Relationship Between High Aortic Pulse Pressure and Extension of Coronary Atherosclerosis in Males

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Summary

A high pulse pressure (PP) is a marker of increased artery stiffness and represents a well-established independent predictor for cardiovascular morbidity and mortality. The objective of the research was to determine whether invasively measured central aortic PP was related to the presence and severity of coronary artery disease. In total 1075 consecutive stable male patients undergoing diagnostic coronary angiography with a preserved left ventricular function were included. Diseased coronary vessel (DCV) was defined by the presence of >50 % stenosis. Men were divided into 3 groups according to the increased value of PP. The average PP in the tertiles was 47.8±7.1 vs. 67.0±4.9 vs. 91.3±12.8 mm Hg (p<0,01). The significant differences of DCV was found among tertiles (1.51±1.11 vs 1.80±1.04 vs. 1.99±0.98 DCV, p<0.01). Aortic PP together with age and hyperlipoproteinemia were found as factors with an independent relationship to DCV according to multivariate linear regression. In conclusions the increased value of aortic PP in the male population is independently connected with more severe atherosclerosis evaluated by the significant number of DCV.

Key words

Pulse pressure • Coronary artery disease • Atherosclerosis

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Introduction

A high pulse pressure is a marker of increased artery stiffness and represents a well-established independent predictor for cardiovascular morbidity and mortality (Benetos *et al.* 2000, Domanski *et al.* 2002, Domanski *et al.* 2001, Millar *et al.* 1999) in hypertensives and even in those considered as having normal blood pressure (Benetos *et al.* 1998). High pulse pressure is associated with an increased risk of heart failure, independently of mean arterial pressure (MAP) and of the occurrence of acute myocardial infarction (Kostis *et al.* 2001). Few studies, involving a limited number of patients, have investigated the relation between aortic PP and angiographically documented diseased coronary vessels (DCV) (Jankowski *et al.* 2004, Nishijima *et al.* 2001) The values of PP are dependent on age and gender (Franklin *et al.* 1997, Franklin *et al.* 2001, Parenica *et al.* 2005). The objective of the research was to determine whether invasively measured aortic PP was related to the presence and severity of DCV in stable male patients with a preserved left ventricular function undergoing diagnostic coronary angiography.

Methods

Study population

From January 2001 to September 2003 in total 4,697 patients were referred to the cathlab of the

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Cardiology Department of Faculty Hospital Brno for diagnostic coronary angiography. Patients with acute myocardial infarction, those with aortic valve disease (aortic stenosis with peak to peak gradient >25 mm Hg, aortic regurgitation greater than grade 1) and those with heart failure and/or ejection fraction (EF) <45 % were excluded from the analysis. Altogether 1075 consecutive men were included. Informed written consent was obtained from all subjects before participation in the trial. The study protocol complied with the Declaration of Helsinki and was approved by the local Ethics Committee.

Definitions and study protocol

Baseline characteristics (history, current symptoms and risk factors) and medication were established before examination. The presence of diabetes mellitus was defined as fasting blood glucose of ≥7 mmol/l or use of an antidiabetic drug or insulin. Hypercholesterolemia was defined as total plasma cholesterol ≥5 mmol/l or LDL cholesterol ≥2.6 mmol/l or being prescribed a lipid-lowering drug. Angina pectoris were assessed according to Canadian Cardiology Society classifications.

Invasive intra-aortic systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a fluid-filled catheter (4Fr pigtail catheter) in the ascending aorta with the patient in the supine position. Aortic PP was calculated as the difference between aortic SBP and aortic DBP, mean arterial pressure was calculated [MAP = DBP + (SBP – DBP)/3]. Heart rate was recorded using electrocardiography monitoring. Diseased coronary vessel was defined by the presence of at least one >50 % reduction of intraluminal diameter on any of the coronary arteries (left main, left anterior descending, left circumflex, right coronary arteries), or the main branches with diameter ≥2.0 mm. Significant left main artery stenosis was coded as two-vessel disease. Analysis of the coronary angiograms was made by the consensus of two out of seven experienced doctors. Ejection fraction was determined by the left ventricle angiography.

Data analysis and statistics

Data were reported as mean ± standard deviation for continuous variables and percentage proportion for discrete variables. For testing differences between groups Student's t-test for continuous variables (all were normally distributed) and Pearson χ^2-test for categorical variables were used. The differences in means of continuous variables among several groups of patients were analyzed using ANOVA followed by the post-hoc LSD test. Pearson's correlation coefficient was used to determinate relation between variables. Univariate and multivariate linear regression were used for adjusting PP and DCV values on influence of patients characteristics, comorbidities and medication. Preselection of variables based on univariate linear regression and expert opinion followed by backward stepwise algorithm were used for the definition of multivariate models.

