ORIGINAL ARTICLES

Pulse Pressure Predicts Mortality in Elderly Patients

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BACKGROUND: Pulse pressure (PP) values increase with age. The impact of PP on mortality in elderly patients has not been established.

OBJECTIVES: To evaluate the effect of PP on mortality among very elderly hospitalized patients.

DESIGN: A prospective clinical study.

PARTICIPANTS AND MEASUREMENTS: The medical records of 420 inpatients aged >60 (187 males, mean age of 81.4±7 years) hospitalized in an acute geriatric ward were reviewed. Patients were followed up for a mean of 3.46±1.87 years. Mortality data were extracted from death certificates. Using relative operating characteristic (ROC) curves, we identified PP of 62.5 mmHg as a cutoff point. Subjects were categorized as having low PP (≤62.5 mmHg; N=116) or high PP (>62.5 mmHg; N=304).

MAIN RESULTS: The mortality rate was greater in patients with high PP than in those with low PP. During the follow-up, 201 patients died, 155 patients (51%) in the high PP group and 46 patients (39.7%) in the low PP group (p=0.038). Pulse pressure was associated with all-cause mortality (HR=1.69, 95% CI=1.19–2.38, p=0.003) even after controlling for gender, age, diabetes mellitus, atrial fibrillation and heart rate.

CONCLUSION: High PP is an independent predictor of mortality among elderly hospitalized patients.

KEY WORDS: pulse pressure; mortality; elderly.

J Gen Intern Med 24(8):893–6

DOI: 10.1007/s11606-009-1008-7

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INTRODUCTION

Isolated systolic hypertension (ISH) is known as a powerful risk factor for cardiovascular disease (CVD), stroke and mortality^{1,2}. In some longitudinal studies, it has been suggested that pulse

This study was presented as a poster in the Second World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy) held from 30 October 2008–2 November 2008 in Barcelona, Spain.

Received December 10, 2008

Revised March 24, 2009

Accepted March 31, 2009

Published online May 27, 2009

pressure (PP) may predict cardiovascular risk better than either systolic or diastolic blood pressure (BP) alone^{3–6}. Only a few studies have looked at the influence of PP on all-cause mortality in very elderly people beyond the 8th decade^{6–8}.

The aim of our study was to determine the association between PP and all-cause mortality among a group of elderly survivors of hospitalization.

PATIENTS AND METHODS

Study Population

From 1 January 1999 through 31 December 2000 inclusively, all individuals admitted to an acute geriatric ward were evaluated for inclusion in a study on orthostatic hypotension. Inclusion and exclusion criteria were previously delineated⁹. For this study we included only patients who had at least three BP readings. During the study period, 1,852 patients were hospitalized, of whom 502 were enrolled in the study. Mortality data were collected from the day of admission through 31 August 2004 using death certificates (follow-up of 0.6 to 6.08 years; mean 3.46±1.87 years). Follow-up data were available for 470 enrolled subjects (93.6%), but only 420 (84%) of them had enough BP measurements to be included in the study.

This study was based on the blind review and analysis of medical records, and was approved by the institutional and Ministry of Health Ethics Committees.

Data Collection

Extracted from the medical records were findings of the clinical evaluations performed at the time of hospitalization. Blood pressure was measured three times during the day upon recovery from an acute disease, towards discharge from the ward.

Diabetes mellitus was defined as: (1) recorded in the patient's medical history, (2) a prescription for hypoglycemic agents or (3) a recording of fasting blood glucose of 126 gm/dl on two or more measurements. Hypertension was defined according to the patient's history or as the presence of a prescription for antihypertensive medications or a BP recording greater than 140/90 mmHg on two or more repeated measurements. Renal failure was defined as serum creatinine of ≥1.5 mg/dl on more than two measurements.

Blood Pressure Measurements

Blood pressure and heart rate were measured in the left arm using the Vital Signs Monitor 52 NTP model (Welch Allyn Inc.,

Skaneateles, NY). Measurements were obtained in the supine position, after at least 5 min of complete bed rest, three times a day. Each time BP was measured twice, and the average was recorded. Pulse pressure was calculated as the difference between the systolic and diastolic BP. The average of the three sets obtained during the day was calculated for the analysis.

Mortality Data

Mortality data from 1 January 1999 through and including 31 August 2004 were extracted from the Population Registry of the Ministry of Interior Affairs. Cause of death was obtained from death certificates and medical records. Cardiovascular mortality was defined as death from myocardial infarction, congestive heart failure, sudden death, aortic aneurysm rupture, arrhythmia or other thromboembolic events.

