The complex nature of arterial stiffness in patients with arterial hypertension

Złożona natura sztywności naczyniowej u chorych z nadciśnieniem tętniczym

Paweł Krzesiński, Adam Stańczyk, Katarzyna Piotrowicz, Grzegorz Gielerak
Department of Cardiology and Internal Diseases, Military Institute of Medicine, Warsaw

Abstract

Introduction. The arterial stiffness has become the target of therapeutic interventions in patients with cardiovascular diseases and the ability to characterize and quantify arterial properties turned out to be of importance. Aim of this study was to evaluate the association of arterial stiffness and peripheral blood flow with clinical characteristics and hemodynamics in patients with arterial hypertension (AH).

Material and methods. The study included 150 patients (111 men; mean age 43.5 years) with AH that underwent clinical evaluation and hemodynamic assessment by impedance plethysmography (IPG) and cardiography (ICG), with analysis of i.e. pulse wave velocity (PWV), mean arterial pressure (MAP), heart rate (HR), stroke index (SI), total artery compliance (TAC), systemic vascular resistance (SVRI), pre-ejection period (PEP) and left ventricular ejection time (LVET).

Results. In comparative analysis PWV was significantly higher in women than men (6.18 ± 0.77 vs 5.91 ± 0.99 m/s; p = 0.035). PWV was also associated with age (R = 0.41), MAP (R = 0.32), HR (R = 0.32), SI (R = –0.47), arterial elasticity (TAC, R = –0.31), vascular resistance (SVRI, 0.38) and sub-periods of heart contraction (PEP, R = 0.59 and LVET, 0.28). Age, MAP, PEP and LVET revealed to be the independent covariates in the multivariate regression model for PWV estimation (R square 0.61).

Conclusions. Bioimpedance methods are complementary for the assessment of complexity of the arterial stiffness. PWV revealed to be associated with hemodynamic parameters characterizing ventricular-vascular interactions, including BP, SVRI, TAC, and characteristics of left ventricle performance (HR, SI, PEP, LVET). In view of the classifying value of PWV in cardiovascular risk evaluation the current patient’s hemodynamic state should be carefully considered.

Key words: arterial hypertension, arterial stiffness, impedance plethysmography, impedance cardiography, pulse wave velocity

(Folia Cardiologica 2015; 10, 1: 1–8)
Introduction

Impaired arterial compliance is one of the main pathophysiological features influencing cardiovascular risk independent from traditional risk factors. In young healthy people arteries are naturally compliant and respond to different clinical and physiological factors assuring optimal perfusion that is dependent on the adequate flow parameters such as blood pressure, volume and its local distribution. The adaptation ability of arterial tree decreases with age, especially in presence of metabolic disturbances, arterial hypertension (AH) and smoking [1–4]. Therefore, the arterial stiffness has become the target of therapeutic interventions in patients with cardiovascular diseases and the ability to characterize and quantify arterial properties turned out to be of importance. Various non-invasive assessment techniques have been developed to evaluate central and peripheral flow. Some markers of arterial remodeling and stiffness such as intima-media thickness and pulse wave velocity (PWV) are recognized as independent risk factors and recommended to be implemented in clinical diagnostics [5]. These methods are easy to perform but more difficult to interpret because characteristics of blood flow depend not only on properties of local arteries but also forward and reflected waves interacting at each level of vasculature.

Impedance plethysmography (IPG) is one of the methods perceived as useful in non-invasive evaluation of peripheral vessels based on the assessment of changes in local tissue electrical properties, mostly deriving from changes in blood volume [6]. It may be performed simultaneously with impedance cardiography (ICG) estimating hemodynamic parameters such as i.e. stroke index (SI), cardiac index (CI), systemic vascular index (SVRI) and total artery compliance (TAC) [7, 8]. The multiparametric hemodynamic assessment enables the possibility to confront peripheral flow with other hemodynamic parameters and indicate its potential relations.

The aim of this study was to evaluate the nature of association of PWV assessed by IPG with clinical characteristics and other hemodynamic parameters in patients with AH.

