

Relationship between the severity of aortic stenosis and different morphological parameters

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Abstract. Introduction and purpose : Research on blood flow in the ascending aorta has demonstrated the association between turbulent blood flow and aortic stenosis, but has not explained the cause. This research aimed to correlate certain morphological features of the aortic orifice generating turbulent flow in the ascending aorta with the severity of aortic stenosis, trying to find the “cutoff” values of these parameters that could predict the severity of aortic valvulopathy. They were also correlated with risk factors, well known in literature, involved in the progression of aortic stenosis (hypertension, dyslipidemia, diabetes mellitus, smoking). Material and Methods: The study consisted of 70 patients diagnosed with degenerative aortic stenosis or aortosclerosis (arteriosclerosis of the aorta) who underwent echocardiography in order to assess the ratio between the diameter of the aortic orifice and that of the ascending aorta (R2), as well as the length of the aortic orifice (LAoOrf). Results: Both parameters studied were correlated with aortic valve orifice area, being influenced by the severity of aortic stenosis ($p < 0.001$, $r = 0.693$ for R2, respectively $p < 0.001$, $r = 0.754$ for LAoOrf). For the determination of the “cutoff” values that distinguish between different degrees of severity of aortic stenosis, an R2 value below 0.2647 strongly indicates severe aortic stenosis, while a value over 0.3871 indicated mild stenosis or aortosclerosis; for LAoOrf, a value below 9 mm accurately indicates tight aortic orifice stenosis and a value over 10 mm indicated large aortic orifice stenosis or aortosclerosis. Chi-square test showed a uniform distribution of risk factors in groups of severity of aortic stenosis. Neither LAoOrf nor R2 were influenced by “traditional” cardiovascular risk factors. Conclusion: Both parameters studied were correlated with aortic valve orifice area, being influenced by the severity of aortic stenosis, obtaining “cutoff” values that differentiate between different degrees of severity of aortic stenosis for each one individually. “Traditional” cardiovascular risk factors did not influence them.

Key Words: aortic stenosis, diameter of aortic orifice, length of aortic orifice.

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Introduction

Research on blood flow in the ascending aorta has demonstrated the association between turbulent blood flow in this area and aortic stenosis, but has not explained the cause (Stein et al 1976, 1977; Segadal et al 1987; Stalder et al 2011) and has not detailed the morphology of degenerative valve (Yoganathan et al 1988; Schoenl et al 2005, Sacks et al 2007). Research fails to explain the triggering factor of the pathophysiological cascade, that results in degenerative valve and in the mechanism that perpetuates these processes (Mohler et al 1997). The drawback in understanding the pathophysiological processes explains why the degree of degeneration is different in patients with similar morphological characteristics, being virtually impossible to predict progression to severe stages of valvulopathy. These reasons, together with insufficient and contradictory literature data led us to propose the study of certain parameters influencing the turbulence in the aortic valve and the initial portion of the ascending aorta.

Knowing that the cross-sectional area of the laminar flow of the jet passing through an orifice is smaller than the area of the orifice, due to fluid particle inertia, this contraction depending on the physical characteristics of the orifice (diameter, edge of the orifice, the ratio between the diameter and the length of

the orifice), laminar flow area reduction outside the hole leading to increased orifice juxtaposed turbulence, thus producing a violent mixture between the jet and the blood downstream of the orifice (Vasilu et al 1999), our research aims to use the ratio between the diameter of the aortic orifice and that of the ascending aorta, as well as the length of the aortic orifice as turbulence parameters.

The correlation between these morphological parameters and the severity of aortic stenosis aimed to find the “cutoff” values of these parameters that could predict the severity of aortic valvulopathy. Moreover, they were correlated with risk factors that are well-known in literature as being involved in the progression of aortic stenosis (dyslipidemia, diabetes mellitus, smoking).

Material and method

The study was conducted at the Fifth Medical Clinic within the Municipal Clinical Hospital of Cluj-Napoca, between August 2013 and April 2014, patients being admitted to internal medicine, cardiology and geriatrics units of the Municipal Clinical Hospital. Patients signed the informed consent form. The study protocol was approved by the Ethics Committee of “Iuliu Hațieganu” University of Medicine and Pharmacy Cluj-Napoca.

