

Influence of arterial stiffness on degenerative changes in the aortic valve and the relationship with cardiovascular risk factors

¹Laurentiu Stoicescu, ¹Caius Duncea, ¹Sorin Crişan, ¹Elena Buzdugan, ²Valer Donca, ¹Dan Radulescu

¹ Department of Internal Medicine, Vth Medical Discipline, Faculty of Medicine, “Iuliu Haţieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania; ² Department of Geriatrics and Gerontology, “Iuliu Haţieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania.

Abstract. Introduction and Purpose: Over recent years, research on cardiovascular disease risk factors has emphasized the crucial role played by arterial stiffness (assessed by pulse wave velocity - PWV). There is no research on the impact of arterial stiffness on degenerative changes in the aortic valve, although elevated pulse wave velocity determined by arterial stiffness causes the reflected wave to return to the level of the aortic valve during systole, compared to the beginning of diastole, as it would be normal, thus resulting in an increase in ventricular pressure and an additional mechanical stress on the aortic valve. This research aimed to study the relationship between two stiffness parameters obtained by means of photoplethysmography and the severity of aortic stenosis, aortic valve calcification, degenerative changes in the initial part of the ascending aorta (diameter growth, the presence of ATS plaques) and cardiovascular risk factors (gender, smoking, hypertension, diabetes mellitus, dyslipidemia). Materials and Methods: The study consisted of 43 patients diagnosed with degenerative aortic stenosis or aortosclerosis, for whom the severity of valvulopathy, the degree of valvular calcification, the presence of ATS plaques in the ascending aorta were assessed by means of cardiac ultrasound and arterial stiffness was determined using photoplethysmography. Results: Rigidity and reflection indices were not correlated with each other. Reflection index was strongly and negatively correlated with the severity of aortic stenosis ($p < 0.001$, $r = -0.673$), but only distinguishing between mild types of disease and aortosclerosis on one side and medium and severe types of disease on the other side. Reflection index was statistically significantly correlated with the degree of aortic valve calcification ($p = 0.002$, $r = 0.458$). Rigidity and reflection indices are not influenced by cardiovascular risk factors, nor by the presence of atherosclerotic plaques in the ascending aorta. Conclusion: Increased arterial stiffness is correlated with more severe types of degenerative aortic stenosis and with a greater degree of valvular calcification, without being influenced by cardiovascular risk factors.

Key Words: arterial stiffness, aortic stenosis, risk factors, photoplethysmography, valvular calcification

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Corresponding Author: L. Stoicescu, stoicescul@yahoo.com

Introduction

Over recent years, research on cardiovascular disease risk factors has emphasized the impact of central aortic pressure as a cardiovascular risk factor of greater importance than systolic pressure and brachial artery pulse pressure, central aortic pressure being the actual pressure felt by the heart directly. This kind of pressure is different from the frequently measured brachial pressure, being modified by its circulating speed or the reflected pulse wave transmitted through the arterial walls (dependent on vascular wall stiffness) and by the magnitude of the reflected wave (Stephanie et al 2008). Therefore, elevated pulse wave velocity (PWV) causes the reflected wave to return to the level of the aortic valve during systole, compared to the beginning of diastole, as it would be normal, thus creating an increase in ventricular pressure and an additional mechanical stress on the aortic valve.

Material and method

Patients were selected from those admitted to the internal medicine, cardiology and geriatric wards of the Municipal Clinical Hospital of Cluj-Napoca. Subjects were included after signing the enrollment and consent forms.

The study consisted of 48 patients diagnosed with aortic stenosis, who signed the informed consent form. The study protocol was approved by the Ethics Committee of “Iuliu Haţieganu” University of Medicine and Pharmacy, Cluj-Napoca. The complete data set could not be obtained for 5 of these patients, so the final statistical analysis consisted of 43 subjects: 26 women (60%) and 17 men (40%), aged between 41 and 91 years (mean age 68 ± 11.5 years).

The following were not included in the study: patients with an ultrasound window that did not allow for accurate measurements, those with atrial fibrillation, compromised left ventricular systolic function, patients with increased arterial stiffness for

whom photoplethysmography could not determine pulse curve parameters, patients with zero systolic aortic distensibility, and patients who did not sign the informed consent.