Material and methods

Study population

This study included 150 patients (111 men; mean age 43.5 ± 10.6 years) with at least 3-month history of AH (grade 1 and 2) defined according to European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guidelines [5]. Exclusion criteria comprised: (1) confirmed secondary AH, (2) AH treated with three or more medicines before recruitment, (3) heart failure, (4) cardiomyopathy, (5) significant heart rhythm disorders, (6) significant valvular disease, (7) impaired renal function (GFR below 60 ml/min/1.73 m²), (8) chronic obstructive pulmonary disease, (9) diabetes, (10) polyneuropathy, (11) peripheral vascular disease, (12) age < 18 years and > 65 years. Patients treated with hypotensive drugs before recruitment (n = 29, 19.3%) were recommended to discontinue pharmacotherapy 7 days before examination.

The group selected to the analysis comprised patients with AH from two clinical studies performed from March 2008 to May 2012. Both studies were conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki, with the approval of local ethics committee. Each patient provided written informed consent to participate in the study. Demographic and clinical characteristics of the study group are shown in Table 1.

Clinical examination

Clinical examination was performed with special consideration of familiar history of AH, cardiovascular risk factors and symptoms indicating secondary cause of AH. Office blood pressure measurement (Omron M4 Plus, Japan) was performed by technique compliant with the ESC guidelines [5]. Laboratory tests included i.e. evaluation of renal function (creatinine, glomerular filtration rate calculated...
Ambulatory blood pressure monitoring
Ambulatory blood pressure monitoring (ABPM) was performed to verify the diagnosis of AH (Spacelabs 90207, Spacelabs, Medical Inc, Redmond, USA). Time from 6 a.m. to 10 p.m. was considered daily activity period (daytime) with automatic blood pressure measurement in 10-minute intervals. During night rest (night-time: 10 p.m.–6 a.m.) the measurement was performed every 30 minutes. The patients were recommended to adjust their circadian activity to those periods of time. The minimum correctness of BP measurement was defined as 70% for both daytime and night-time. Test results were interpreted according to European Society of Cardiology guidelines [5].

Impedance cardiography and impedance plethysmography
All measurements were performed using the Niccomo™ device (Medis, Ilmenau, Germany) with registration of impedance signals of central (ICG, impedance cardiography) and peripheral (IPG, impedance plethysmography) flow assessed on left thigh as presented on Figure 1. Data was recorded in a quiet room after minimum 10 minutes of rest in a supine position and exported to a dedicated software (Niccomo Software, Ilmenau, Germany). The simultaneous registration of ICG and IPG curves enabled the calculation of pulse wave propagation parameters (Figure 2).

The final analysis included mean values of hemodynamic parameters calculated from 10-minute long recording:
1) Basal hemodynamic parameters: systolic blood pressure (SBP, [mm Hg]); diastolic blood pressure (DBP, [mm Hg]); mean blood pressure (MBP, [mm Hg]); pulse pressure (PP, [mm Hg]); heart rate (HR, [bpm]);
2) ICG parameters: sub-periods of cardiac contraction – pre-ejection period (PEP [ms]) and left ventricular ejection time (LVET [ms]); stroke index (SI [ml/m²]), calculated using the Sramek and Bernstein formula SI = VEPT × dZmax × LVET /[Z0] × [BSA], accounting for weight, height and gender (variable VEPT), the amplitude of the systolic wave of the ICG (dZmax), LVET and body surface area (BSA); cardiac index (CI [ml/m²/min]), calculated as CI = SI × HR; systemic vascular resistance index (SVRI, [dyn × s × m⁻⁵/cm⁵]); SVRI = 80 × [MAP-CVP]/[CI], where CVP is central venous pressure (assumed value 6 mm Hg); total arterial compliance (TAC, [ml/mm Hg]), TAC = SV/[PP];
3) IPG parameters: heart to femoral pulse wave velocity (PWV [m/s]) calculated from the formula PWV = [electrode distance]/[PT], where electrode distance was calculated with estimation of length of the thoracic aorta as 0.2 × [height] and pulse wave propagation time (PT [ms]) was the time from the opening of the aortal valve to the beginning of the systolic wave slope in the plethysmogram.