The study included 70 patients diagnosed with degenerative aortic stenosis or aortosclerosis (46 women - 66% and 24 men - 33%) aged between 41 and 92. Mean age was 71 ± 11.5 years, 72.5 years for women and 68.5 years for males.

The following subjects were not included in the study: patients with an ultrasound view that did not allow an accurate performance of the measurements, those with atrial fibrillation, compromised left ventricular systolic function, and patients who did not sign the informed consent form.

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

Aortic stenosis was confirmed and quantified by echocardiography, using an Aloka 2000 device for examination, equipped with a cardio transducer. Cardiac ultrasound examination of patients involved both B and M modes and color and continuous-wave Doppler, obtaining morphological and hemodynamic data. Thus, the opening of the aortic cusps and the ratio between the opening of the cusps and the aortic diameter and the length of the mobile portion of the cusps were measured in parasternal long axis view. The aortic valve orifice area, the maximum diameter of the orifice and the aortic diameter in this area were measured by direct planimetry in parasternal short axis view. Hemodynamic data were obtained from the five-room apical section, where continuous Doppler examination at valvular level led to obtaining a flow that allowed the determination of the maximum velocity of the blood expelled from the aorta.

Quantification of aortic stenosis was done using the current classification of the European Society of Cardiology (The joint task force 2012).

Thus, aortic stenosis was considered large at a maximum velocity of > 2 m/s, with an aortic valve orifice area between 1.5 and 2 cm², moderate at a maximum velocity of > 3 m/s, with an aortic valve orifice area between 1 and 1.5 cm², and severe at a maximum velocity of > 4 m/s, with an aortic valve orifice area of less than 1 cm². When the maximum transvalvular velocity was between 1.5 and 2 m/s, the case was defined as early valvular degeneration (aortosclerosis).

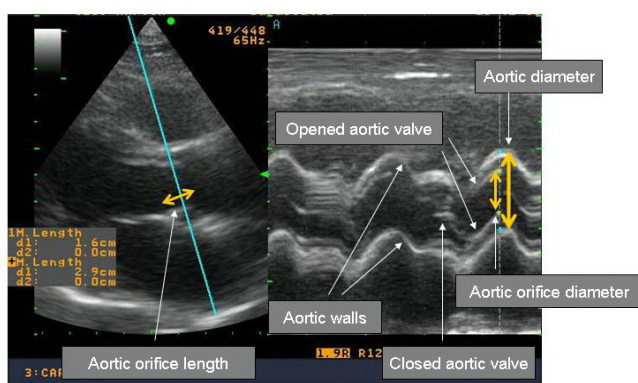


Figure 1. M mode examination of the aortic valve in parasternal long-axis view

A research data sheet with the following items was drawn up for each patient:

- demographics: age, gender, place of origin (urban or rural)
- general data: height, weight, smoking status
- associated cardiovascular risk factors: hypertension, dyslipidemia, diabetes mellitus

The following biochemical parameters were considered:

- Glucose,
- Total cholesterol,
- Lipid fractions (LDL, HDL, TGL)
- C-reactive protein,
- Calcium.

The following parameters were examined by echocardiography:

- the systolic and diastolic diameter of the ascending aorta, measured in millimeters (VN = 20-37 mm)
- the maximum diameter of the aortic orifice measured in parasternal short axis view, as well as the diameter of the aorta where the orifice was measured, expressed in millimeters
- the diameter of the aortic orifice in parasternal long axis view (VN = 15-26 mm) and the diameter of the aorta where the orifice was measured, expressed in millimeters
- aortic valve orifice area measured by planimetry in parasternal short axis view, expressed in cm² (VN > 2 cm²)
- the presence of concurrent calcification in the mitral valve
- the presence of atheromatous plaques in the ascending aorta

The "turbulence" parameters were determined:

- the length of the aortic orifice identified by ultrasound in parasternal long axis view, represented by the length of the aortic cusps measured in systole
- R1 ratio obtained by dividing the diameter of the ascending aorta to the diameter of the aortic orifice, measured in parasternal short axis view
- R2 ratio obtained by dividing the diameter of the ascending aorta to the diameter of the aortic orifice, measured in parasternal long axis view

Microsoft Excel XP programs were used for statistical analysis, for organizing the database, and SPSS (Statistical Package for the Social Sciences) version 16 was used for the analysis itself. Univariate analysis of continuous variables with normal distribution included the use of t test for independent variables (comparison of two groups), Pearson correlation (correlation of two variables within the same group), ANOVA (comparison of three or more groups). Univariate analysis of dichotomous variables was performed using the chi-square test. Differences were considered statistically significant when P value was lower than 0.05. Moreover, 95% confidence intervals were also calculated (CI 95%).