This is an observational, prospective, analytical, cross-sectional cohort study.

Confirmation and quantification of aortic stenosis was performed by means of echocardiography, using an Aloka SSD-2000 examination device, equipped with a cardiovascular transducer. Ultrasound imaging was done in both B-mode and M-mode and color Doppler and continuous wave mode for all patients, obtaining morphological and hemodynamic data. The parasternal short-axis view provided direct planimetry of the aortic valve area. Hemodynamic data were obtained from the apical five-chamber view, where continuous wave Doppler interrogation of the aortic valve yielded a flow velocity that allowed for the determination of the maximum velocity of the blood ejected through the aorta.

Quantification of the degree of aortic stenosis was done using the current classification of the European Society of Cardiology. Thus, mild aortic stenosis was defined by a maximum velocity of >2 m/s and an aortic valve area between 1.5 and 2 cm², moderate aortic stenosis by a maximum velocity of >3 m/s and an aortic valve area between 1 and 1,5 cm², and severe aortic stenosis by a maximum velocity of >4 m/s and an aortic valve area of less than 1 cm². When the maximum transvalvular velocity was between 1.5 and 2 m/s, it was defined as early valvular degeneration (aortosclerosis).

A parameter set and used in this study was the degree of aortic valve calcification (Calcif.Ao). It helped assess the number of calcific valve areas taking into account the cusps and commissures. Thus, the degree of calcification could vary between 1 and 6 (Figure 1).

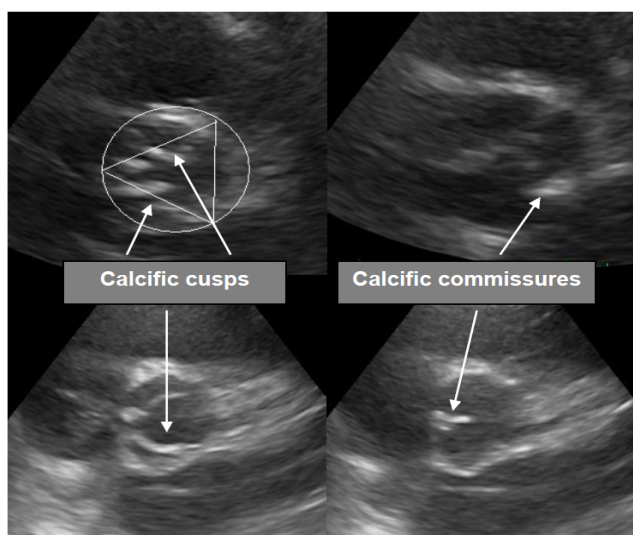


Figure 1. Assessing the degree of aortic valve calcification

In this study, photoplethysmography was used for assessing arterial stiffness, by means of a Pulse Trace PCA2 device. It is a simple-to-use method, the device having the advantage of a single sensor unit, easy to install due to its design, the integrated software providing complete pulse wave analysis (Figures 2 and 3). Several comparative studies have shown it being superposed with the method determining arterial stiffness by applanation tonometry (Kelly et al 1989, Imholtz et al 1988).

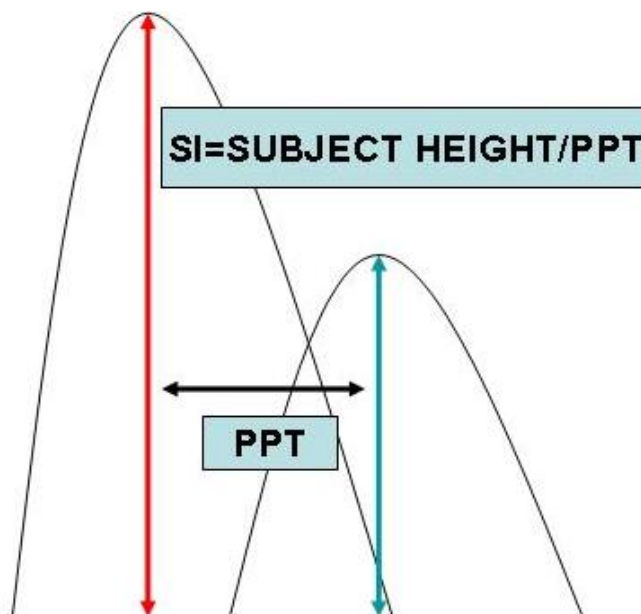
Two “stiffness” parameters result from the analysis of the pulse wave detected by photoplethysmography:

