ANNUAL RATE OF PROGRESSION OF AORTIC-JET VELOCITY AND SURVIVAL IN CASES OF SEVERE ASYMPTOMATIC AORTIC STENOSIS

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Abstract: The aim of the study was to establish the predictive role of maximal aortic-jet velocity, i.e. its annual rate of progression, in the decision in favour of aortic valve replacement (AVR), as well as in the event appearance and/or patients’ survival with severe asymptomatic aortic stenosis.

49 patients were analysed who belonged to the clinical and echocardiography group with severe asymptomatic valve aortic stenosis, with an average of 22 ± 10 months follow-up period.

The echocardiography parameters were: ejection fraction, maximal aortic-jet velocity (AV_Vmax), trans-valve maximal gradient and aortic valve area, as well as calcification rate, all of which were included in the predictive model. The progression rate of the aortic-jet velocity was established, reduced to an annual level. The variable ECHO status worsening was defined as worsening when the progression rate of the AV_Vmax at the annual level was ≥ 0.3 mps per year.

The results show that in 20% of the patients an annual rate of progression of the aortic-jet velocity over ≥ 0.3 mps per year was registered.

For the follow-up period, event appearance was registered in 20% of the patients, where the risk of event appearance is 4.3 times higher in patients with ECHO worsening status, in relation to those without ECHO worsening status.

It was established that the probability of survival of the asymptomatic patients with severe AS over a period of 3 years was 0.57 ± 0.11. The average length of survival in patients without ECHO worsening status was 32.8 ± 1 months, while in patients with ECHO worsening status it was 23.5 ± 4 months.
It can be conclude that the maximal trans-valve aortic-jet velocity, especially the rate of its annual progression, is a significant predictor of the rapid progression of the disease, which contributes to the risk stratification in the risk group of patients with severe asymptomatic aortic stenosis while referring for AVR.

**Key words:** severe asymptomatic valve aortic stenosis, echocardiography, annual rate of progression of the maximal aortic-jet velocity, survival.

**Introduction**

The poor outcome of patients with symptomatic aortic stenosis (AS) has been evaluated and is well known [1–5]. Because of this, valve replacement is recommended as an absolute indication for these patients. In contrast, the treatment of asymptomatic aortic stenosis becomes controversial. The occurrence of sudden death without preceding symptoms [1, 6] and a potential risk of irreversible myocardial damage [7] are the parameters which favour early elective surgery. However, prospective studies have suggested that in the absence of preceding symptoms, sudden death occurs rarely [8, 9]. If we analyse the wide variability of the outcome in individual patients, and the potential risk of complications because of the prosthesis as an operative risk on its own, the decision to undertake surgery on asymptomatic patients remains difficult [10, 11, 12].

For all these reasons, outcome predictors which will help in the selection of asymptomatic patients with a high risk level should be identified for early referral for aortic-valve replacement (AVR).

**Patients and methods**

In our study 49 (forty nine) patients with severe asymptomatic aortic stenosis were involved, all examined at the University Cardiology Clinic in Skopje, R. Macedonia. the asymptomatic patients were included in the study in April 2004 and monitored until April 2008, i.e. an average monitoring period of 22 ± 10 months.

The criteria for including the patients in this study were: patients with severe asymptomatic aortic stenosis: maximal aortic-jet velocity > 4.0 mps; maximal trans-valve gradient (LV/Ao) > 60 mmHg; aortic valve area ≤ 1 cm²; moderate or severe expressed aortic valve calcification and normal systolic function of the left ventricle defined as EF > 50%.

Criteria for not including a patient in this study were: patients with mild and moderate aortic stenosis; patients with "Low Gradient" severe aortic ste-
nosis, acute myocardial infarction in the last six months; patients with aortic regurgitation higher than mild; patients with mitral valve disease and mitral regurgitation higher than mild and other heart defects; patients with sub- and supra-valvular aortic stenosis; patients with kidney disease; patients with severe lung disease and patients with anaemia and haemoglobin < 100 g/L.

Echocardiography

The first echocardiograph test on each patient was made at the beginning of the study, and the following echocardiograph tests were made every six months or earlier if the condition was aggravated, and with vivid symptoms.