Results

Clinical characteristics of the 3 groups (tertiles) according to the increased value of pulse pressure are listed in Table 1. Pulse pressure significantly correlated with systolic blood pressure (Pearson's correlation coefficient was 0.90), determination coefficient from linear regression model was 0.818. Pearson's correlation coefficient between PP and diastolic blood pressure was 0.23, the coefficient of determination was low – 0.057. No correlation was found between aortic pulse pressure and heart rate. Pulse pressure rose with age (Pearson's correlation coefficient was 0.41; $p<0.01$) (Figure 1), but the coefficient of determination was 0.17, i.e. only 17 % of variability of pulse pressure could be explained by age.

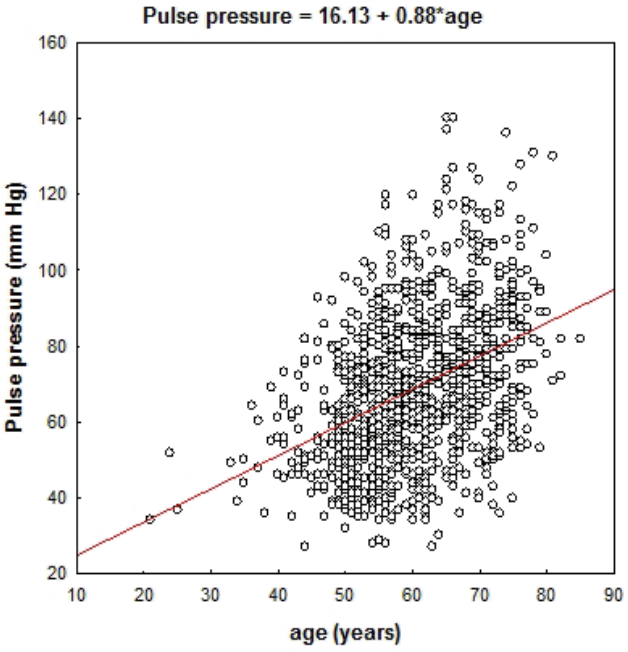

Fig. 1. Relation of pulse pressure and age.

Table 1. Characteristics and medication of population according to the increasing pulse pressure.