- Stiffness index (SI) - an indicator of large-artery stiffness, assessed based on the time interval between the direct wave and the reflected wave, being strongly correlated with PWV (Woodman et al 2005).

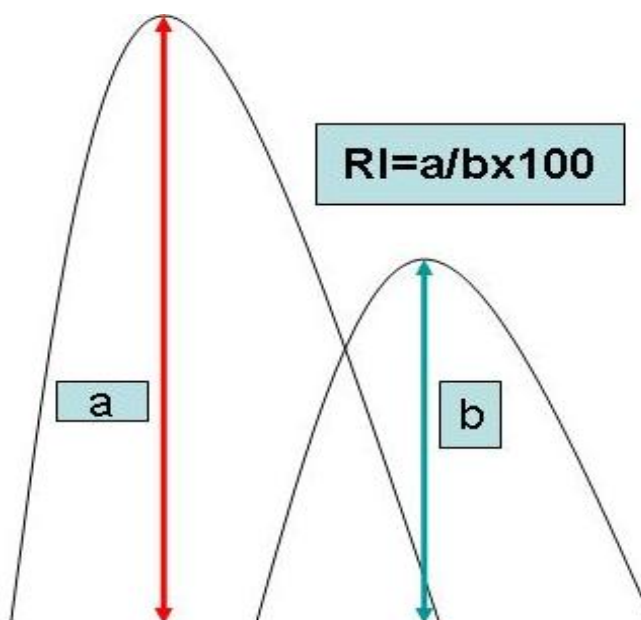
- Reflection index (RI) - an indicator of vascular muscle tone, representing the ratio between the direct wave height and the reflected wave height (Millasseau et al 2002, Chowienczyk et al 1999). A low RI indicates more relaxed arteries.

Pulse wave curve was determined using photoplethysmography, marking the two parameters:

- SI, arterial stiffness index (Figure 2)



- RI, vascular muscle tone (Figure 3)



A research sheet was drawn up for each patient, containing the following:

1. Demographic data: age, gender, area of origin (urban or rural);
2. Other data:
 - general data: height, weight;

- associated cardiovascular risk factors: hypertension, dyslipidemia, diabetes, smoking status;

3. Biochemical parameters: blood sugar concentration, total cholesterol, lipid fractions (LDL, HDL, TGL), C-reactive protein. Statistical analysis was performed using Microsoft Excel XP, for database organization, and SPSS (Statistical Package for the Social Sciences) version 16, for the analysis itself. Univariate analysis of normally distributed continuous variables included the use of the independent-samples t test (comparison between two groups), Pearson's correlation (correlation between two variables in the same group), ANOVA (comparison between three or more groups). Univariate analysis of dichotomous variables employed the chi-squared test. Differences were considered statistically significant for a p value of less than 0.05. The 95% confidence intervals were also calculated (CI 95%).

Results

Cardiovascular risk factors (hypertension, dyslipidemia, type II diabetes, smoking) in the group of 43 patients with degenerative aortic stenosis were present as follows: hypertension in 79% of subjects, dyslipidemia in 42%, diabetes mellitus in 23%, and smoking in 21% of patients (Figure 4).

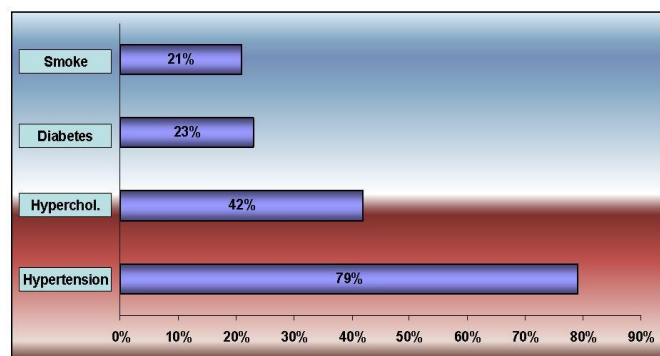


Figure 4. Distribution of patients with degenerative aortic stenosis according to the presence of risk factors

In terms of disease severity, 11 subjects had tight stenosis (26%), 9 had moderate stenosis (21%), 18 had wide stenosis (41%) and 5 had aortosclerosis (12%) (Figure 5).