The inner dimensions and volumes of the left ventricle and the thickenings of the walls were measured under the criteria given by the American Echocardiography Society [13]. The ejection fraction and the fraction shortening were obtained by M-mode in the Teicholtz formula [13].

The maximal aortic-jet velocity was obtained from the window which provides the highest velocity in a five-cavity apical view using continuous Doppler echocardiography (AV_max, mps), and using the pulse Doppler echocardiography from the same view, immediately proximal to the stenotic aortic valve (using 5–10 mm length of the volume sample), the left ventricle outflow tract velocity was registered (LVOT_V, mps). Both velocities are necessary to calculate the aortic area (AVA, cm²) with a continuous equation (AVA = LVOT-area x LVOT_V / AV_max). The diameter of the left ventricle outflow tract (LVOT, mm) was obtained from a parasternal long axis view, in the middle of the systole, immediately proximal to the aortic annulus.

The maximal trans-valve gradient LV/Ao (AV_max.Grad., mmHg) was obtained by using the Bernoulli equation (AV_max.Grad.= 4 x AV_max²).

The wall kinetics of the left cavity was analysed using the 16-segment model. Mitral and aortic regurgitation was graded between 0–4 degrees using colour Doppler echocardiography.

The degree of distinction of aortic calcification (CALCIF.) was classified as: 1 = no calcification; 2 = mildly calcified – small isolated spots (Mild); 3 = moderately calcified – many and larger spots (Moderate) and 4 = heavily calcified – extensive thickening and calcification of all cusps (Severe) [14].

The annual rate of progression of the aortic-jet velocity (mps per year) for each patient was calculated by dividing the difference between the velocities measured at the first and the last examination, on one side, with the time between examinations (brought down to an annual level) on the other side.
We made a variable ECHO status aggravation, defined as aggravation, if the degree of progression of AV Vmax on annual level was ≥ 0.3 mps per year.

**Follow-up**

The follow-up was made possible for all patients with a mean follow-up period of 22 ± 10 months, with personal interviews with the patients or with their relatives. The data collected was specifically related to the cardiac symptoms at the time the AVR was performed and the manner of death.

The outcome was defined as a death occurrence and/or symptoms occurrence (or AVR performed because of the occurrence of the symptoms).

The death was defined as a sudden death (SD), death with prior shown symptoms, death in the waiting period for AVR and death from other causes.

**Statistical Analysis**

The statistical analysis was performed by using the SPSS computer program (13.0). All data were presented as an average value and a standard deviation or with percentages. The comparison of the categorical parameters amongst the groups was performed by the Chi-square test and in relation to the continuous parameters by the Wilcoxon rank-sum test. Event-free survival during the follow-up was examined by Kaplan-Meier curves, compared with the Log-rank method. The Cox’s regression model was used to establish the temporal dependence predictive value of the ultrasonic characteristics for events, including death, after it was determined that the covariant which was to enter the predictive model of linear regressive analysis had a significant connection with the events.

In all statistical tests, p < 0.05 was regarded as statistically important.

**Results**

In this study 49 patients aged 59 ± 13 years were analyzed, 31 men (63%), 18 women (37%), with an average maximal jet velocity of 4.3 ± 0.5 mps. All patients had regular function of the left ventricle, with an average value of ejection fraction of 69.9 ± 5.5%.

The distribution of the characteristic echocardiography parameters in asymptomatic patients with severe AS are given in Tables 1 and 2.
Table 1 – Таблица 1

<table>
<thead>
<tr>
<th>Calcification</th>
<th>Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>4</td>
<td>8.2%</td>
</tr>
<tr>
<td>Moderate</td>
<td>24</td>
<td>49.0%</td>
</tr>
<tr>
<td>Severe</td>
<td>21</td>
<td>42.8%</td>
</tr>
</tbody>
</table>

Wanting to establish whether asymptomatic patients have a worsening of the trans-valve maximal aortic-jet velocity during the follow-up period we compared the AV_Vmax value at their entering the study with the AV_Vmax value at the end of the follow-up. We established the existence of a statistically significant difference in the benefit of the higher value of AV_Vmax at the end of the follow-up in relation to the same value gathered at the beginning of the study (t = -5.12, df = 48 and p < 0.05), which means that asymptomatic patients with severe AS had a worsening of the trans-valve maximal aortic-jet velocity during the follow-up period.

