561 (16%) patients died of all-causes and 3048 (14%) patients of cardiovascular (CV) causes. In multivariate analysis, patients from the fourth category had the highest risk of all-cause mortality (hazard ratio of 1.69; 95% CI: 1.53–1.86) and CV mortality (hazard ratio of 1.78; 95% CI: 1.60–1.97).
Conclusions: There is an interaction between HR and PP in patients with HF following MI, with the highest risk being conferred by a clinical status with both an elevated HR and a lower PP. These findings identify a high-risk population likely to require an aggressive diagnostic and management strategy.

1. Introduction

Pulse pressure (PP) is determined by a complex and dynamic interaction between stroke volume, heart rate (HR), and arterial compliance [1]. In normal populations as well as in patients with hypertension, stable coronary artery disease (CAD) or mild to moderate chronic heart failure (HF), when stroke volume is relatively preserved, PP is principally a reflection of the arterial stiffness. Thus, in these conditions, a higher PP is associated with adverse outcomes [2–5]. An elevated HR is also associated with adverse outcomes in general populations, as well as in patients with hypertension, stable CAD and chronic HF [6]. In general populations, high PP and high HR have synergistic effects of mortality [7]. In contrast, in acute conditions, such as acute HF, or in severe chronic HF, PP is primarily a reflection of decreased stroke volume, and consequently, a lower PP is associated with adverse outcomes [8,9]. Heart rate may play an important role in this complex interaction as HR changes are the principal mechanism to increase cardiac output according to hemodynamic requirements.

To date, few studies assessed the relationship between HR, PP, and clinical outcomes in cardiovascular (CV) populations. In patients with stable CAD referred for non-urgent coronary artery bypass (CABG) surgery, Aboyans et al. [10] reported that elevated HR and high PP are independent predictors of complications after intervention. The relationship between HR and PP in high-risk patients following acute myocardial infarction (MI) is not clearly established.

"The High-Risk Myocardial Infarction Database Initiative" is a pooled database of three randomized clinical trials (RCTs) evaluating pharmacologic interventions in patients with acute MI complicated by signs of acute HF or evidence of left ventricular (LV) systolic dysfunction: VALIANT, OPTIMAAL, and EPHESUS trials. The aim of the current study was to assess the relationship between HR, PP, and their association

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with clinical outcomes in this large population of high-risk patients following acute MI.

2. Methods

We performed an analysis of patients included in "The High-Risk Myocardial Infarction Database Initiative", a pooled database of three (out of originally four) randomized clinical trials (RCTs) evaluating pharmacologic interventions in patients with acute MI complicated by signs of HF or evidence of left ventricular (LV) systolic dysfunction: VALIANT (Valsartan in Acute Myocardial Infarction), OPTIMAAL (Optimal Trial in myocardial infarction with Angiotensin II antagonist Losartan), and EPHESUS (Eplerenone post Acute Myocardial Infarction Heart Failure Efficacy and Survival study) trial [11]. In short, the VALIANT trial tested the effect of valsartan versus captopril versus both drugs in patients with MI complicated by HF, LV dysfunction or both. Valsartan was as effective as captopril while the combination of the two drugs increased the rate of adverse events without improving survival. The OPTIMAAL trial tested the effect of losartan versus captopril in patients with acute MI and signs or symptoms of HF. The two drugs had similar effects on mortality although a non-significant effect on CV mortality in favour of captopril was observed. Finally, the EPHESUS trial tested the effect of eplerenone in patients with acute MI complicated by signs of HF or LV dysfunction, and demonstrated a beneficial effect of eplerenone on top of background therapy, included angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), and beta blockers. Patients with valvular disease were excluded from these studies. The three trials were similar to each other in demographics and medical background.

The merged data contained information on the background medical treatment, but not on the randomized study drug. In OPTIMAAL trial, although specific information on the randomized study drug (ACEI or ARB) was not provided, we adjusted for the use of either an ACEI or an ARB, and in the VALLIANT trial for the use of an ACEI, an ARB or a combination of the two drugs. In addition, we adjusted in these two trials for beta-blocker and other HF medication use. For EPHESUS trial, we adjusted for the use of an ACEI or an ARB, a beta blocker, but not for eplerenone use, the randomized study drug. Patients from the Capricorn trial were also merged in this database; however, patients from this trial were excluded from our analysis because in this population we could not adjust for beta-blocker use, the randomized study drug.

Heart rate does not have the same predictive value in patients with sinus rhythm and those with atrial fibrillation (AF). Thus, for this analysis we excluded patients with AF and only included patients in sinus rhythm and without a device from VALIANT, OPTIMAAL, and EPHESUS trials, resulting in a total population of 22,398 patients. Models using only baseline variables used the entire sample of patients. There were missing values at baseline for few clinical variables used for adjustment; therefore, the final multivariate analysis included 22,130 patients.

2.1. Statistical analysis

At baseline, continuous variables were described as median (25th, 75th percentile), and categorical variables as frequencies (percentages). Pulse pressure was calculated as the difference between systolic blood pressure (BP) and diastolic BP.

Cox proportional hazard models were fit to assess the association between baseline HR, PP and two adjudicated clinical outcomes, all-cause mortality and cardiovascular (CV) mortality. We checked the log-linearity of the continuous variables and the Cox proportionality assumptions of all variables. The log-linearity was assessed by generating one dummy variable per quintile of each variable, entering these in the Cox model, and plotting the resulting Cox estimators against the mean values of the quintiles. Both HR and PP respected the linearity assumption. Assumptions of risk proportionality was assessed statistically by testing the cofactor × time interaction and visually by plotting the log [−log(survival)] curves. All variables significantly associated with clinical outcomes in univariate survival analysis were included in the multivariate analysis. We calculated the model discrimination (C Index) with and without PP added to the model including HR only.