Echocardiography
Two-dimensional echocardiography was performed using standard parasternal, apical, and subcostal views (VIVID 4 and VIVID 7 GE Medical System, 2.5 MHz transducer). The left ventricular hypertrophy was diagnosed according to the ASE-recommended formula for estimation of LV mass from 2D linear LV measurements and indexed to body surface area (cut-off values for men LVMi > 115 g/m², for women > 95 g/m²). The assessment of diastolic dysfunction was performed according to current guidelines [9, 10].

Statistical analysis
The statistical analysis of the results was performed using Statistica 7.0 (StatSoft, Inc.). The distribution and normality of data were assessed by visual inspection and using the Shapiro-Wilk test. Continuous variables were presented as means ± standard deviations (SD) and categorical variables as absolute and relative frequencies (percentages).
Table 2. Hemodynamic characteristics of the study group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study group (n = 150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP [mm Hg], mean ± SD</td>
<td>137.0 ± 11.9</td>
</tr>
<tr>
<td>DBP [mm Hg], mean ± SD</td>
<td>88.4 ± 7.9</td>
</tr>
<tr>
<td>MAP [mm Hg], mean ± SD</td>
<td>100.5 ± 8.6</td>
</tr>
<tr>
<td>PP [mm Hg], mean ± SD</td>
<td>48.6 ± 8.1</td>
</tr>
<tr>
<td>SVRI [dyn × s × m²/cm²], mean ± SD</td>
<td>2346.4 ± 473.5</td>
</tr>
<tr>
<td>HR [bpm], mean ± SD</td>
<td>70.5 ± 10.2</td>
</tr>
<tr>
<td>SI [ml/m²], mean ± SD</td>
<td>48.0 ± 8.8</td>
</tr>
<tr>
<td>CI [ml/m²/min], mean ± SD</td>
<td>3.33 ± 0.53</td>
</tr>
<tr>
<td>TAC [ml/mm Hg], mean ± SD</td>
<td>2.06 ± 0.50</td>
</tr>
<tr>
<td>LVET [ms], mean ± SD</td>
<td>318.6 ± 37.1</td>
</tr>
<tr>
<td>PEP [ms], mean ± SD</td>
<td>97.7 ± 17.5</td>
</tr>
<tr>
<td>PWV [m/s], mean ± SD</td>
<td>5.98 ± 0.94</td>
</tr>
</tbody>
</table>

SBP — systolic blood pressure; SD — standard deviation; DBP — diastolic blood pressure; MAP — mean arterial pressure; PP — pulse pressure; SVRI — systemic vascular resistance index; HR — heart rate; SI — stroke index; CI — cardiac index; TAC — total arterial compliance; LVET — left ventricular ejection time; PEP — pre-ejection period; PWV — pulse wave velocity

Assessment of the relations between hemodynamic parameters was performed using univariate regression. Then, the most correlated and representative variables (age, sex, body mass index, MAP, PEP, SI, SVRI, TAC, LVET, PEP) were included into multivariate regression models to identify the independent covariates of PWV variance. A p value of < 0.05 was taken to indicate statistical significance.

Results

Hemodynamic characteristics of the study group are presented in Table 2.

In comparative analysis PWV was significantly higher in women than men (6.18 ± 0.77 vs 5.91 ± 0.99 m/s, p = 0.035). Smoking status has no significant influence on and PWV (6.03 ± 0.94 vs 5.83 ± 0.97 m/s, p = 0.410).

Univariate regression

In the univariate linear regression analysis the clearest correlations were observed for PWV with age, SI, SVRI, HR, MAP and PEP. Distinctly weaker correlations were found for the other analyzed parameters (Figure 3, Table 3).