Special attention was paid to the annual rate of AV_Vmax progression in asymptomatic patients with severe AS and we discovered that it has a range from 0.0 to 2.4 mps per year.

We divided the patients into two groups: a group with ECHO worsening status if the annual rate of AV_Vmax progression was ≥ 0.3 mps per year and a group without an ECHO worsening status, if such a rate of progression was not achieved. In our study we obtained the result where 10 patients (20%) showed a worsening of the ECHO status, i.e. 20% of the patients had an annual rate of progression of aortic-jet velocity of over ≥ 0.3 mps per year.
In our series of 49 asymptomatic patients examined for an average follow-up period of 22 ± 10 months, we registered 10 (20%) event appearances. One of these was a death outcome after previously shown symptoms in a patient who refused AVR; in 5 (10%) patients AVR was successfully performed, and the remaining 4 (8%) fulfilled the criteria for performing AVR and are on a waiting list.

Wanting to establish the probability of survival we made an actuary curve of survival for each year in all asymptomatic patients with severe AS, shown in Figure 1.

![Survival Function](image)

Figure 1 – Curve of survival in asymptomatic patients with severe AS

Using the live chart, we established that the probability of survival in asymptomatic patients with severe AS for a period of 1 (one) year is 0.98 ± 0.02; for a period of two years it is 0.89 ± 0.05, and for a period of 2 or 3 years the probability for survival is 0.57 ± 0.11.

The average time period of survival is: 31.5 ± 1.2 months (95% CI 29–34 months), percentage median: 34.0 ± 0.8 months (95% CI 32–36 months).

Comparing the Kaplan-Meier survival curves with the Log-rank test in asymptomatic patients with severe AS with ECHO worsening status (23.5 ± 4 months, 95% CI 15.5–32 months), with the patients without ECHO worsening status (32.8 ± 1 months, 95% CI 30.8–34.7 months), we established that there is a statistically significant difference in the average survival time between patients with or without ECHO worsening status (p < 0.05) in favour of a smaller survival time in the patients who have an ECHO worsening status (Figure 2).
Using the univariate Cox’s regression model, we established that the risk of event appearance is 4.3 times (95% CI 1.1–17.6) higher in asymptomatic patients with ECHO worsening status in comparison with those without ECHO worsening status, where the attained difference had the significance of p<0.05, shown in Figure 3.

**Figure 2** – Review of survival curves in asymptomatic patients with severe AS, with or without ECHO worsening status (for $AV_{Vmax} \geq 0.3$ m/sec/year)

**Figure 3** – Review of risk of event appearance in asymptomatic patients with severe AS, with or without ECHO worsening status (for $AV_{Vmax} \geq 0.3$ m/sec/year)
In the period from April 2004 to April 2008 we analysed 49 patients with severe asymptomatic stenosis (trans-valve aortic-jet velocity of average 4.3 mps, maximal trans-valve gradient of average 75 mmHg and aortic valve area of average 0.8 cm²) and normal systolic function of the left ventricle, at an average age of 59 ± 13 years.

During the follow-up period, with control examinations, we established that even though asymptomatic, the illness in the patients was progressing, manifesting an increase of the maximal trans-valve aortic-jet velocity at the end of the follow-up period in relation to the value gathered at the beginning of the study, which emphasizes the significance of this echocardiography parameter. In addition, 20% of the examined patients had an annual rate of progression of aortic-jet velocity over ≥ 0.3 mps per year.

In our examined series over the average monitoring period of 22 ± 10 months, we registered event appearance in 20% of the patients. In these, there was one outcome of death in a patient who rejected AVR after symptoms previously appeared; of the rest of the patients, in 10% of them AVR has already been performed, i.e. 8% are waiting for AVR.

Using the life chart, we established that the probability of survival in asymptomatic patients with severe AS for a period of 1 (one) year is 0.98 ± 0.02; for a period of two years it is 0.89 ± 0.05, and for a period of 2 or 3 years the probability of survival is 0.57 ± 0.11.