	Totally (n = 1075)	**1st tertile (n = 343)**	**2nd tertile (n = 368)**	**3rd tertile (n = 364)**	
Aortic PP (mm Hg)	69.1 ± 19.9	47.8 ± 7.1	67.0 ± 4.9	91.3 ± 12.8	p < 0.01 [a]
Range of aortic PP (mm Hg)	27 - 140	27 - 58	59 - 75	76 - 140	
Aortic systolic BP (mm Hg)	138.0 ± 24.5	113.7 ± 13.0	135.9 ± 11.4	162.9 ± 17.2	p < 0.01 [a]
Aortic diastolic BP (mm Hg)	68.9 ± 10.4	65.8 ± 9.8	68.9 ± 10.1	71.8 ± 10.4	p < 0.01 [a]
Aortic MAP (mm Hg)	91.9 ± 13.6	81.8 ± 10.4	91.3 ± 10.3	102.2 ± 11.5	p < 0.01 [a]
Heart rate (min^{-1})	67.5 ± 11.7	68.3 ± 11.6	67.9 ± 11.4	66.5 ± 12.0	p = 0.32 [a]
Diabetes mellitus	25.0 %	20.1 %	23.9 %	30.8 %	p < 0.01 [b]
History of cerebrovascular disease	4.2 %	0.9 %	5.4 %	6.0 %	p < 0.01 [b]
Smoking	64.2 %	71.8 %	63.6 %	57.9 %	p < 0.01 [b]
Dyslipidemia	54.1 %	51.3 %	58.7 %	51.9 %	p = 0.09 [b]
History of hypertension	64.9 %	55.1 %	64.7 %	74.5 %	p < 0.01 [b]
Creatinine (µmol/l)	(n = 761) 102.3 ± 30.1	(n = 249) 97.5 ± 14.1	(n = 254) 102.3 ± 24.4	(n = 258) 108.2 ± 42.9	p < 0.01 [a]
Ejection fraction LV (%)	60.3 ± 7.7	60.1 ± 7.7	60.4 ± 7.9	60.3 ± 7.6	p = 0.88 [a]
Diseased coronary vessels	1.77 ± 1.06	1.51 ± 1.114	1.80 ± 1.04	1.99 ± 0.98	p < 0.01 [a]
Angina pectoris according to CCSC					p < 0.01 [b]
- Without angina pectoris	44.5 %	49.6 %	43.8 %	40.4 %	
- CCSC 1	6.5 %	8.2 %	6.3 %	5.2 %	
- CCSC 2	28.8 %	26.8 %	30.2 %	29.4 %	
- CCSC 3	14.0 %	8.7 %	14.1 %	19.0 %	
- CCSC 4	1.3 %	1.2 %	0.5 %	2.2 %	
- Missing	4.8 %	5.5 %	5.2 %	3.8 %	
Body Mass Index (kg/m^2)	28.4 ± 3.8	28.7 ± 4.0	28.3 ± 3.8	28.3 ± 3.6	p = 0.18 [a]
Weight (kg)	86.7 ± 13.5	89.5 ± 14.5	85.9 ± 13.4	84.9 ± 12.1	p < 0.01 [a]
Age (years)	60.5 ± 9.3	56.0 ± 9.2	60.4 ± 8.4	64.8 ± 8.2	p < 0.01 [a]
Medication					
Peroral antidiabetics and/or Insulin	14.1 %	8.8 %	12.2 %	20.9 %	p < 0.01 [b]
Fibrates	9.2 %	8.2 %	10.3 %	9.1 %	p = 0.61 [b]
Statins	42.5 %	36.7 %	47.3 %	43.1 %	p = 0.02 [b]
Diuretics	23.4 %	23.6 %	21.7 %	25.0 %	p = 0.58 [b]
AT_2 blockers	1.1 %	0.9 %	1.4 %	1.1 %	p = 0.83 [b]
ACE inhibitors	51.3 %	43.7 %	51.4 %	58.2 %	p < 0.01 [b]
Calcium antagonists	22.9 %	18.1 %	22.3 %	28.0 %	p = 0.01 [b]
Nitrates	57.5 %	47.8 %	60.6 %	63.5 %	p < 0.01 [b]
Beta-blockers	70.6 %	68.2 %	70.4 %	73.1 %	p = 0.40 [b]
Digoxin	4.7 %	5.0 %	4.4 %	5.0 %	p = 0.91 [b]
Antiplatelets	87.4 %	84.8 %	85.9 %	91.2 %	p = 0.22 [b]

[a]Analysis of variance, [b]Goodness-of-fit test. PP, Pulse pressure; BP, Blood pressure; CCSC, Canadian Cardiology Society Classification; AT_2, antagonist for type 2 of receptor for angiotensin II; ACE, angiotensin-converting enzyme

Table 2. Univariate and multivariate linear regression to define medications with independent relationship to the pulse pressure.

	Univariate			Multivariate including age		
	Coefficient	Confidence interval	p[1]	Coefficient	Confidence interval	p[1]
Age	0.876	0.759; 0.993	**<0.001**	0.816	0.695; 0.936	**<0.001**
ACE-AT$_2$	5.332	2.978; 7.687	**<0.001**	2.521	0.324; 4.718	**0.025**
ACE	5.311	2.957; 7.664	**<0.001**	–		
AT$_2$ blockers	3.624	–7.672; 14.920	0.529	–		
Beta-blockers	1.504	–1.088; 4.096	0.255	–		
Fibrates	–0.703	–4.808; 3.402	0.737	–		
Statins	1.809	–0.590; 4.207	0.139	–		
Diuretics	1.307	–1.494; 4.108	0.360	–		
Ca-blockers	5.333	2.525; 8.140	**<0.001**	3.485	0.894; 6.075	**0.008**
Nitrates	5.899	3.524; 8.274	**<0.001**	2.174	–0.096; 4.444	0.060
Digitalis	–0.684	–6.268; 4.900	0.810	–		
Antiplatelets	3.647	0.083; 7.211	**0.045**	0.836	–2.479; 4.152	0.621

[1] test of statistical significance of regression coefficients of linear regression; statistically significant coefficients are given in bold

Table 3. Univariate and multivariate linear regression to define variables with independent relationship to the number of diseased vessels.