Data Analysis

Analysis of data was carried out using SPSS 9.0 statistical analysis software (SPSS Inc., Chicago, IL). Relative operating characteristic (ROC) curves including death as the test variable were used to identify the PP cutoff point at 62.5 mmHg. Based on this, subjects were categorized as having mean PP less than or equal to 62.5 (low PP group) or greater than 62.5 mmHg (high PP group). Distributions of continuous variables were assessed for normality using the Kolmogorov-Smirnov test (cutoff at $p < 0.01$). Continuous variables were described using the mean $\pm$ standard deviation. Categorical variables are described using frequency distributions and are presented as frequency (%). The t-test for independent samples or the Mann-Whitney U test was used to compare continuous variables by PP group. The chi-square test (exact as needed) was used to assess associations between the PP group and other categorical variables. Cox proportional hazards were used to model all-cause survival and to estimate hazard ratios (HR) with 95% confidence intervals (CI). All tests are two-sided and considered significant at $p < 0.05$.

RESULTS

Patients' Characteristics

Table 1 shows the patients' characteristics. The subjects with high PP were more likely to be females and to have hypertension, diabetes mellitus and atrial fibrillation and had higher BP (both systolic and diastolic) but lower heart rate.

No difference was found in the laboratory values between the two groups except for the levels of folic acid, which were marginally higher in patients with low PP (Table 1).

Mortality Data

The mortality rate was greater in patients with high PP than in those with low PP (Fig. 1). During the follow-up 201 patients died, 155 patients (51%) in the high PP group and 46 patients (39.7%) in the low PP group ($p = 0.038$).

A total of 230 causes were recorded for 201 deaths because more than one cause of death was identified for some patients. The most common causes for death were CVD and sepsis (Table 2). The increased mortality in patients with high PP was

Table 1. Patient Characteristics by Pulse Pressure Group

Population characteristics	PP>62.5mmHg (n = 304)	PP≤62.5mmHg (n = 116)	P value
Age (years)	81.3+/-6.7	81.6+/-6.5	0.621
Sex (% females)	56	44	0.028
BMI (kg/m ²)	25.4+/-4.3	24.7+/-4.7	0.131
Comorbidities (%)			
Hypertension	69.6	44.8	<0.0001
Ischemic heart disease	54.5	61.2	0.210
Congestive heart failure	28.4	34.8	0.200
Diabetes	31.9	22	0.037
Chronic renal failure	19.7	27.6	0.082
Atrial fibrillation	15.6	29.6	0.001
Smokers	14.8	19.8	0.217
Admitting Diagnosis* (%)			
Elective admission for investigation	10.5	16.4	0.1
Neurological problems	13.8	11.2	0.5
Respiratory system disease	11.8	12.9	0.8
Functional decline (due to fever, delirium)	14.1	12.1	0.6
Cardiovascular disease	12.2	13.8	0.7
Hemodynamic values			
Heart rate (bpm)	79.5+/-11.7	82.2+/-13.2	0.043
Systolic blood pressure (mmHg)	151.5+/-17.8	121.2+/-12.3	<0.0001
Diastolic blood pressure (mmHg)	73.4+/-11.3	65.8+/-10.2	<0.0001
Mean arterial pressure (mmHg)	100+/-12.6	93.3+/-12.4	<0.0001
Pulse pressure (mmHg)	78.1+/-11.3	55.4+/-5.8	<0.0001
Prescribed medications (%)			
Diuretics	31.3	37.1	0.256
ACEI/ARBs	31.3	30.2	0.831
Calcium channel blockers	32.2	24.1	0.105
Nitrates	25.3	28.5	0.516
Beta blockers	19.1	17.2	0.665
Tranquilizers	28	25.00	0.542
Laboratory parameters			
Hgb (g/dL)	12.1 $\pm$ 1.7	12.4 $\pm$ 1.7	0.182
Glucose (mg/dL)	122.2 $\pm$ 51.0	113.2 $\pm$ 34.4	0.295
Urea (mg/dL)	42.4 $\pm$ 20.7	43.0 $\pm$ 22.8	0.967
Creatinine (mg/dL)	1.17 $\pm$ 0.6	1.16 $\pm$ 0.59	0.747
Potassium (mEq/L)	4.19 $\pm$ 0.5	4.22 $\pm$ 0.5	0.539
Sodium (mEq/L)	139.4 $\pm$ 3.4	139.5 $\pm$ 3.8	0.790
TSH (mIU/L)	2.7 $\pm$ 7.2	3.4 $\pm$ 10.7	0.389
Vitamin B12 (pmol/L)	487.4 $\pm$ 400.2	418.1 $\pm$ 304.9	0.374
Folic acid (nmol/L)	8.3 $\pm$ 4.5	7.4 $\pm$ 4.3	0.055
Urine albumin (mg/dL)	18.8 $\pm$ 56.5	15.6 $\pm$ 53.4	0.208

PP = Pulse pressure, BMI = Body mass index, ACEI/ARBs = angiotensin converting enzyme inhibitors, angiotensin receptor blockers.

*The 5 most common admitting diagnoses

mainly driven by the increased mortality from sepsis (Table 2; $p = 0.013$).