Analysing the Kaplan-Meier survival curves we established the existence of a statistically significant difference between the average survival time in the patients without ECHO worsening status (32.8 ± 1 months, 95% CI 30.8–34.7 months) in relation to the average survival time in the patients with ECHO worsening status, and it is significantly lower and reads 23.5 ± 4 months (95% CI 15.5–32 months). At the same time, using the univariate Cox’s regression model, we established that the risk of event appearance is 4.3 times higher in patients with ECHO worsening status in comparison with those without ECHO worsening status.

With these results, the importance of the value of the trans-valve maximal aortic-jet velocity is confirmed once more, i.e. the rate of its annual progression, of survival and the risk in general of event appearance, i.e. referral of the asymptomatic patients to AVR.

There is still no consensus about the referral of asymptomatic patients to AVR [15], as well as the fact that patients themselves refuse AVR when they are asymptomatic. Nevertheless, there is a concern among the doctors about the possibility of sudden death occurrence and/or irreversible myocardic damage. After postponing AVR, myocardic fibrosis and distinct hypertrophy cannot be
reversible. Gjertsson P. et al. in Sweden 2007, emphasize that late diagnosis and late referral of patients with AS is a common occurrence, and the long waiting time after referral for surgery increases the mortality immediately after AVR [16].

On the other hand, the risk of preoperative, late complications as well as the operative mortality in asymptomatic patients with severe AS is higher than the benefit of earlier referral for AVR. Patients with distinct symptoms have significantly higher operative mortality, and AVR performed as an urgent procedure brings a higher risk than elective surgery. Thus the operative mortality and the risk of perioperative complications is 3–4%, operation on elderly patients brings a risk of 10%, and if there is a need for by-pass surgery the risk is >10%.

Regarding sudden death, the majority of studies underline that the risk of SD is around 1% per annum. In our study of patients with severe asymptomatic AS, over a period of 4 years and an average follow-up period of 22 ± 10 months, we had one death after symptoms appeared previously. In Kelly’s study [4] of a 1.5 year follow-up, SD without the prior appearance of symptoms is not published, but a significant percentage of the patients did not have severe aortic stenosis. The sole study which monitors a bigger cohort group of patients with severe stenosis is the one by Pellika et al. [17]. In a period of average follow-up of 20 months, it has two cases of heart death where the symptoms developed at least three months prior to death. In the series by Rosenhek et al. [14] of 128 monitored patients in 27 months, one sudden heart death occurred, but without any preceding symptoms. Their suggestion is that SD is not frequent and has an incidence of less than 1% annually. Their group submits one death case during the period awaiting AVR.

Quite often patients do not give information about the development of their symptoms soon enough or are dying while waiting for AVR. Otto CM et al., 2006, [18] emphasize that in the majority of asymptomatic patients, the risk of surgery is higher than the risk of attentive monitoring of these patients, so the treatment means and includes education of the patients and periodic echocardiography as well as modification of the risk factors in cardiovascular diseases.

For all the above-mentioned reasons, there is a need to identify the patients at risk where the symptoms will be shown very soon, i.e. those who will have need of earlier AVR.

Rosenhek et al. [14] give 67 event appearances in 128 asymptomatic patients in an average follow-up period of 22 ± 18 months (0–54 months) (including 8 cases of death and 59 AVRs performed because of the appearance of symptoms).

In Rosenhek et al.’s work [14] the accent is put on the rate of progression of the aortic-jet velocity ≥ 0.3 mps per year as a significant independent
predictor for the clinical course, together with the intensity of valve calcification (moderate and/or severe) and age of over 50 years.

Pellika PS (8) et al. emphase the importance of a maximal aortic-jet velocity of $\geq 4.5$ mps as well as the existence of the ejection fraction $\leq 50\%$ as significant predictors of the clinical course.

The rate of progression of the aortic-jet velocity of $\geq 0.3$ mps per year and the level of the aortic valve calcification (in four successive levels) [14] are two parameters which were incorporated for the first time in 2002 in the Recommendations on the management of the asymptomatic patient with valvular heart disease [19].