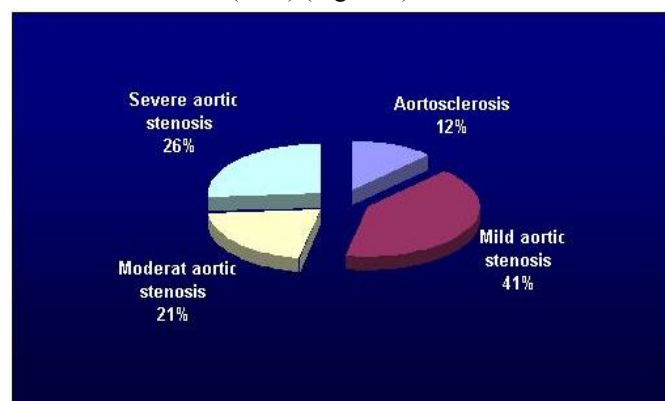


Figure 5. Distribution of patients according to the severity of degenerative aortic stenosis

Given that both SI and RI are parameters describing arterial stiffness, the purpose was to assess whether SI and RI values are correlated, or if there is an interdependence between their

variation. Therefore, Pearson's correlation was used, the result being negative ($p=0.077$, $r=-0.272$). This proves that large artery stiffness was not correlated with the increased vascular tone in medium/small vessels, which suggests possible different implications of the two parameters on aortic valve and ascending aorta. The correlation between the two stiffness parameters and aortic valve area proved that only RI is strongly and negatively correlated with aortic valve area ($p<0.001$, $r=-0.673$, Figure 6), without any existing correlation between SI and aortic valve area.

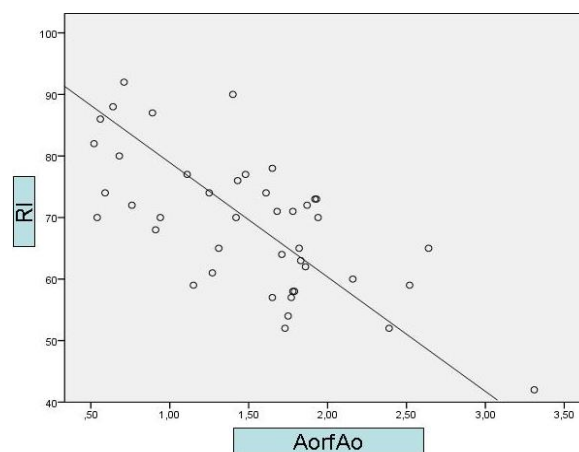


Figure 6. The correlation between the reflection index and aortic valve area

This shows a strong interdependence between the variation in RI values and aortic valve area, the latter not being influenced by SI variation.

ANOVA was used to see if there are any statistically significant differences between RI values depending on the severity of aortic stenosis, obtaining a positive result ($p<0.001$).

However, post-hoc analysis showed that the differences in RI values are only significant when comparing severe and moderate aortic stenosis, on the one hand, with mild aortic sclerosis and aortosclerosis, on the other hand, without being able to distinguish between severe and moderate aortic sclerosis or mild aortic sclerosis and aortosclerosis.

Besides being correlated with aortic valve area, RI was also moderately correlated with the degree of aortic valve calcification ($p=0.002$, $r=0.458$), which indicates a higher degree of valvular calcification together with the increased RI value. The correlation between RI and the presence of mitral annular calcifications was at the border of statistical significance ($p=0.051$). Regarding the influence of cardiovascular risk factors (gender, hypertension, diabetes, dyslipidemia) on arterial stiffness parameters, Levene's test found that the value of these parameters is not influenced by the presence of risk factors. Moreover, the presence of ATS plaques in the ascending aorta does not influence RI and SI values. This evidence suggests that arterial stiffness is influenced by other factors than those considered by the classical theory.