Results

Cardiovascular risk factors in the group of 70 patients with degenerative aortic stenosis (hypertension, dyslipidemia, type II diabetes, smoking) were present in 81% of subjects for arterial hypertension, 35% for dyslipidemia, 18% for diabetes mellitus and 15% smoking.

In the study group, 14 subjects had tight stenosis (20%), 25 had moderate stenosis (36%), 24 had large stenosis (34%), and 7 had aortosclerosis (10%).

Chi-square tests were employed for the analysis of dichotomous variables in order to see if there were any differences in the distribution of the variables investigated. The results indicated a uniform distribution in the groups of different types of severity of aortic stenosis ($p > 0.05$).

Pearson correlation was employed to determine if there is a correlation between R1 ratio and aortic valve orifice area and resulted in a low positive correlation ($p = 0.045$, $r = 0.241$; Figure

2). The correlation between R1 ratio and age resulted in an average positive correlation ($p=0.002$, $r=0.356$).

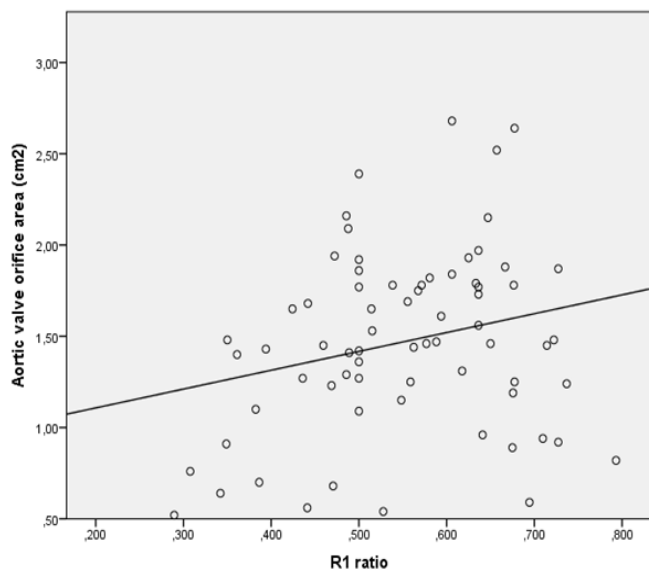


Figure 2. The correlation between R1 ratio and aortic valve orifice area

Pearson correlation also indicated the positive correlation between R2 ratio and TGL (average correlation) and aortic valve orifice area (high correlation) (Figure 3).

