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Prognostic value of pulse pressure after an acute coronary syndrome

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ABSTRACT

Background and aims: Pulse pressure (PP) is a surrogate of aortic stiffness (AS) easily obtainable. The link between AS and cardio-vascular disease is documented, however, data regarding acute coronary syndrome (ACS) patients are scarce and contradictory. We aimed to assess the prognostic value of PP measured at admission, with regard to major adverse outcomes (all-cause mortality, recurrence of MI, and stroke), during the first year following an acute coronary syndrome (ACS).

Methods: The SPUM–ACS project is a prospective cohort study of patients with ACS conducted in 4 Swiss University hospitals. Patients with no PP at admission or with severe clinical heart failure or cardiogenic shock were excluded. Cox regression analyses were performed to determine associations between PP and outcomes (all-cause mortality, recurrence of myocardial infarction (MI), and stroke). Three multivariate Cox regression models were adjusted for hemodynamic, cardiovascular, and non-cardiovascular confounders, added successively.

Results: Of 5635 eligible patients, 5070 met the inclusion criteria. Mean patient age was 63 years (range: 54–72), 79.6% were male, and mean blood pressure and PP were 93.9 ± 15.6 and 54 ± 17 mmHg, respectively. Multivariate analyses confirmed the prognostic significance of PP for each 10-mmHg increase for the composite endpoint, hazard ratio (HR) 1.126 [1.051–1.206], $p = 0.001$; all-cause mortality, HR1.129 [1.013–1.260], $p = 0.029$; and recurrence of MI, HR1.206 [1.102–1.320], $p < 0.001$; but not for stroke, HR1.014[0.853–1.205].

Conclusions: PP measured at admission is a strong, independent prognostic marker predicting mortality and recurrence of MI after ACS. PP should be considered for the management of secondary prevention.

1. Introduction

High pulse pressure (PP) is a powerful, independent predictor of outcome in various populations of patients. However, there is a gap in knowledge regarding PP and patients with an acute coronary syndrome (ACS). PP data on patients with an acute coronary syndrome (ACS) are scarce, contradictory and outdated. Blood pressure (BP) is a rather complex variable, which can be dissociated into a steady state component (mean BP) and a pulsatile one (pulse pressure). PP is defined as the difference between systolic and diastolic BP. Mean BP and PP have different physiological meanings. PP is considered a surrogate for aortic stiffness (AS), i.e. the higher the PP, the stiffer the aorta. However, PP also reflects cardiac

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performance and stroke volume. This dual significance may be particularly relevant in the context of ACS as it could explain discrepancies in the current literature and provide a unique clinical tool to help stratify risk after diagnosis of ACS. In particular, high PP may play a role in triggering plaque complications at the coronary and cerebral levels [1]. On the other hand, a low PP may help identify patients at risk due to severe left ventricular dysfunction. Currently, clinicians caring for patients with ACS hardly perform PP measurements because the prognostic information conveyed at the time of ACS is unclear. Thus, the present study aimed to assess, in a prospective large real world ACS registry, whether PP measured at admission would predict a one-year composite endpoint encompassing all-cause mortality, recurrence of myocardial infarction (MI), and stroke.

2. Materials and methods

2.1. Study population

The SPUM–ACS study (Special Program University Medicine–Acute Coronary Syndromes) is a prospective cohort study of consecutive ACS patients hospitalized in Switzerland. The study was designed to identify new determinants and consequences of coronary heart disease. Details concerning the SPUM–ACS study have been reported previously [2]. Briefly, all patients hospitalized with ACS in four Swiss university hospitals were encouraged to participate, with no exclusion criteria except severe physical disability, inability to give consent owing to dementia, and life expectancy of <1 year for non-cardiac reasons. Inclusion criteria were age ≥18 years, ST-segment elevation myocardial infarction (STEMI), non-ST-segment–elevation myocardial infarction, or unstable angina. A large proportion of patients received adequate discharge drug treatment [2]. In the present study, patients with no PP at admission or with severe clinical heart failure or cardiogenic shock were excluded.