Discussion

This study aimed to determine whether there is a connection between increased arterial stiffness and aortic stenosis severity. It also tried to establish if cardiovascular risk factors influence arterial stiffness.

Research on PWV has clarified the influence that arterial stiffness has on cardiovascular events, as an independent risk factor. Hypertension and age are among the primary factors incriminated for increased aortic PWV (Stephanie *et al* 2008, Laurent *et al* 2003). Another factor shown to have a role in arterial stiffness is inflammation, measured by CRP, IL-6 and TNF-alpha (Mahmud *et al* 2005, Amar *et al* 2005). It was shown that there was no difference in PWV between patients with bicuspid aortic valve and those with tricuspid valve, suggesting that valvular malformation is not associated with changes in the aorta that would increase arterial stiffness (Patrick *et al* 2013).

In this study, photoplethysmography was used for the assessment of arterial stiffness. Two “stiffness” parameters resulted from the analysis of the pulse wave detected by means of this method:

- Stiffness Index (SI) - an indicator of large artery stiffness, assessed based on the time interval between the direct wave and the reflected wave, being strongly correlated with PWV (Woodman *et al* 2005). As PWV, SI is also influenced by age (Kelly *et al* 1989).

- Reflection index (RI) - an indicator of vascular muscle tone, representing the ratio between the direct wave height and the reflected wave height (Millasseau *et al* 2002, Chowienczyk *et al* 1999). A low RI indicates more relaxed arteries. Vascular muscle tone is mostly influenced by paracrine mediators (endothelin, nitric oxide), recent research showing that RI may be an alternative to indirect measurement of endothelial function (Dzau *et al* 1986, Yanagisawa *et al* 1988, Hark *et al* 2011).

First, the two stiffness parameters, SI and RI, were compared with each other to see if there is any correlation between their variation, given that they both reflect arterial stiffness at a different level: SI reflects large artery stiffness, while RI reflects vascular muscle tone (some researches equate it with a marker of nitric oxide synthesis, Hark *et al* 2011). Statistical analysis showed that the two parameters are not correlated, which proves that they are independent markers and that the structure of the arterial wall is likely to determine different types of stiffness, with different consequences on cardiac structures. There are studies that notice the independent evolution of the two parameters with age (Gary *et al* 2004), but there is no data in the literature regarding the comparison and correlation between the two parameters.

Further, the comparison between the two markers and aortic valve area yielded a strong statistically significant negative correlation for RI ($p < 0.001$, $r = -0.673$). This shows a strong interdependence between the variation in RI values and aortic valve area, the higher the RI, the smaller the aortic valve area. The study aimed to find out whether the RI is correlated with the degree of aortic stenosis. The use of ANOVA yielded a positive result ($p < 0.001$), which shows that RI values are significantly different between these groups. The post-hoc analysis was used to determine whether this difference in RI values is maintained for each degree of aortic stenosis. Tukey's test only showed significant differences between mild aortic sclerosis and aortosclerosis, on the one hand, and moderate and severe aortic sclerosis, on the other hand. This shows that elevated RI values are associated with moderate or severe aortic stenosis. There is no data in the literature on the connection between RI and aortic stenosis severity. There are some studies that show lower survival rate in patients with severe aortic stenosis and a higher afterload (Briand *et al* 2005, Zeineb *et al* 2007, Kristian