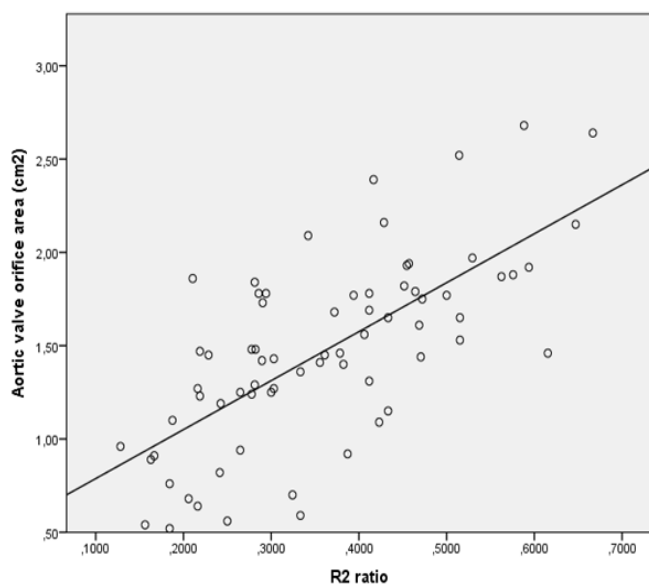


Figure 3. The correlation between R2 ratio and aortic valve orifice area

After establishing the correlation between the two ratios (R1, R2) and aortic valve orifice area, Levene's test was applied for the two ratios to observe if their value changes depending on the value of the aortic valve orifice area and the severity of aortic stenosis, noting that only the value of R2 ratio was influenced ($p<0.05$). Observations did not show that the value of the two ratios was influenced by the presence of hypertension, diabetes mellitus, dyslipidemia, the presence of mitral annular calcification or atherosclerotic plaques in the ascending aorta. ANOVA was applied to see if the values of R1 and R2 ratios are different for each group of severity of aortic stenosis. The

test showed that only R2 value differs significantly depending on the degree of severity of degenerative aortic stenosis.

Among other continuous variables analyzed (age, cholesterol, CRP) to see if their value changes depending on the severity of aortic stenosis, ANOVA only revealed significant differences between groups for CRP ($p=0.003$).

Given that R2 value is influenced by the severity of aortic stenosis, we tried to determine the cutoff values for this ratio which delineates the categories of severity by applying ROC curves to establish the R2 value that helps differentiate severe aortic stenosis from the other categories (average, large, aortosclerosis), resulting in a value of 0.2647 (AUC = 0.883, sensitivity 78.5%, specificity 85.7%, Figure 4), as well as the R2 value that helps differentiate mild aortic stenosis and aortosclerosis from the other categories (average and severe), resulting in a value of 0.3871 (AUC = 0.864, sensitivity 77.4%, specificity 87.1%, Figure 5).

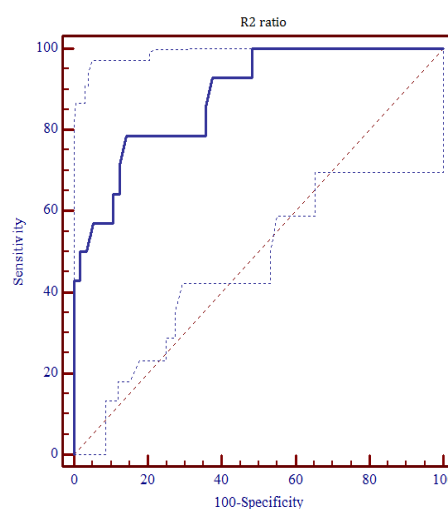


Figure 4. ROC curve for the value of R2 ratio that can detect severe aortic stenosis

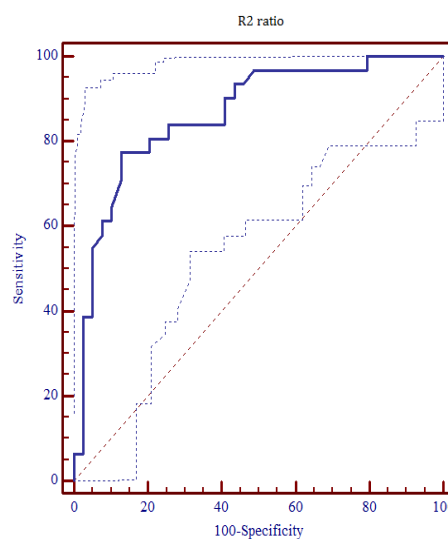


Figure 5. ROC curve for the value of R2 ratio that can detect mild aortic stenosis, aortosclerosis

As for LAoOrf, Pearson correlation obtained positive correlations with: the maximum diameter of the aortic orifice (PAL) (high correlation, $p < 0.001$, $r = 0.630$), the R2 ratio (high correlation, $p < 0.001$, $r = 0.590$) and the aortic valve orifice area measured by planimetry (high correlation, $p < 0.001$, $r = 0.754$, Figure 6).