In E. Hristova’s work in 1999–2001 (20), a co-relational analysis was made of the maximal trans-valve gradient between the left ventricle and the aorta, obtained by continuous Doppler echocardiography and catheterization of patients with severe aortic stenosis and a very high positive co-relation was achieved ($r = 0.97$). This means that the increasing of the maximal gradient obtained by continuous Doppler echocardiography is accompanied by the increasing of the maximal gradient obtained by the catheterization. At the same time, the echocardiography parameters were compared among the three groups of aortic stenosis: a mild, moderate and severe group, divided by the maximal gradient determined during the heart catheterization, which at that time was regarded as a golden standard. With analysis of the trans-aortic flow, it was discovered that the differences of the values of the variables AVA, AV_Vmax. and AV_Max.Grad. between mild and moderate, as well as between moderate and severe, are statistically significant, which means that the most advanced groups of AS have a more distinct illness, i.e. progression, registered by echocardiography examination. Thus the significance of echocardiography was confirmed as a supreme method in diagnostic evaluation of the expression of the aortic stenosis as well as referring patients for AVR, as compared to catheterization.

**Conclusion**

During the follow-up period, using control checkups, it was established that in asymptomatic patients with severe AS progression of the illness is happening, manifested by the increasing of the trans-valve maximal aortic-jet velocity at the end of the follow-up period in relation to the value obtained when entering on the study. Thus 20% of the examined patients had an annual rate of progression of the aortic-jet velocity of over $\geq 0.3$ mps per year.

In connection with survival, it was established that the probability of survival in asymptomatic patients with severe AS over a period of 3 years reads
0.57 ± 0.11. The average period of survival in the patients without ECHO worsening status is 32.8 ± 1 months, but in patients with ECHO worsening status it is 23.5 ± 4 months.

Over an average monitoring period of 22 ± 10 months an event appearance was registered in 20% of the patients, while at the same time the risk of event appearance was 4.3 times higher in the patients with ECHO worsening status in comparison with those without ECHO worsening status.

It can be concluded that the maximal trans-valve aortic-jet velocity, and especially the rate of its annual progression, represent significant predictors of the rapid progression of the disease, which are contribute to risk stratification in the risk group of patients with severe asymptomatic aortic stenosis while referring for AVR.

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Целта на студијата беше да се одреди претскажувачката улога на максималната брзина на аортниот млаз, односно нејзиниот годишни степен на прогресија, во одлуката за упатување на аортен валвуларен репласман (АВР), како и во појавата на збиднувања и/или преживувањето на пациентите со асимптоматска тешка аортна стеноза.

Беа анализирани 49 пациенти кои клинички и ехокардиографски припааа на групата асимптоматска тешка валвуларна аортна стеноза со среден период на следење од 22 ± 10 месеци. Ехокардиографските параметри: ексекциона фракција, максимална брзина на аортен млаз (AV_Vmax), трансвалвуларен максимален градиент и аортна валвуларна ареа, како и степенот на калцификација беше вклучени во предикативниот модел. Беше одреден степенот на прогресија на брзината на аортниот млаз, сведен на годишно ниво. Варијаблата EXO статус влошувание, беше дефинирана како влошувание, доколку степенот на прогресија на AV_Vmax на годишно ниво е ≥ 0,3 м/sec/год.

Резултатите покажаа дека кај 20% од пациентите беше регистриран годишни степен на прогресија на брзината на аортниот млаз над ≥ 0,3 m/sec/год. За периодот на следење, кај 20% од пациентите регистрирана е појава на збиднување, при што ризикот за појава на збиднување е 4,3 пати поголем кај пациентите со EXO статус влошувание, во споредба со оните без EXO статус влошуваше. Утврдено е дека веројатноста за преживување кај асимптоматските пациенти со тешка АС, за период од 3 години изнесува 0,57 ± 0,11. Просечното време на преживување, кај пациентите без EXO статус влошуваше е 32,8 ± 1 месец, додека истото, кај пациентите со EXO статус влошуваше изнесува 23,5 ± 4 месеци.

Може да се заклучи дека максималната трансвалвуларна брзина на аортен млаз, а особено степенот на нејзината годишна прогресија, претставуваат значајни предикатори на брзата прогресија на болеста, кои при-

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донесуваат во ризик стратификацијата на ризичната група на пациенти со асимптоматска тешка аортна стеноza при упатувањето на АВР.

Ключни зборови: асимптоматска тешка валвуларна аортна стеноza, ехокардиографија, годишен степен на прогресија на максималната брзина на аортнот млаз, преживување.

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