et al 2008, Patrizio *et al* 2010). Based on the fact that RI is an indicator of vascular muscle tone, determinant afterload factor, the association found between higher RI values and moderate or severe aortic stenosis suggests that increased vascular muscle tone, by increasing afterload, reduces survival, accelerating the progression of valvulopathy beyond blood pressure per se. Besides the correlation with aortic valve area, RI was also statistically significantly correlated with the degree of aortic valve calcification ($p = 0.002$, $r = 0.458$), which shows a higher degree of valvular calcification together with the increase in RI values. The correlation between RI and mitral annular calcifications level was at the border of statistical significance ($p = 0.051$). These results are even more important as both the increase in RI values and aortic valve degeneration seem to have a common pathogenetic element, namely the decrease in the production of nitric oxide (Hark *et al* 2010, Shahbudin *et al* 2013). Aortic or mitral calcifications were not correlated with the other stiffness parameter associated with the increase in pulse wave velocity (SI), this being reported by other researchers as well (Raggi *et al* 2007). Regarding the influence of cardiovascular risk factors (gender, smoking, hypertension, diabetes, dyslipidemia) on stiffness parameters, the value of the latter proved not to be influenced by the presence of risk factors. There is no correlation with SI, in contrast to literature data, where age, smoking, hypertension, diabetes and dyslipidemia proved to significantly increase arterial stiffness (Failla *et al* 1997, Benetos *et al* 2002, Feely *et al* 2003, Lekakis *et al* 2005, Safar *et al* 2006). There was no data in the literature regarding RI, that would prove the connection between arteriolar tone and cardiovascular risk factors, except for age, which is known not to influence arteriolar tone (van der Heijden *et al* 2000).

Additionally, the presence of ATS plaques in the ascending aorta proved not to influence the values of two parameters, RI and SI. Data from the literature states that there is a strong positive association between arterial stiffness and the degree of severity of aortic and carotid atherosclerotic damage (Nicole *et al* 2001). This divergence in results may result from the fact that our study has only focused on the atherosclerotic load, expressed by the presence of ATS plaques, in the initial part of the ascending aorta.

All this evidence suggests that arterial stiffness is also influenced by other factors than those considered in the classical theory, being produced outside the atherosclerotic load too, probably by reducing the synthesis of nitric oxide. This different mechanism that results in arterial stiffness, besides atherosclerosis, underlies the consideration of arterial stiffness as an independent risk factor for cardiovascular events (Laurent *et al* 2001, Laurent *et al* 2003, Sutton-Tyrrell *et al* 2005).

Conclusion

Rigidity and reflection indices are not correlated with each other. Reflection index was strongly and negatively correlated with aortic stenosis severity, only distinguishing between mild aortic stenosis and aortosclerosis, on the one hand, and moderate and severe aortic stenosis, on the other hand. Reflection index is statistically significantly correlated with the degree of aortic valve calcification. Rigidity and reflection indices are not influenced by cardiovascular risk factors, nor by the presence of atherosclerotic plaques in the ascending aorta.

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Authors

- Laurentiu Stoicescu, Vth Medical Discipline, Faculty of Medicine, "Iuliu Hațieganu" University of Medicine and Pharmacy, 11th Tabacarilor Street, 400139, Cluj-Napoca, Cluj, Romania, EU, email: stoicescul@yahoo.com
- Caius Duncea, 5th Medical Discipline, Faculty of Medicine, "Iuliu Hațieganu" University of Medicine and Pharmacy, 11th Tabacarilor Street, 400139, Cluj-Napoca, Cluj, Romania, EU, email: crduncea@yahoo.com
- Sorin Crisan, 5th Medical Discipline, Faculty of Medicine, "Iuliu Hațieganu" University of Medicine and Pharmacy, 11th Tabacarilor Street, 400139, Cluj-Napoca, Cluj, Romania, EU, email: crisan.sorin@gmail.com
- Elena Buzdugan, Department of Internal Medicine, Vth Medical Clinic, "Iuliu Hațieganu" University of Medicine and Pharmacy,

11th Tăbăcarilor Street, 400139, Cluj-Napoca, Cluj, România, EU, email: buzelena@yahoo.com

•Valer Donca, Department of Geriatrics, “Iuliu Hațieganu” University of Medicine and Pharmacy, 11th Tăbăcarilor Street, 400139, Cluj-Napoca, Cluj, Romania, EU, email: valerdonca@gmail.com

•Dan Rădulescu, 5th Medical Discipline, Faculty of Medicine, “Iuliu Hațieganu” University of Medicine and Pharmacy, 11th Tabacarilor Street, 400139, Cluj-Napoca, Cluj, Romania, EU, email: dan_rad31@yahoo.com

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