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Pulse pressure as a risk factor for cardiovascular events: myth or reality?

Pressão de pulso como fator de risco para eventos cardiovasculares: mito ou realidade?

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ABSTRACT – Background: Elevated systolic blood pressure and decreased diastolic blood pressure increase systolic load, with concurrent decrease in coronary perfusion pressure. Researches suggested a relation between elevated pulse pressure and morbidity and mortality due to cardiovascular events. This study set out to investigate whether pulse pressure is a predisposing risk factor for coronary heart disease or an aggravating risk factor in patients with coronary artery disease. **Methods:** A total of 5,027 pressure registers were evaluated. Pulse pressure was determined invasively in the ascending aorta. Coronary artery disease was diagnosed in the presence of obstructive lesion with luminal diameter reduction of 50% or more in at least one major epicardial vessel. Intergroup comparisons were performed using the unpaired Student's t test or Mann-Whitney test, as indicated. Categorical variables were compared using the Chi-squared test. Long-term survival was assessed using Kaplan-Meier curves. The p values ≤ 0.05 were considered significant. **Results:** Pulse pressure ranged from 20.0 to 160.0mmHg (mean $\pm$ standard deviation: 68.4 $\pm$ 22.3; median: 66.0mmHg; 75th percentile: 82.0mmHg). Pulse pressure was associated with risk factors for coronary artery disease when patients with and without obstructive coronary artery disease were compared. However, pulse pressure was not an independent predictor of mortality. **Conclusion:** Pulse pressure is not an independent predictor of mortality in patients with coronary artery disease undergoing angiography.

Keywords: Blood pressure; Pulse; Risk factors; Survival; Cardiovascular diseases; Atherosclerosis

RESUMO – Introdução: A pressão sistólica elevada e a pressão diastólica reduzida aumentam a carga sistólica e reduzem a pressão de perfusão coronária. Pesquisas sugeriram a existência de uma relação entre pressão de pulso elevada e morbimortalidade por eventos cardiovasculares. O objetivo deste estudo foi investigar o valor da pressão de pulso enquanto fator de risco predisponente para doença arterial coronariana, ou fator de risco agravante em pacientes com esta doença. **Métodos:** Foram avaliados 5.027 registros pressóricos. A pressão de pulso foi determinada de forma invasiva na aorta ascendente. A doença arterial coronariana foi diagnosticada na presença de lesão obstrutiva com redução do diâmetro luminal de 50% ou mais, em pelo menos um vaso epicárdico principal. As comparações entre os grupos foram realizadas empregando-se o teste t de Student não pareado ou o teste de Mann-Whitney, conforme indicado. As variáveis categóricas foram comparadas empregando-se o teste qui-quadrado. A sobrevivência em longo prazo foi avaliada com base nas curvas de Kaplan-Meier. Valores de $p \leq 0,05$ foram considerados significantes. **Resultados:** A pressão de pulso variou de 20,0 a 160,0mmHg (média $\pm$ desvio padrão: 68,4 $\pm$ 22,3; mediana: 66,0mmHg; percentil 75: 82,0mmHg). A pressão de pulso mostrou-se associada a fatores de risco para doença arterial coronariana quando pacientes com e sem doença obstrutiva das artérias coronárias foram comparados. Entretanto, a pressão de pulso não foi preditor independente de mortalidade. **Conclusão:** A pressão de pulso não é um preditor independente de óbito em pacientes com doença arterial coronariana submetidos à angiografia.

Palavras-chave: Pressão sanguínea; Pulso; Fatores de risco; Sobrevida; Doenças cardiovasculares; Aterosclerose

BACKGROUND

Pulse pressure (PP) is the difference between systolic (SBP) and diastolic blood pressure (DBP). PP may be elevated due to increased SBP and decreased DBP,¹ resulting in higher SBP load and lower coronary perfusion pressure.² Importantly,

SBP elevation leads to a disproportionate increase in end-systolic stress, which is the major hemodynamic factor behind cardiac hypertrophy, increased ventricular oxygen consumption and left ventricular (LV) hypertrophy, with significant coronary perfusion compromise.

