RELATIONSHIP BETWEEN CLINICAL, 24–HOUR, AVERAGE DAY-TIME AND NIGHT-TIME BLOOD PRESSURE AND MEASURES OF ARTERIAL STIFFNESS IN ESSENTIAL HYPERTENSION

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SUMMARY

Arterial wall stiffness is considered an independent cardiovascular risk factor. Aim of this study was to evaluate relationship between clinical, 24-hour, average day-time and night-time blood pressure (BP) and measures of arterial stiffness assessed by pulse wave velocity (PWV) (using SphygmoCor applanation tonometer) in essential hypertension /severe-resistant (n-29) (RH) and moderate hypertension (n-35) (EH)/ and in normotensive control subjects (n-29) (NCS) matched by age. After multiple regression analysis, PWV remains significantly correlated mainly with night-time pulse pressure and to a lesser extent with age. PWV was significantly higher in RH compared to moderate EH and NCS.

MAIN BODY OF TEXT

Hypertension is a major risk factor for the development of cardiovascular diseases and the benefits of reducing blood pressure (BP) are well established (MacMahon et al.1990). The role of large arteries in the genesis and maintenance of hypertension has been recently widely studied. Their function is twofold: 1. to conduct blood to distributing networks of smaller arteries and the microvasculature, 2. to act as compliant elements buffering the changes in pressure arising during the cardiac cycle. Both these functions depend on the mechanical properties of the vessel wall. These properties can change in response to disease and, conversely, may also contribute to disease progression. Arteries become stiffer with increasing age and

disease (e.g. hypertension, diabetes and atherosclerosis). Structural changes contributing to an increase in arterial stiffness include fragmentation of elastin, increased deposition of collagen fibres and cross-linking of collagen molecules by advanced glycation end-products (Hope et al. 2007). Although structural changes may be quantified pathologically, clinical evaluation of arterial stiffness mechanical properties is more complex and a complete description of the stress-strain relationship of arteries in vivo is not possible. Commonly applied methods include the measurement of transit times between different sites in the vasculature and calculation of arterial pulse wave velocity (PWV), measurement of regional arterial stiffness (Van Bortel et al. 2002). Large variety of predictors of arterial stiffness can be found in the literature. PWV appears to be a reliable parameter of arterial stiffness measurement influenced by few factors – age, heart rate (HR), diastolic blood pressure (DBP) (Nürnberger et al. 2003). Furthermore, arterial stiffness, determined by carotid-femoral PWV, may predict cardiovascular and all-cause mortality beyond classic risk factors in hypertensive, end-stage renal disease, diabetic patients and in general population (Laurent et al. 2001).

We studied the determinants of arterial stiffness with special interest in the relationship between clinical BP, 24h BP, average day-time and night-time BP and PWV. At the same time arterial stiffness assessed by use of carotid-femoral PWV in patients with severe-resistant hypertension (RH) was evaluated in comparison to patients with moderate essential hypertension (EH) and to normotensive control subjects (NCS).

We studied 29 patients with RH, 35 patients with moderate to severe EH and 29 NCS. Patients with moderate to severe arterial hypertension were investigated during hospitalization. Subjects were recruited from patients recommended to our Hypertension centre from other health care facilities, mostly from middle Czech region in order to exclude secondary hypertension. Common forms of secondary hypertension (primary aldosteronism, pheochromocytoma, Cushing's syndroma, renal parenchymal disease or renovascular hypertension) were excluded in all patients. RH was defined before hospitalization as follows: 1.clinical arterial BP 140/90 mmHg and higher by use of three or more antihypertensive drugs including diuretics, or 2. home arterial BP 135/85 mmHg or more by use of three or more antihypertensive drugs including diuretics, or 3. 24h mean BP 130/80mmHg or higher by use three or more antihypertensive drugs including diuretics (Mancia et al. 2007).The diagnosis of EH was made by the exclusion of secondary hypertension and the exclusion of RH diagnosis. All patients discontinued their usual antihypertensive

therapy and were switched to an alpha blocker (doxazosine) and slow releasing calcium channel blocker (verapamil) at least 14 days before investigation to standardize the treatment not affecting renin angiotensin aldosteron system and to minimize the influence of several drugs on arterial wall properties (PWV). Normotensive controls were recruited from subjects without history of hypertension or cardiovascular disease, mostly from staff of hospital, who were free of antihypertensive medication.

The following parameters were measured in all studied objects: carotid-femoral PWV measurement was performed by use of the applanation tonometer Sphygmocor (AtCor Medical, West Ryde, Australia). Clinical blood pressure values were obtained using an oscillometric sphygmomanometer (Dinamap, Critikon, Tampa, FL, USA). 24-hour ambulatory blood pressure monitoring (ABPM) during hospitalization was performed using an oscillometric device (SpaceLabs 90207; SpaceLabs Medical, Redmond, Washington, USA). All biochemical parameters were analyzed using multi-analyzers (Hitachi 717, Boehringer Mannheim, Germany) in the institutional central laboratory.