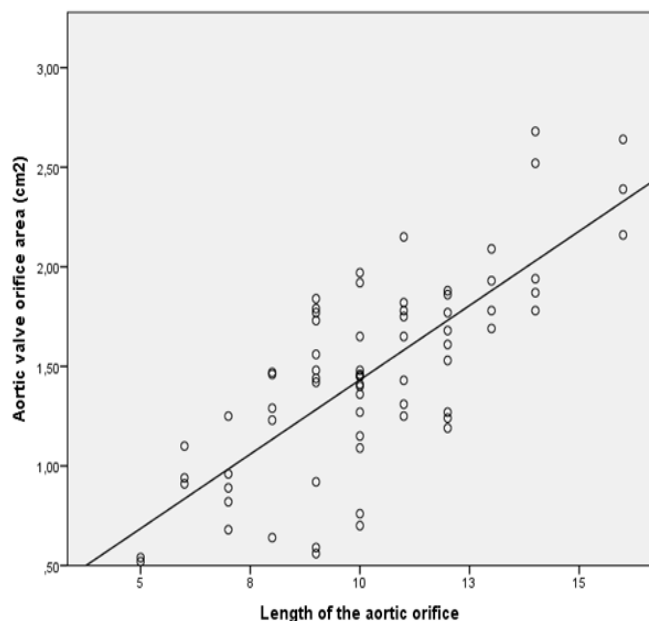


Figure 6. The correlation between the length of the aortic orifice and aortic valve orifice area.

LAoOrf parameter was not modified by variables such as gender, smoking status, hypertension, diabetes mellitus, dyslipidemia, mitral annular calcifications.

We used ANOVA to see if the value of the aortic orifice length are different for each group of severity of aortic stenosis, significant differences between these categories of LorfAo ($p < 0.005$). ANOVA was employed to indicate if the values of the length of the aortic orifice are different for each group of severity of aortic stenosis. The results showed significant differences of LAoOrf values between these categories ($p < 0.005$).

Further we tried to find the cutoff values of LAoOrf that could help divide subjects into different categories of severity of aortic stenosis by applying ROC curves determining the cutoff value for the length of the aortic orifice that helps differentiate severe aortic stenosis from the other categories. Therefore, the result was a cutoff value of 9 (AUC=0.895, sensitivity 85.7%, specificity of 75%, Figure 7). The aim was also to determine the cutoff value for the length of the aortic orifice that helps differentiate mild aortic stenosis and aortosclerosis from the other categories, obtaining a cutoff value of 10 (AUC=0.857, sensitivity 74.1%, specificity 84.6, Figure 8).

Therefore, patients could be divided into three groups of aortic stenosis based on LAoOrf: severe aortic stenosis (LAoOrf ≤ 9), average aortic stenosis ($9 < \text{LAoOrf} < 10$), large aortic stenosis / aortosclerosis (LAoOrf > 10).

The comparison between these groups of severity of aortic stenosis defined by the cutoff values of the length of the aortic orifice and the groups of severity defined by R2 ratio cutoff values, using Cohen's kappa coefficient, resulted in a moderate concordance between R2 ratio and LAoOrf regarding the classification of the severity of aortic stenosis ($\text{kappa} = 0.481$, $p < 0.001$).

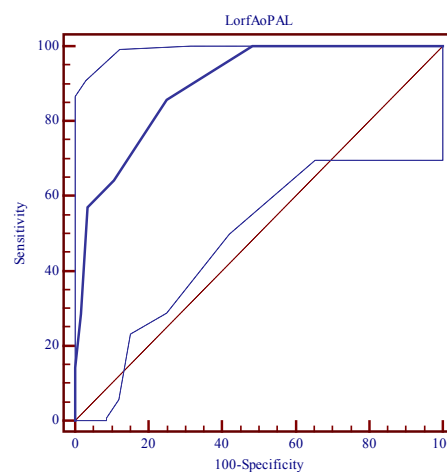


Figure 7. ROC curve for LAoOrf value that can detect severe aortic stenosis

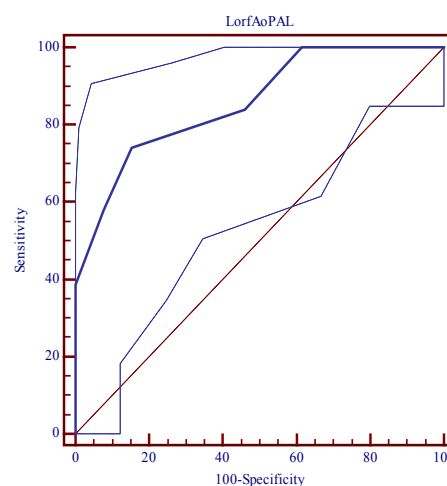


Figure 8. ROC curve for LAoOrf value that can detect mild aortic stenosis, aortosclerosis