A relation between PP elevation and morbidity and mortality due to cardiovascular events has been suggested in previous research and would be a potential physiopathological explanation for coronary artery disease (CAD).²⁻⁶ However, although cross-sectional analyses have supported the hypothesis that wide PP is an independent risk factor for cardiovascular diseases, in general, and particularly for CAD, the prospective analyses failed to confirm this assumption.⁷

This study aimed to investigate the potential value of PP as a marker of cardiovascular mortality. It was hypothesized PP may be a risk factor for coronary disease. Correlations with patient age were also investigated.

METHODS

This study was evaluated and approved by the Research Ethics Committee of the *Faculdade de Medicina de São José do Rio Preto* (CAAE 82755418.0.0000.5415). This sample comprised 12,997 consecutive patients with and without obstructive CAD undergoing cardiac catheterization at the interventional cardiology service of an university hospital. Patients with valvulopathy, congenital heart diseases or hemodynamic instability, heart transplant patients and those submitted to previous myocardial revascularization procedures were excluded. The final sample comprised 5,027 blood pressure records.

Pulse pressure was measured invasively as the absolute difference between SBP and DBP in the ascending aorta, in the initial stage of the hemodynamic assessment. Coronary artery disease was diagnosed in the presence of obstructive lesion with luminal stenosis $\geq 50\%$, in at least one major epicardial vessel (right coronary artery, left anterior descending or diagonal artery, left circumflex or obtuse marginal artery) or the left main coronary artery (LMCA). Obstructive lesions were graded advanced whenever three major vessels were involved, regardless of LMCA disease.

Long-term mortality was the primary outcome, tracked via telephone contact or death records. Cutoff values for PP as a risk factor were established based on the median and 75th percentile of the values measured in the selected sample. Electronic medical records were prospectively analyzed. Long-term mortality assessment was based on three empirically established cutoff ranges: PP greater than 40.0mmHg, 60.0mmHg or 80.0mmHg. Intergroup comparisons were based on the unpaired Student's *t* test or the Mann-Whitney test, according the variable distribution (Gaussian or non-Gaussian). Categorical variables were compared using the Chi-squared test. Long-term survival was assessed using Kaplan-Meier curves.

The logistic regression analysis was performed using sex, age, body mass index (BMI), SBP, DBP, coronary obstruction and PP as potential independent variables. In the first step of the logistic regression analysis, all variables were included and a cutoff level of $p < 0.20$ was set to determine the significance of variables as independent risk factors. Statistical analyses were performed using StatsDirect software, version 3. The *p*-values ≤ 0.05 were considered significant.

RESULTS

Out of the 5,027 blood pressure records included in this study, 3,052 (60.7%) were male, and age range 20-92 years (59.0 ± 11.0 years). Pulse pressure ranged from 20.0 to 160.0mmHg (mean $\pm$ standard deviation: 68.4 ± 22.3 ; median: 66.0mmHg; 75th percentile: 82.0mmHg). Using the median as cutoff value, 2,453 (48.8%) patients had elevated PP. Of these, 1,481 had $\geq 50\%$ obstruction in at least one major vessel. On the other hand, 1,549 out of 2,574 patients with PP of 66.0mmHg or less, had obstructive CAD (OR=1.00; 95%CI 0.900-1.128; $p=0.905$).

Advanced obstructive disease was defined as a criterion in this analysis. Multivessel disease and LMCA compromise were detected in 411 and 27 patients with PP above the median, respectively, compared to 368 and 20 patients with PP equal to or below the median (OR=1.18; 95%CI 0.998-1.390; $p=0.053$).

When the 75th percentile (82.0mmHg) was set as cutoff value, 1,217 (24.2%) patients had elevated PP. Of these, 750 had $\geq 50\%$ obstruction in at least one major vessel. On the other hand, 2,280 out of 3,810 patients with PP of 82mmHg or lower had obstructive CAD (OR=1.08; 95%CI 0.944-1.230; $p=0.283$). As regards the degree of obstructive disease and three-vessel involvement, 208 patients with PP above the 75th percentile, and 571 with PP below the 75th percentile were found. Concurrent LMCA compromise was detected in 8 and 39 patients with PP above and below the 75th percentile, respectively (OR=1.19; 95%CI 0.987-1.442; $p=0.075$).