Multivariate regression

In the multiple regression model the most representative basal characteristics, that can be easily estimated in office (age, HR and MAP), explained 27% variance of PWV:

$$[PWV] = 0.587 + 0.030 \times [age] + 0.025 \times [HR] + 0.023 \times [MAP] \ (R \ squared \ value \ of \ 0.27).$$

However, the model including the most representative ICG parameters (SI, SVRI, TAC, PEP and LVET) provided additional independent covariates and significantly increased explanatory value of the formula (R squared value of 0.61):

$$[PWV] = 2.068 + 0.035 \times [age] + 0.029 \times [MAP] - 0.009 \times [LVET] + 0.025 \times [PEP] \ (HR \ was \ not \ included \ in \ the \ model \ because \ of \ redundancy \ with \ LVET \ and \ PEP).$$

Thus, the multivariate regression model revealed that PWV depends mostly on modifiable hemodynamic variables.

Discussion

In recent years the idea of evaluation of vessels has been emerging from the shadow of the heart muscle imaging. Our study was aimed to assess the relation of arterial stiffness to the general hemodynamic state. We focused on the identification of determinants of pulse wave propagation and velocity because the arising awareness of important interaction between heart and vessels imposed the evaluation of arterial properties together with cardiac function [11]. The presented results proved that such approach has important pathophysiological and clinical implications.

Arterial stiffness and wave reflection phenomenon were identified as important cardiovascular risk factors in patients with i.e. hypertension, diabetes mellitus and renal disease. In recent years the evaluation of arterial stiffness has been transferred from research field to clinical cardiological practice. PWV is a well known, simple and reproducible method characterizing spreading pulse wave (but not flow volume) in arterial tree. The gold standard is carotid-femoral PWV (cfPWV) that revealed to be the independent predictor of the cardiovascular events. The additive value of PWV above traditional risk factors has been well quantified [5, 12]. The impedance plethysmography — the method we used for PWV assessment — revealed to be useful in some clinical applications. Bodula et al. [13] used IPG in the assessment of the effect of pharmacotherapy (pentoxyphylline and suledoxide) in patients with lower limb ischemia. Irzmańska et al. [14] evaluated IPG assessing local blood flow in immobilized patients endangered with decubitus ulcer. They concluded that this simple non-invasive method can be useful in repeatable monitoring of peripheral flow not only in extremities but also in the trunk compartment.

In our study pulse wave propagation was associated with non-modifiable variables such as age, gender and anthropometrics. The strongest independent covariate in multiple regression models was age. This observation has its pathophysiological explanation. Arterial remodeling with aging is related to the structural changes in media and intima caused by elastic fibres destruction accompanied with collagen and calcium deposition. Stiffer arteries can dilate to compensate the loss of compliance but...
this mechanism is insufficient to prevent hemodynamic consequences such as increase in SBP, PP and PWV [15]. Sex differences in peripheral flow were presented in detail by Albaladejo et al. [16] who examined large cohorts of women and men. Multiple regression revealed that in women PWV depended only on age and SBP (R square respectively 0.27 and 15.4). Mean additional covariates were weight and heart rate (R square for normotensives 0.27, hypertensives — 0.29).

The relation of lower TAC and higher SVRI with higher PWV indicates high contribution of the central arterial compliance to the arterial stiffness. Ng et al. [17] reported the association of higher MAP and PWV with aortic wall degeneration in hypertensive rats. Observations in twin

Figure 3. Correlation plots of pulse wave velocity (PWV) with age (A), mean arterial pressure (MAP) (B), heart rate (HR) (C), stroke index (SI) (D), left ventricular ejection time (LVET) (E) and pre-ejection period (PEP) (F)
women revealed that increased PWV is related to aortic calcification (but not IMT and noncalcified atheromas) and strongly dependent on genetic factors [18]. Association of the increased PWV with thoracic artery calcification was confirmed in other studies [19, 20].