Discussion

This study aimed to correlate these parameters, the ratio between the diameter of the aortic orifice and the diameter of the ascending aorta (R1, R2) and the length of the aortic orifice (LAoOrf) with the severity of aortic stenosis, together with the elaboration of "cutoff" thresholds of the values of these parameters that predict the severity of aortic stenosis. They were also correlated with the classical factors involved in the progression of aortic stenosis (gender, age, smoking, hypertension, diabetes mellitus, dyslipidemia, inflammation) (Palta et al 2000; Rajamannan et al 2008).

Among the risk factors mentioned in literature as being in charge of the development and progression of aortic stenosis (Palta et al 2000), the most common were hypertension (81%), followed by dyslipidemia (35%), diabetes mellitus (18%) and smoking (15%). Chi-square test showed a uniform distribution of risk factors in groups of severity of aortic stenosis, which was somewhat surprising if taking into consideration literature data. In other studies (O'Brien et al 1996; Palta et al 2000;

Rajamannan *et al* 2003), these risk factors were confirmed to produce an accelerated reduction in aortic valve orifice area. As a result, it would have been normal that their aggregation to be higher as the severity of aortic stenosis is greater, which was not confirmed in our research. This may suggest that these are not the only risk factors that influence the progression of aortic stenosis, as in the study group they were offset by other factors. On the other hand, the ANOVA analysis of inflammation, quantified by CRP in the present study, proved that it was related to the severity of aortic stenosis.

Regarding the correlation between these “traditional” risk factors and the new parameters considered in our study, statistical analysis revealed a statistically significant direct positive correlation between R1 ratio and age which showed a moderate interdependence in the variation of the two variables, and a positive correlation between R2 ratio and TGL. This indicated a strong interdependence between the variation in R2 ratio values and triglyceride levels. No correlation was identified between LAoOrf and cardiovascular risk factors. The lack of correlation between the original parameters and the risk factors shows that the influence of the first ones on aortic stenosis is probably achieved through a different mechanism than those investigated so far in the literature, where the focus is on inflammation. There was an interesting connection between R2 and triglycerides, which have not yet been accused in the literature as having an impact on the pathology of degenerative aortic stenosis. This finding might open new pathways for research using therapies that especially reduce serum TGL levels, as the failure of statin therapy in preventing the progression of aortic stenosis is well known (Rossebo *et al* 2008).

Next, the correlation between R1 and R2 ratios and aortic valve orifice area was analyzed, achieving a statistically significant correlation for both ratios, low correlation for R1 and high correlation for R2. This shows a low interdependence between the variation in aortic valve orifice area and R1 on one hand, and a strong interdependence between the variation in aortic valve orifice area and R2 on the other. There was no literature data on these associations.

After establishing the correlation between the two ratios (R1, R2) and aortic valve orifice area, Levene’s test was applied on the two ratios to ascertain if their value changes depending on the value of the aortic valve orifice area and the severity of aortic stenosis. The results showed that only the value of R2 ratio was influenced. This confirms the low statistical association between the R1 values and aortic valve orifice area and suggests the possibility of determining the severity of aortic stenosis according to R2 value. ANOVA confirmed that there is a statistically significant variation in the value of R2 ratio for each group of severity of aortic stenosis.

R2 value was not observed to be influenced by the presence of hypertension, diabetes mellitus, dyslipidemia, the presence of mitral annular calcification or atherosclerotic plaques in the ascending aorta, which suggests that this ratio might be an independent factor that correlates with the severity of aortic stenosis. Further, cutoff values were determined for R2 ratio in order to help predict either severe or mild valvulopathy, thus dividing the group into three other groups: severe stenosis, average stenosis, mild stenosis + aortosclerosis. Therefore, at a ratio value below 0.2647 severe aortic stenosis could highly accurately

be detected, while a value over 0.3871 could highly accurately help detect mild aortic stenosis or aortosclerosis.