	Univariate			Multivariate		
	Coefficient	Confidence interval	p[1]	Coefficient	Confidence interval	p[1]
Age	0.031	0.024; 0.037	**<0.001**	0.027	0.020; 0.034	**<0.001**
BMI	–0.010	–0.027; 0.007	0.233	–		
Smoking	0.062	-0.075; 0.199	0.377	–		
Diabetes	0.165	0.019; 0.312	**0.027**	–		
HLP	0.129	0.002; 0.256	**0.047**	0.172	0.050; 0.295	**0.006**
Adjusted Pulse P[2]	0.010	0.007; 0.014	**<0.001**	0.005	0.002; 0.009	**0.002**
Adjusted Systolic BP[2]	0.004	0.001; 0.007	**0.003**	–		
Adjusted Diastolic BP[2]	–0.015	–0.021; –0.009	**<0.001**	–		
Adjusted Mean BP[2]	–0.002	–0.006; 0.003	0.489	–		

[1] test of statistical significance of regression coefficients of linear regression; statistically significant coefficients are given in bold;
[2] adjusted for ACE-AT$_2$, Beta-blockers, Fibrates, Statins, Diuretics, Ca-blockers, Digitalis

According to multivariate analysis ACE inhibitors and/or AT 2 blockers and Ca blockers modify the pulse pressure (Table 2). Smokers had lower PP (67.5±19.5 mm Hg vs. 72.5±19.5 mm Hg; p<0.01) and a comparable average number of DCV (1.79±1.04 vs. 1.73±1.12; p=NS), but after adjustment for age, the difference in PP was insignificant and they had a significantly higher number of diseased coronary vessels (p<0.01).

Patients with diabetes had higher PP (73.7±20.2 vs. 67.6±19.5 mm Hg; p<0.01) and a significantly higher number of DCV (1.90±1.05 vs. 1.73±1.06; p=0.03); after adjustment for age, the difference in PP was still significant, but there was no significant difference in DCV.

Patients with hyperlipoproteinemia had comparable PP (69.0±18.9 vs. 69.2±20.9 mm Hg, p=NS) even after adjustment for age, but they had a significantly

higher number of DCV (1.83±1.03 vs. 1.70±1.10, $p<0.05$) even after adjustment for age ($p<0.01$).

Patients with a history of hypertension had a significantly higher pulse pressure (71.8±19.8 mm Hg vs. 64.1+19.0 mm Hg; $p<0.01$) even after adjustment for age. After adjustment for age, there was no significant difference in DCV.

We found a statistically significant difference of DCV in tertiles according to increased PP ($p<0.01$; Table 1). To ensure an independent influence of pulse pressure on the number of diseased vessels without an influence of other possible factors, univariate and multivariate linear regression was done (Table 3). Values of PP, SBP, DBP and MAP adjusted for medication were used. Although there were found significant relationships between PP, SBP, DBP and number of DCV in univariate analysis, only PP together with age and hyperlipoproteinemia were revealed as factors with an independent relationship to DCV according to multivariate analysis.

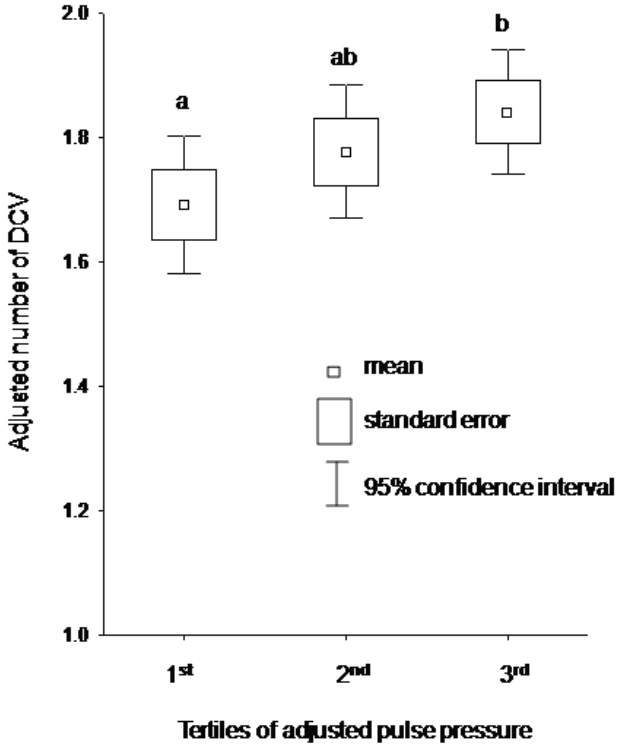

Fig. 2. Increasing number of significantly diseased coronary vessels in tertiles according to increasing pulse pressure adjusted to age and medication. Number of diseased vessels was adjusted for age and hyperlipoproteinemia. a,b – denotes statistically homogeneous groups revealed by LSD post hoc test

The Figure 2 demonstrates the difference of adjusted number of DCV according to the tertiles of the adjusted pulse pressure. The PP was adjusted for age and medications. The number of diseased vessels was adjusted for age and hyperlipoproteinemia as the independent variables found according to multiple linear regression. The adjusted pulse pressure was divided into tertiles and the adjusted number of diseased vessels was compared by ANOVA and post hoc LSD test. The differences in number of diseased vessels significantly differed among tertiles (ANOVA, $p=0.049$, $F=3.16$, $df_1=2$, $df_2=1072$). Statistically significant differences in the number of the adjusted diseased vessels were found between 1st tertile and 3rd tertile.