The observed independent relation of PWV to BP corresponds with the conclusions from the systematic review by Cecelja and Chowienczyk [21] and the study performed by Zheng and Murray [22] that examined the influence of change in BP on PWV in 100 healthy subjects in a controlled manner. They induced change in transmural pressure using long arm cuff inflated to maximum of 40 mm Hg and observed that arterial distensibility was significantly related to resting BP and age. A reduction of transmural pressure by 40 mm Hg effected in significant decrease of PWV (from 12 to 8 m/s). This trend was confirmed by our results where MAP revealed to be independent covariate in the regression model. The second strong hemodynamic covariate that contributed to PWV was HR. Also Millasseau et al. [23] reported significant influence of provoked tachycardia on PWV and this effect was independent from BP, as in our study. Langham et al. [24] point that PWV can change from beat to beat because of the unstable arterial compliance associated with R-R interval variations. The significant relation of PWV with LVET supplemented the conclusions from correlation with HR. The shorter LVET the more increased central-to-peripheral pressure amplification resulting in the higher “functional” stiffness [15]. On the other hand, the correlation with PEP suggests that the isovolumetric contraction time is prolonged in subjects with higher PWV and the arterial stiffness influences the left ventricular performance. This phenomenon was also observed in other studies and corresponded with left diastolic dysfunction and ventricular hypertrophy [25–27].

Our observation suggests that the assessment of PWV as a predictive factor can be limited in some patients, especially those with mostly “functional” than structural cardiovascular disturbances. The regression models revealed that the key determinants of PWV can be evaluated by simple clinical examination. However, the evaluation of arterial stiffness can definitely be more objective if LVET and PEP are known.

Being aware that the assessment of arterial stiffness could reclassify patient’s cardiovascular risk [5], we suggest the considered approach to the peripheral flow evaluation, especially PWV. Following ideas of other scientists [16] we suggest the PWV assessment after correcting hemodynamic disturbances, especially abnormal BP and tachycardia. In this context increased stiffness in the presence of well controlled HR and BP should be interpreted as a worse arterial condition. In opinion of McEniery et al. [19] such observation may concern patients potentially more resistant to the treatment.

The authors are aware that the small sample size limits the study. The method of PWV assessment used in this study (based on distance from ascending aorta to the peripheral artery) cannot be treated as equivocal to “gold standard” cervical-femoral PWV. Moreover, our observations are limited to untreated hypertensives without other clinically important cardiovascular diseases, therefore the results should be considered carefully as relating to a particular group of patients.

**Conclusions**

Impedance plethysmography and cardiography are complementary methods for the assessment of cardiovascular system. The arterial stiffness revealed to be related to age, gender, anthropometrics and strongly associated with hemodynamic profile. In view of the classifying value of PWV in cardiovascular risk evaluation it should be interpreted considering current hemodynamic state.

**Conflicts of interest**

The authors declare no conflicts of interest.
Streszczenie

Wstęp. Sztylkość naczyeniowa jest obecnie celem interwencji terapeutycznych u pacjentów z chorobami układu sercowo-naczyniowego. Dlatego możliwość oceny właściwości układu naczyennego okazuje się szczególnie istotna. Celem pracy była ocena charakteru powiązań prędkość fali tętna (PWV) z parametrami klinicznymi oraz hemodynamicznymi u chorych z nadcisnieniem tętniczym.

Materiał i metody. Analizą objęto grupę 150 pacjentów (w tym 111 mężczyzn; średni wiek 43,5 roku) z nacisnieniem-

8.

7.

6.

5.

4.

3.

2.

1.

Śwolowymi słowa kluczowe: nacisnienie tętnicze, sztywność naczyń, pletyzmografia impedancyjna, kardiografia impedancyjna, powinna być interpretowana z uwzględnieniem bieżącego stanu hemodynamicznego badanej osoby. Wnioski. Wartość PWV okazała się istotnie większa u kobiet niż u mężczyzn (6,18 ± 0,77 v. 5,91 ± 0,99 m/s; p = 0,035). W ocenie wzajemnych relacji wartość PWV najistotniej korelowała z wiekiem (R = 0,41), MAP (R = 0,32), HR (R = 0,32), SI (R = –0,47), TAC (R = –0,31), SVRI (R = 0,38) oraz podokresami skurczu serca: PEP (R = 0,59) i LVET (R = 0,28). W modelu wieloczynnikowym (R² = 0,61) niezależnymi zmiennymi związanymi z PWV okazały się: wiek, MAP, PEP i LVET.