A multivariate Cox proportional hazards model analysis demonstrated that PP [HR=1.69 (95% CI: 1.19–2.38) $p = 0.003$], male gender [HR=1.609 (95% CI: 1.21–2.14) $p = 0.001$], age [HR per 1 year=1.099, (95% CI: 1.07–1.13) $p < 0.0001$], diabetes mellitus [HR=1.686, (95% CI: 1.23–2.31) $p = 0.001$], atrial fibrillation [HR=1.427, (95% CI: 1.02–2.00) $p = 0.039$] and elevated heart rate [HR for increase in 1 bpm=1.017 (95% CI: 1.01–1.03) $p = 0.004$] increased all-cause mortality risk.

Further analysis indicated that PP>62.5 mmHg remains a significant, independent predictor of all-cause mortality even when modeled in each sex separately. In men, survival could be predicted by age (HR 1.08, 95% CI 1.05–1.11, $p < 0.0001$), PP (HR 1.59, 95% CI 1.02–2.44, $p = 0.04$) and mean heart rate

Figure 1. Survival by pulse pressure group, PP=pulse pressure.

(HR 1.02, 95% CI 1.0–1.03, $p=0.048$). In women, survival was predicted by age (HR 1.1, 95% CI 1.06–1.15, $p<0.0001$), PP (HR 1.79, 95% CI 1.03–3.03, $p=0.04$), mean heart rate (HR 1.02, 95% CI 0.99–1.03, $p=0.06$), diabetes (HR 2.3, 95% CI 1.5–3.6, $p<0.0001$) and body mass index (HR 0.90, 95% CI 0.85–0.95, $p<0.0001$).

In subjects older than 80 years, PP remained a significant, independent predictor of all-cause mortality (HR 1.82, 95% CI 1.19–2.70, $p=0.001$) even after controlling for other predictor variables. In subjects younger than or equal to 80 years, PP was no longer significantly associated with all-cause mortality (HR 1.30, 95% CI 0.69–2.38, $p=0.42$).

DISCUSSION

In this study of very elderly hospitalized patients, PP greater than 62.5 mmHg was found to be a significant predictor of all-cause mortality.

This finding is consistent with results from other studies in less elderly subjects^{10–15}. Some investigators did not observe an association between PP and mortality in cohorts of middle-aged and elderly subjects^{8,16–18}. This lack of consistency between the studies could be explained, at least in part, by

different settings and different age groups and races. Benetos et al., who studied a very large cohort of subjects in the age range of 40–69 years, found an association between PP and CVD mortality¹⁵, whereas Protogerou et al., who studied 331 hospitalized very elderly patients (85±7 years old), did not observe any association between PP and mortality¹⁶.

Unexpectedly, PP in our study was associated only with non-CVD mortality, findings consistent with other reports^{17,18}. One possible explanation for this observation is selection bias,

Table 2. Major Causes of Death by PP Group

P value	PP≤62.5 mmHg (n=116)		PP>62.5 mmHg (n = 304)		Total mortality Causes of death
	% died	N	% died	N	
0.038	39.7	46	51	155	CVD*
0.572	19.8	23	22.4	68	Sepsis
0.013	14.7	17	26	79	CVA**
0.92	5.2	6	4.9	15	Cancer
0.651	6	7	4.9	15	

CVD*—Cardiovascular disease

CVA**—Cerebrovascular accident

such that subjects with CVD could have been systematically excluded from the study by virtue of hospitalization in other departments. Alternatively, this observation might reflect a 'survivors' effect' of these very old subjects who survived the deleterious effect of PP.

Among those with higher PP, more people died of sepsis. Elevated PP is a marker of atherosclerosis, and both atherosclerosis and sepsis share several pathophysiologic similarities, including immune dysregulation, increased thrombogenesis and systemic inflammation. Moreover, statins reduce atherosclerosis and inflammation and also reduce the risk of sepsis-related mortality¹⁹.

Elevated PP can result from either elevated systolic BP or low diastolic BP, or both. In our study, elevated PP was related to increased systolic BP with less elevated diastolic BP. Other studies showed that increased PP due mainly to low diastolic pressure is also associated with increased mortality²⁰. These findings suggest that the PP itself and not elevated systolic BP or low diastolic BP is associated with increased mortality.

An important limitation of our study is that we included only hospitalized geriatric patients who were willing to cooperate and could stand up on their feet nearly by themselves and who survived the hospitalization. This prevents us from generalizing our findings to community-dwelling elderly with a great deal of confidence. However, since we included subjects who had recovered from acute illness and we measured the BP before hospital discharge, we believe the population may be similar to community-residing elderly.

It follows that similar prospective studies, both observational and interventional, should be done in elderly community residents to confirm our results.

Acknowledgments: None

Conflict of interest: None disclosed.

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