A total of 922 patients with compromise of at least one major branch were prospectively evaluated. They were followed for up to 225.0 months (142.7 ± 35.2 months). Comparisons were based on different cutoff values. The group with PP greater than 40mmHg included 821 patients and 112 deaths; the group with PP of 40mmHg or lower comprised 101 patients and 11 deaths (OR=1.13; 95%CI 0.57-2.23; $p=0.73$). Survival at the end of the follow-up period corresponded to $69.5 \pm 5.6\%$ and $81.3 \pm 7.3\%$ among patients with PP greater than 40mmHg and equal to or lower than 40mmHg, respectively.

The group with PP greater than 60mmHg comprised 488 patients and 61 deaths; the group with PP of 60mmHg or lower comprised 434 patients and 62 deaths (OR=0.99; 95%CI: 0.69-1.41; $p=0.955$). Survival at the end of the follow-up period was $75.4 \pm 5.2\%$ and $68.6 \pm 7.3\%$ among

patients with PP greater than 60mmHg and equal to or lower than 60mmHg, respectively.

The group with PP greater than 80mmHg comprised 220 patients and 27 deaths; the group with PP of 80mmHg or lower comprised of 702 patients and 96 deaths (OR=1.11; 95%CI 0.72-1.71; $p=0.63$). Survival at the end of the follow-up period was $80.9\pm3.5\%$ and $69.6\pm6.0\%$ among patients with PP greater than 80mmHg and equal to or lower than 80mmHg, respectively.

Kaplan-Meier survival curves are shown in figures 1 to 3. Mortality did not differ significantly between groups in any of the combinations tested. Age, BMI, LMCA and left anterior descending artery involvement were the only significant independent predictors of mortality. Pulse pressure was not a significant predictor ($p=0.845$).

Figure 1. Kaplan-Meier curves for comparing of survival between patients with pulse pressure >40mmHg and ≤40mmHg. PP: pulse pressure.

Figure 2. Kaplan-Meier curves for comparing of survival between patients with pulse pressure >60mmHg and ≤60mmHg. PP: pulse pressure.

Figure 3. Kaplan-Meier curves for comparing of survival between patients with pulse pressure >80mmHg and ≤80mmHg. PP: pulse pressure.

Assuming PP would only be significant in the presence of severe coronary impairment, logistic regression was repeated using PP and LMCA involvement only. Still, PP was not associated with cardiovascular events ($p=0.496$). Given age was as an independent variable significantly associated with mortality, the potential significance of the relation between PP and age was investigated. Again, PP was not a significant independent variable ($p=0.726$).

DISCUSSION

Elevated PP causes vascular wall damage and is associated with increased left ventricular stress, which may lead to ventricular hypertrophy and heart failure (HF). Increased SBP rises myocardial oxygen consumption, whereas reduced DBP may limit coronary perfusion, leading to ischemia. The result of these concurrent effects is that elevated PP may be a predictor of a variety of adverse cardiovascular outcomes. There is an ongoing debate about the significance of blood pressure components for cardiovascular risks.⁸

With increasing age, PP tends to correlate more closely with SBP as compared to DBP. For this reason, PP has also been reported as a good predictor of cardiovascular disease among the elderly. In some cases, this parameter has higher predictive value than SBP alone.^{9,10} Elevated PP is thought to be an independent predictor of cardiovascular events in elderly individuals.¹¹

Strong evidence shows a relation between PP, which is directly related to vascular stiffness, and cardiovascular events after myocardial infarction in patients with left ventricular dysfunction.² In the Framingham Heart Study, for example, every 10mmHg increase in PP was associated with a 23% increase in CAD risk.¹ Vaccarino et al.¹¹ followed up 2,152 elderly patients (>65 years) for 10 years, who had no history of cardiovascular events at baseline. The sample

comprised 328 cases of CAD, 224 cases of HF and 1,046 deaths due to other causes. The authors concluded that PP showed a strong linear correlation with each specific event. This correlation was evident in both, normotensive individuals and patients with isolated systolic hypertension. These findings were not confirmed in this study, at least where mortality and CAD were concerned.