Wnioski. Metody bioimpedancyjne okazują się przydatne w ocenie złożonej natury sztywności naczyniowej. Prędkość fali tętna wykazuje powiązania z innymi parametrami hemodynamicznymi charakteryzującymi interakcję lewej komory mięśnia sercowego z układem naczyennym, w tym najsilniejsze z ciśnieniem tętniczym (BP), SVRI, TAC oraz wskaźnikami funkcji mięśnia sercowego jako pompy (HR, SI, PEP, LVET). Otrzymane wyniki wskazują, że wartość rokownicza PWV powinna być interpretowana z uwzględnieniem bieżącego stanu hemodynamicznego badanej osoby.

Słowa kluczowe: nadcisnienie tętnicze, sztywność naczyniowa, pletyzmografia impedancyjna, kardiografia impedancyjna, prędkość fali tętna

References

Komentarz

prof. dr hab. n. med. Krzysztof Narkiewicz
Katedra Nadcisnienia Tętniczego i Diabetologii Gdańskiego Uniwersytetu Medycznego

W zaleceniach dotyczących leczenia nadciśnienia tętniczego podkreślono znaczenie nieinwazyjnych badań służących ocenie struktury i funkcji dużych tętnic [1]. Do tradycyjnych metod należy zaliczyć badanie ultrasonograficzne tętnic szyjnych (z pomiarem grubości kompleksu blony środkowej i wewnętrznej lub oceną obecności blaszek miażdżycowych) oraz wskaźnik kostka–ramię. Zmiany w tętnicach szyjnych są predyktorem zarówno udaru mózgu, jak i zawału serca. Niski wskaźnik kostka–ramię wskazujący na chorobę tętnic obwodowych i ogólnie na zaawansowaną zmiany miażdżycowe wiąże się z rozwojem choroby wieńcowej, niewydolnością serca oraz udaru mózgu.

W ostatnich latach obserwujemy stały wzrost zainteresowania znaczeniem sztywności dużych tętnic i zjawiska odbicia fali tętna. Wynika to z wielu przesłanek patofizjologicznych i klinicznych. Po pierwsze, pomiar prędkości fali tętna (PWV, pulse wave velocity) pozwala na całościową, nieinwazyjną ocenę sztywności tętnic. Po drugie, proces sztywnienia naczyń leży u postawy rozwoju izolowanego nadciśnienia skurczowego i wzrostu ciśnienia tętniczego. Nieproporcjonalny do wieku wzrost szybkości fali tętna jest uznawany za wykładniki „przedwczesnego starzenia się naczyń” (EVA, early vascular aging) [2, 3]. Po trzecie, sztywność dużych naczyń jest niezależnym czynnikiem ryzyka wystąpienia incydentów sercowo-naczyniowych u pacjentów z nadciśnieniem tętniczym. Dodana wartość PWV wykracza poza tradycyjne czynniki ryzyka ujęte w skalach SCORE (Systematic Coronary Risk Evaluation) i Framingham [4–6]. Dodatkowo pomiar sztywności tętnic umożliwia reklasyfikację znacznego odsetka pacjentów z grupy pośredniego ryzyka do grupy większego lub mniejszego ryzyka sercowo-naczyniowego [4].

We wcześniejszych badaniach dowiedziono, że sztywność dużych naczyń jest związana z upośledzeniem funkcji małych naczyń [7] oraz wzrostem zmienności ciśnienia tętniczego [8]. Otwartym pytaniem pozostaje, czy odwrócenie sztywności naczyń może przynieść większe korzyści niż sama normalizacja ciśnienia tętniczego [9]. W nowatorskiej pracy Krzesińskiego i wsp. wykazano, że wartość PWV powinna być interpretowana z uwzględnieniem bieżącego stanu hemodynamicznego badanego. Co więcej, metody biolimpedancyjne mogą być przydatne w ocenie mechanizmów odpowiedzialnych za występowanie sztywności naczyniowej. Wykorzystanie tych metod w przyszłych randomizowanych badaniach klinicznych może się przynieść do precyzyjniejszej oceny związku sztywności naczyń z ryzykiem sercowo-naczyniowym, a co ważne jest – do poznania optymalnych metod leczenia chorób z nadciśnieniem tętniczym.

Piśmiennictwo