Discussion

Only men were evaluated, because there is a significant difference between pulse pressure of men and women and the predictive value of pulse pressure for coronary artery disease was demonstrated above all for males (Franklin *et al.* 1997). It is necessary to evaluate the relation of PP and CAD for women separately.

Based on our best knowledge, the present study is so far the largest among those documenting an association between the value of invasively determined aortic PP and the extent of atherosclerosis of coronary arteries assessed from the number of diseased coronary vessels of men (Danchin *et al.* 2004). Our results are consistent with smaller studies previously presented. Philippe *et al.* (2002) represented in 99 patients that only invasive aortic pulse pressure, but not non-invasive brachial pulse pressure, and male gender were in a multiple regression analysis independently associated with the extent of coronary heart disease. Jankowski *et al.* (2004) found that pulse pressure, fractional systolic and diastolic blood pressure (systolic and diastolic blood pressure normalized to the mean blood pressure) of the ascending aorta was related to the risk of three-vessel disease in 445 patients (350 men) with coronary artery disease and a preserved left ventricular function. Weber *et al.* (2004) evaluated augmentation index and augmented pressure as manifestations of arterial stiffness in 465 men. Augmented pressure was defined as the difference between the second and the first systolic peak, augmentation index was augmented pressure expressed as a percentage of the calculated aortic pulse pressure. Augmentation index and augmented pressure were independent risk markers for premature coronary artery disease. More over there was demonstrated the aortic augmented pressure predicted adverse outcomes in patients with CAD independently of pulse pressure and

other risk markers (Chirinos *et al.* 2005).

We did not find a significant relation between PP and heart rate. The rise of non-invasively established brachial PP with increasing heart rate, but not aortic PP, is in the result of an increase of PP amplification (Laurent *et al.* 2003).

We made univariate and then multivariate linear regression to detect a significant relationship between the previous treatment and the values of the pulse pressure. We revealed that there was an independent positive correlation of the aortic pulse pressure with previous treatment only by ACE inhibitors and/or AT_2 blockers and Ca blockers. This result can be explained by the fact that the patients with high pulse pressure had more severe hypertension and they were more often treated by these drugs (subjects in the 3rd tertile used more often ACE inhibitors, Ca antagonists, nitrates and statins and more often they had a history of hypertension and in average more severe symptoms of angina pectoris). Our results did not assess the direct effect of the drugs on the aortic PP. Published data about the effect of antihypertensive drug classes on brachial PP are not unique (Chang *et al.* 2003, Cushman *et al.* 2001); besides this, individual antihypertensive classes have a different effect on brachial and central pulse pressure (Morgan *et al.* 2004). CAFE study (a sub study of the ASCOT trial, which compared the active treatments based on calcium antagonist amlodipine with or without perindopril with treatment based on beta-blocker atenolol) demonstrated clearly that beta-blockers do not lower central systolic and pulse pressure as much as calcium antagonists (Williams *et al.* 2006).

It was interesting to find relationship between aortic pulse pressure and the number of diseased coronary vessels independently on age. Based on published prospective studies in patients <50 years of age, brachial diastolic blood pressure was the strongest predictor of coronary heart disease risk, age 50 to 59 years was a transition period when all 3 blood pressure indexes were comparable predictors and from 60 years of age on, diastolic blood pressure was negatively related to coronary heart disease risk so that brachial pulse pressure became superior to systolic blood pressure (Franklin *et al.* 2001).

Arterial stiffness, which leads to higher pulse pressure, has deleterious effects on left ventricular afterload, increases left ventricular mass, decreases coronary perfusion and leads to increased cardiovascular morbidity and mortality in different populations. Our results confirming the relationship between the extension of atherosclerosis of coronary vessels and the value of PP could explain the possible sequence of higher cardiovascular mortality in patients with higher pulse pressure.

In conclusion, increasing value of central aortic pulse pressure in male population is connected to more severe atherosclerosis. According to multivariate analysis the pulse pressure, age and hyperlipoproteinemia were evaluated as independent factors with relationship to the number of significantly diseased coronary vessels.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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