This research proved that the ratio between the diameter of the aortic orifice and the aortic diameter, measured by ultrasound in parasternal long axis view, correlates with the severity of aortic stenosis and can discriminate between different categories of severity of aortic stenosis, also being a parameter which is independent from traditional risk factors incriminated in the development of aortic stenosis.

The data obtained within this study have an innovative character, suggesting a new method for assessing the severity of aortic stenosis.

Analysis of the second parameter considered in our study, the LAoOrf, demonstrated the existence of several statistically significant correlations with: the maximum diameter of the aortic orifice (PAL), R2 ratio and aortic valve orifice area measured by planimetry. This showed a strong interdependence between the variation in LAoOrf values, the maximum diameter of the aortic orifice, R2 ratio and aortic valve orifice area measured by planimetry. There was no literature data on this parameter or the associations described.

These findings show that as early as this phase of statistical analysis there is a relationship between the morphological parameters of the functional unit achieved by the ascending aorta and the aortic valve orifice (orifice diameter, the diameter of the ascending aorta - included in R2 ratio, the length of the aortic orifice) and aortic valve orifice area.

Levene’s test was further used to indicate if the value of the LAoOrf parameter is only influenced by the presence of atherosclerotic plaques in the ascending aorta. There were no changes in the length of the aortic orifice, variables such as gender, smoking status, hypertension, diabetes, dyslipidemia, mitral annular calcifications. This suggests that together with R2 ratio, LAoOrf is another independent factor that correlates with the severity of aortic stenosis. There was no literature data on the influence of these cardiovascular risk factors on LAoOrf.

ANOVA was used in order to show if the value of the aortic orifice length differs for each group of severity of aortic stenosis. The analysis revealed significant differences in LAoOrf between these categories. Therefore, we determined the cutoff values of this parameter that were able to detect severe aortic stenosis or mild aortic stenosis. Thus, a value below 9 mm could highly accurately detect tight aortic stenosis, while a value over 10 mm could highly accurately detect large stenosis or aortosclerosis. Thus, this study aimed to prove that the length of the aortic orifice, measured by ultrasound in parasternal long axis view, correlates with the severity of aortic stenosis, a parameter which was independent from traditional risk factors incriminated in the development of aortic stenosis. These data are important as they are not described in the literature and they bring in a new method for assessing the severity of aortic stenosis.

At the end of the study, given that the two parameters were alternatives in the quantification of aortic stenosis severity, we investigated consistency by which R2 and LAoOrf differentiate between different categories of severity of aortic stenosis. The use of Cohen’s kappa coefficient when comparing the groups of severity of aortic stenosis defined using the cutoff values of aortic orifice length with the severity groups defined using the cutoff values of R2 ratio, established a moderate concordance

between the categories of R2 ratio and LAoOrf regarding the classification of severity of aortic stenosis. This ensures that the use of these parameters will provide good predictability in quantifying the severity of aortic stenosis.

Conclusions

1. "Classical" Risk factors for degenerative aortic stenosis did not influence the severity of valvulopathy, having a uniform distribution in relation to the degree of severity of aortic stenosis.
2. CRP values differ significantly depending on the severity of aortic stenosis.
3. The relation between aortic orifice diameter and aortic diameter (measured by ultrasound in parasternal long axis view) correlates with the severity of aortic stenosis.
4. A value of the ratio below 0.2647 highly accurately indicates severe aortic stenosis, while a value over 0.3871 indicates mild stenosis or aortosclerosis.
5. Aortic orifice length (measured by ultrasound in parasternal long axis view) correlates with the severity of aortic stenosis.
6. An aortic orifice length value below 9 mm accurately indicates tight aortic stenosis and a value over 10 mm indicates large stenosis or aortosclerosis.
7. Both R2 ratio and LAoOrf were not influenced by traditional cardiovascular risk factors.
8. There is a moderate concordance between R2 ratio and LAoOrf regarding the classification of patients according to the severity of aortic stenosis.

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Citation Stoicescu L, Duncea C, Buzdugan E, Donca V, Radulescu D. Relationship between the severity of aortic stenosis and different morphological parameters. HVM Bioflux 2014;6(2):49-55.

Editor Stefan C. Vesa

Received 30 May 2014

Accepted 2 July 2014

Published Online 3 July 2014

Funding None reported

**Conflicts/
Competing
Interests** None reported