Depending on the normal/non-normal distribution (Shapiro-Wilks W test) of particular variables, the data are shown as means±standard deviation (SD) or median (interquartile range). Multiple-group comparisons were performed by one-way analysis of variance (ANOVA), followed by the Scheffe's post hoc test. Differences between both hypertensive groups were analyzed using a two-tailed t-test. Kruskal-Wallis test was used for non-normal distributed variables. Pearson's correlation analysis was applied to detect correlations of PWV to measured parameters and confounding factors in hypertensive patients. Multiple regression analysis, stepwise forward method, was applied to only those parameters which significantly correlated with PWV. A p-value < 0,05 was considered to be significant. The statistical software Statistica (StatSoft, Inc. (2003), STATISTICA Cz, version 6) was used for the analysis.

The characteristics of the studied groups are shown in Table 1. There were no significant differences in most confounding factors like age, duration of hypertension, BMI, lipid profile, fasting glucose, creatinine levels between RH and EH groups. PWV was significantly higher in RH group when compared to EH and to NCS, while clinical BP was comparable. Results might be affected by lowering effect of medication on PWV. This might be the cause of relatively small difference in PWV between both hypertensive groups and NCS. However, 24h ABPM values were significantly higher in the RH group than in the EH group. PWV correlated with age, clinical systolic blood pressure (SBP), brachial pulse pressure (PP), 24h SBP and PP, day SBP and PP, night SBP and PP. After multiple regression analysis, PWV remains significantly correlated mainly

with night PP and to a lesser extent with age. Results of simple and multiple regression analysis are shown in Table 2. Our findings are in line with other studies, where association of circadian variations of BP and night-time BP with target organ damage has been reported (Mancia et al. 2007, Routledge et al. 2007).

Our data indicate, that night-time BP appears to be a more accurate predictor of PWV in essential hypertension. It suggests the importance of 24h ABPM in order to identify higher cardiovascular risk patients and the importance of whole day hypertension control. Patients with RH have higher arterial stiffness (represented by carotid-femoral PWV) when compared to moderate EH patients. This difference appears to be independent of clinical blood pressure at the time of measurement.

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Table 1. Characteristics of studied subjects

	RH	EH	NCS	p-value
Number of subjects, n	29	35	29	-
Age [years]	51±10	49±10	44±15	0,989
Duration of hypertension [years]	16 (6-26)	11 (6-16)	-	0,204
Body mass index [kg.m^{-2}]	29,2±4,9†††	28,8±4,3††	24,8±3,6	<0,001
Total plasma cholesterol [mmol/l]	5,3±1,2	5,2±1,1	5,1±1,2	0,870
Triacylglycerides [mmol/l]	1,8±0,9†	1,8±1,0†	1,2±0,5	<0,05
Fasting plasma glucose [mmol/l]	4,9 (4,5-5,4)	4,8 (4,4-5,2)	4,9 (4,5-5,5)	0,717
Creatinine [mmol/l]	82 (71-104)	83 (69-92)	81,5(69,5-93,5)	0,655
Clinical brachial BP [mmHg]	173±22†††/94±11†††	169±18†††/93±12†††	120±14/70±9	<0,001
Brachial pulse pressure [mmHg]	80±20†††	76±15†††	51±9	<0,001
Heart rate [bpm]	74±12††	70±12	63±10	<0,01
24h BP [mmHg]	160±16/98±11	141±15/89±12	-	<0,01
24h pulse pressure [mmHg]	62±13	52±10	-	<0,005
24h heart rate [bpm]	76±10	74±10	-	0,386
Day BP [mmHg]	161±17/100±12	145±16/92±13	-	<0,05
Day pulse pressure [mmHg]	61±13	53±11	-	<0,01
Day heart rate [bpm]	79±10	77±12	-	0,558
Night BP [mmHg]	154±16/91±10	132±15/82±11	-	<0,001
Night pulse pressure [mmHg]	63±14	15±9	-	<0,001
Night heart rate [bpm]	67±9	65±9	-	0,267
Pulse wave velocity [m/s]	9,3±2,2***†††	7,2±1,0†	6,2±1,3	<0,001

Values are shown as means±SD, medians (interquartile range) or absolute numbers. Variables are compared by ANOVA followed by the Scheffe's post hoc test or Kruskal Wallis test or unpaired t-test where appropriate; *p<0,05, **p<0,01, ***p<0,001 vs. EH; †p<0,05, ††p<0,01, †††p<0,001 vs. NCS

Table 2. Simple regression analysis and multiple regression analysis using PWV as dependent variable

	Simple regression		Multiple regression	
	r	p-value	β	p-value
Age [years]	0,4870	<0,001	**0,3471**	**<0,001**
Clinical brachial SBP [mmHg]	0,3989	<0,01	-	-
Brachial pulse pressure [mmHg]	0,5057	<0,001	**-**	**-**
24h SBP [mmHg]	0,5196	<0,001	-	-
24h pulse pressure [mmHg]	0,5982	<0,001	-	-
Day SBP [mmHg]	0,4896	<0,001	0,2087	0,094
Day pulse pressure [mmHg]	0,5555	<0,001	-	-
Night SBP [mmHg]	0,5425	<0,001	**-**	-
Night pulse pressure [mmHg]	0,6396	<0,001	**0,3919**	**<0,005**

r = Pearson's correlation coefficient, β = multiple regression analysis coefficient