In other studies, such as the National Health and Nutrition Examination Survey (NHANES), PP had little predictive value compared to SBP or DBP, as this parameter increased, reduced or had no impact on risks, depending on the values measured. Pulse pressure was not thought to be a relevant factor to estimate prognosis or therapeutic decisions.⁸

This study aimed to investigate the potential value of PP as a marker of cardiovascular mortality. Given PP was not a risk marker for CAD, efforts were made to determine whether PP might be associated with disease prognosis in a subgroup of CAD patients. Higher oxygen consumption due to a greater systolic work and lower diastolic oxygen supply would be logical pathophysiological mechanisms in severe myocardial damage, at least in theory. The analysis of a significant numbers of cases (5,027) provided evidence that elevated PP was not more common in patients with obstructive CAD than in patients with non-coronary arterial disease, not even when normal individuals and advanced coronary involvement were compared. Associations between CAD and elevated PP were investigated. There were no differences in CAD rates when the median (66.0mmHg) or the 75th percentile (82.0mmHg) was set as cutoff value.

Elevated PP was not detected in more advanced cases of CAD. Since no associations were detected, we investigated whether PP would be a cardiovascular event marker, at least among patients with confirmed diagnosis of CAD. There were no differences in mortality across the three PP cutoff values (40.0, 60.0 and 80.0mmHg) in patients with more advanced disease, despite the suggested pathophysiological mechanism. A study with 588 patients investigated associations between PP and risk of hospitalization due to cardiovascular events among type 2 diabetes patients. A total of 2,920 age-matched, sex-matched control subjects with type 2 diabetes were selected via risk-based sampling. A nonlinear relation between PP and risk of hospitalization due to cardiovascular events was detected ($p<0.001$). Pulse pressure of 61.0mmHg was associated with the lowest risk of hospitalization due to cardiovascular events. Pulse pressure was a good predictor of the risk of hospitalization due to cardiovascular events in patients with type 2 diabetes, with lower risks in patients with PP ranging from 57.0 to 63.0mmHg.¹²

Elevated PP may also be associated with structural damage to target organs, particularly in elderly patients, leading to increased cardiovascular risk. One study analyzed a cohort of treated hypertensive patients selected from the Registro Campania Salute Network ($n=7,336$). Participants who had echocardiography and carotid ultrasound available

were required to have no cardiovascular diseases, ejection fraction $\geq 50\%$, and no more than stage III chronic kidney disease. Median follow-up time was 41 months and the outcome was the occurrence of major cardiovascular events. As per current guidelines, $PP \geq 60.0$ mmHg upon initial consultation was defined as elevated ($n=2,356$), whereas $PP < 60.0$ mmHg was normal ($n=4,980$). Patients with elevated PP were older, more likely to be women and diabetic, and on more antihypertensive medications than patients with normal PP ($p<0.0001$). Patients with elevated PP had a higher prevalence of left ventricular hypertrophy and carotid plaque than those with normal PP ($p<0.0001$). As per the Cox regression analysis, the risk of major cardiovascular event was 57% higher in patients with elevated PP as compared to normal PP (OR=1.57; 95%CI 1.12-2.22; $p=0.01$). Therefore, elevated PP can be used as a functional marker of target organ damage.¹³

The study by Selvaraj et al.¹⁴ provided robust evidence on the role of PP in cardiovascular risk outcomes. However, when the predictive value of a 10-mmHg increase in PP was evaluated, a protective effect of elevated PP was found.^{15,16} Dissociation of central and peripheral PP may be determined by high prevalence of hypertension and use of antihypertensive medications, given the greater impact of these drugs on central compared to corresponding brachial pressures, due to significant effects on wave reflections.¹⁷⁻¹⁹ In this study, logistic regression analysis excluded PP as an independent variable and age was the only prognostic marker.

CONCLUSION

Despite pathophysiological assumptions, pulse pressure was not a predictor of mortality among patients with suspected coronary artery disease undergoing angiography.

SOURCE OF FINANCING

None.

CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest.

CONTRIBUTION OF AUTHORS

Conception and design of the study: MFG; data collection: MRSB, MAS, WPGN, JCQF and IGC; data interpretation: MRSB and MFG; text writing: MRSB and MFG; approval of the final version to be published: MRSB, MAS, WPGN, JCQF, IGC and MFG.

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