2.2. Pulse pressure

PP was defined as systolic BP (SBP) minus diastolic BP (DBP). SBP and DBP were measured using a brachial sphygmomanometer at first assessment in an emergency room. Mean BP was defined as [SBP + 2DBP]/3. A quality-control check of the number of BP readings ending in zero showed that 23.43% of SBP and 23.41% of DBP readings did so (20% expected) [3], which compares favorably to other studies in the setting of hypertension and to a recent study on PP [4].

2.3. Clinical outcomes

Occurrences of clinical events during the first year after an index event were obtained by questioning participants by telephone 30 days after discharge and at a face-to-face clinical consultation one year after ACS. The composite endpoint was defined as all-cause mortality (cardiac, vascular, or non-cardiovascular death), recurrence of MI (using the universal definition of MI [5]), and stroke. To account for potential pathophysiological differences in event types, PP prognostic value was measured on each outcome separately (secondary outcomes). A panel of three certified cardiologists serving as independent experts, blinded to BP values, adjudicated on all the endpoints used in this analysis.

2.4. Covariates

Hypertension was defined as SBP ≥140 mmHg, DBP ≥90, or use of BP lowering drugs. Smoking status was defined as current, former, or never. Diabetes mellitus was either self-reported or diagnosed from the use of antihyperglycemic medication or a hemoglobin A1c level ≥6.5% at admission. Dyslipidemia was defined as a total cholesterol level >5 mmol/l or use of any lipid-lowering drug.

2.5. Statistical analysis

Continuous variables are presented as means and standard deviation; categorical variables as counts and percentages. PP was considered as either a continuous or categorical variable. Intervals of 10 mmHg were used to define categories of PP: < 35 mmHg, 36–45 mmHg, 46–55 mmHg, 56–65 mmHg, 66–75 mmHg, and >75 mmHg. Patients' characteristics in each PP category were compared using p for trend.

Cubic splines and multivariable Cox proportional hazard models were built to assess associations between PP and outcomes. HRs and their 95% CIs were plotted, with 50 mmHg PP as a reference, to graphically represent relationships between PP and outcomes. Plotted HRs were based on the univariate Cox proportional hazard model with a restricted cubic spline transformation of PP using knots at 30, 42, 52, 63, and 87 mmHg. For Cox analysis, three incremental models were constructed, adding potential confounders known to influence PP and prognosis after a diagnosis of ACS. Additionally, Model 1 was adjusted for hemodynamic variables, *i.e.* mean BP, heart rate, and left ventricular ejection fraction (LVEF). Model 2 included Model 1 plus cardiovascular variables, *i.e.* diabetes, hypertension, age, sex, dyslipidemia, smoking, history of coronary artery disease, vascular disease (peripheral vascular disease or stroke), type of MI, Killip class, type of revascularization, and medication using statins. Model 3 included potential non-cardiovascular confounders, *i.e.* renal function and history of malignancy.

Based on previous works [4], the statistical interaction terms between PP and sex, age, LVEF, renal function, and type of ACS were tested for each outcome. Interactions with a p-value < 0.05 were retested in each appropriate subgroup. Exploratory analysis only found one significant interaction: between PP and LVEF, for all-cause mortality, $p = 0.03$.

Further unadjusted and fully adjusted cox regression analyses were performed considering PP as a categorical variable.

Additional analysis was performed to evaluate whether the inclusion of PP on top of a fully adjusted model helps reclassify participants into categories of predicted outcomes risk. Using the cut-off risk categories of <5%, 5–10%, and ≥10%, we assessed the categorical net reclassification improvement (NRI) as well as the integrated discrimination improvement (IDI), which integrates the NRI over all possible cutoffs of predicted risk [6,7].

2.6. Further sensitivity analyses were performed

- SBP and DBP were tested in turn, to replace mean BP in the multivariate models.
- In a subset of 3854 patients with an available GRACE score, this was added to Cox models to replace appropriate variables.
- Additional adjustment was performed on peak creatine kinase MB (CKMB) in a subset of 2324 patients in whom the dosage was available.

Finally, Kaplan–Meier representations of each outcome were built considering the lowest and highest PP groups according to LVEF phenotypes, *i.e.* ≤ 40% or not.

All hypothesis tests were two-sided, and the significance level was set at 5%. Statistical analyses were performed using SPSS version 24 (IBM SPSS Statistics, IBM Corporation, Armonk, New

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