We checked the model for multicollinearity, and, as expected, we found a high correlation ($r = 0.7$) between PP and systolic BP. Thus, systolic BP was not included in the final model. Mean arterial pressure (MAP), calculated as the sum of 1/3 systolic BP and 2/3 diastolic BP, was not highly correlated with PP, and it was maintained in the model.

We checked the interactions between HR and PP, and between these variables and the other significant variables from the final model. In multivariate analysis, there was a significant interaction between HR and PP, for both all-cause mortality ($p = 0.004$) and CV mortality ($p = 0.01$). Consequently, based on median HR (75 bpm) and median PP (50 mm Hg), patients were divided in four equal categories: (1) HR < 75 bpm and PP ≥ 50 mm Hg (reference group) (2), HR < 75 bpm and PP < 50 mm Hg, (3) HR ≥ 75 bpm and PP ≥ 50 mm Hg, and HR ≥ 75 bpm and PP < 50 mm Hg (4). The reference group of HR < 75 bpm and PP ≥ 50 mm Hg was selected based on the literature data suggesting that in high-risk HF populations a higher PP and a lower HR are associated with a lower risk of mortality. The difference in clinical variables, medical history and medication between the four groups was tested using chi-square test or Kruskal-Wallis test, as required.

The association between the four classes and clinical outcomes was studied using a Cox proportional hazard model. In a first Cox model, we adjusted for age, sex and race. Second, we adjusted for all significant variables ($p < 0.05$) in the univariate Cox analysis. The following variables were included in the final multivariate model: age, sex, race, smoking status, Killip class, body mass index (BMI), MAP, estimated Glomerular Filtration Rate (eGFR), medical history of angina, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD), previous MI, previous hospitalisation for HF, history of percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass (CABG), and treatment with an ACEI/ARB or both, beta blocker, diuretic, aspirin, statin, digoxin or vit K antagonist. All variables were reported at hospital discharge.

We performed an additional analysis testing the interaction between systolic BP and HR, without the inclusion of PP in the model. The interaction between systolic BP and HR was only of borderline significance ($p = 0.05$) for the primary outcome (all cause mortality) and not significant for the secondary outcome (CV mortality), while the interaction between PP and HR was significant for both all-cause ($p = 0.004$) and CV mortality ($p = 0.01$). Thus, we presented the results of the interaction between HR and PP. There was no other significant interaction in this population.

All analyses were performed using SPSS version 24. Results were estimated as hazard ratios (HRs) with 95% confidence intervals (CIs). The two-tailed significance level was set at $p < 0.05$.

2.2. Subgroup analysis

Left ventricular ejection fraction (LVEF) was available only in two of the three included RCTs (EPHESUS and partly VALIANT). Thus, the main multivariate analysis did not include adjustment for LVEF. In order to measure the potential impact of LVEF on the final results, we performed a subgroup analysis in 14,933 patients who had this variable available.

3. Results

Table 1 presents the main characteristics of patients included in this analysis. Overall, median age of patients was 65 (56–73) years, 70% were male, and 19% were in Killip class 3–4. Median PP was 50 (40–58) mm Hg, and median HR was 74 (66–82) bpm. Patients presented a broad range of comorbidities, including hypertension (54%), diabetes (26%), and angina (42%). Most patients (95%) were on an ACEI, an ARB or a combination of the two drugs, and 68% of patients were on beta blockers. Patients from the third (HR ≥ 75 bpm and PP ≥ 50 mm Hg) and the forth (HR ≥ 75 and PP < 50) categories, were more often in Killip class 3–4, and had more often a history of diabetes, COPD, and previous hospitalisation for HF. Importantly, patients from the third and the fourth categories received less often treatment with a beta-blocker at hospital discharge, i.e. 59% and 63% vs. 73% in the reference category. In contrast, these patients received more often treatment with a loop diuretic or with digoxin.

3.1. Interaction between heart rate and pulse pressure

In multivariate model, a higher HR and a lower PP were independently associated with all-cause mortality (Hazard ratio 1.02; CI 1.014–1.02; $p < 0.001$; Hazard ratio 0.99; CI 0.98–0.99; $p < 0.001$); and with CV mortality (Hazard ratio 1.02; CI 1.016–1.021; $p < 0.001$, and Hazard ratio 0.99; CI 0.98–0.99; $p < 0.001$). The model discrimination was superior when PP was added to the model including HR only (C index 0.732; CI 0.722–0.742; versus CI 0.730; CI 0.720–0.740; p value = 0.0006). In multivariate model, there was a significant interaction between HR and PP, on both all-cause mortality ($p = 0.004$) and CV mortality ($p = 0.01$).

3.2. Univariate survival analysis

After a median follow-up of 24 (18–33) months, 3561 (16%) patients died of all-causes and 3048 (14%) patients died of cardiovascular (CV) causes. In univariate analysis, patients from the third category with an elevated HR and an elevated PP (HR ≥ 75 bpm and PP ≥ 50 mm Hg) presented the highest risk of adverse outcomes, followed by the patients from the forth category, who presented an elevated HR and a low PP (HR ≥ 75 and PP < 50) (Table 2).

3.3. Multivariate survival analysis

After adjustment for age, sex and race, compared to the reference group, the risk of all-cause and CV mortality was highest in patients from the forth category (Hazard ratio 1.69; 95% CI 1.54–1.85; $p < 0.001$