The effects of arterial hypertension on aortic valve stenosis

Uticaji arterijske hipertenzije na stenozu aortnog zaliska

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Key words: hypertension; aortic valve stenosis; antihypertensive agents.

Introduction

Since the first descriptions of acquired aortic stenosis (AS) by Stokes in 1845 and Mönckeberg in 1904, there has been a dramatic increase in the incidence of this disease. Today, in terms of frequency, it is the third most common cardiovascular disease after arterial hypertension and coronary artery disease. At the same time, it is the most frequent valvular disease, and, according to data published in Euro Heart Survey on Valvular Heart Disease, it is found in 43% of all patients with valvular diseases. The most frequent cause of AS in adult patients is calcification of the normal tricuspid valve or congenital bicuspid valve. Risk factors in the development of calcified AS have been the same to factors responsible for the development of atherosclerosis. A prospective population-based cardiovascular health study, which included 5,621 patients older than 65 years of age, examined the influence of age, sex, smoking, hyperlipidemia, hypertension and obesity in the development of calcified aortic stenosis (Table 1). As it is shown in Table 1 arterial hypertension is a very important risk factor in the development of calcified aortic stenosis right after older age, male gender and smoking.

The role of arterial hypertension is the most important in the initial phase of the aortic stenosis development. Changes in the dynamics of blood flow play a role in the creation of lesions on the aortic side of the valve, the region of higher exposure to tension stress. An endothelial defect in these places represents a principal site for the initiation of oxidative stress and inflammatory processes.

Arterial hypertension is found in one-third of patients with symptomatic aortic stenosis. Apart from the causative relationship of arterial hypertension and calcified aortic stenosis, arterial hypertension may affect clinical development and assessment of the aortic stenosis severity. On the other hand, aortic valve stenosis may interfere with the efficiency of the treatment of arterial hypertension.

The impact of arterial hypertension on clinical development and diagnosis of aortic stenosis

Increased arterial pressure may lead to an increase in peripheral vascular resistance and a decrease in vascular compliance. According to this it may be expected that arterial hypertension may affect the time of occurrence and severity of symptoms in patients with AS.

Antonini-Canterin et al. found that the distribution of clinical symptoms and NYHA class were similar between hypertensive and normotensive patients with aortic stenosis who underwent this testing. They found that in patients with AS associated with hypertension arterial symptoms occurred in the earlier stage of the disease than in normotensive patients with AS. In the absence of reliable evidence of the differences in the remodeling pattern of the left ventricle in hypertensive and normotensive patients with AS it was difficult to understand how hypertension caused the earlier appearance of symptoms. This was explained by the fact that the
The absence of an impact of arterial hypertension on structural and functional changes of the left ventricle in patients with aortic stenosis

The left ventricle responds to the pressure load in patients with AS and patients with arterial hypertension by different adaptive mechanisms. During the coexistence of AS and arterial hypertension, the left ventricle suffers under a double load: valvular (AS) and vascular (systemic hypertension). Antonini-Canterin et al. and Linhartova et al. gave an answer to a question about which load affects more significantly structural and, consequently, functional left ventricle changes. They found that there was no significant difference in remodeling the left ventricle in normotensive and hypertensive patients with AS. Based on such findings they concluded that in the case of AS there was a “fixed” mechanical obstruction of the aortic valve with a more significant role in remodeling and hypertrophy of the left ventricle than the arterial hypertension. At the same time they eliminated the impact of arterial hypertension on diastolic and systolic functions of the left ventricle in patients with AS.

Despite consensus on the results of the two most important researches on the relationship between arterial hypertension and aortic stenosis, the impact of arterial hypertension on the change of ascendant aorta dimension was not determined.

The impact of arterial hypertension on the assessment of aortic stenosis severity

Determination of a mean transvalvular pressure gradient and aortic valve area has been routinely used for assessing AS severity. Theoretically, the increase of arterial blood pressure may lead to an increase of peripheral vascular resistance and a decrease of vascular compliance, and consequently affects the aortic transvalvular flow and compromises the assessment of AS severity. The data on this impact has been controversial; some researchers have shown that there is a direct influence of an increased blood pressure on the hemodynamics parameters for the assessment of AS severity, while other researchers have disputed such an influence.

Using a catheterization study, Laskey et al. showed that an increase of peripheral vascular resistance led to a decrease of the transvalvular pressure gradient and severity of AS. In an animal model of supravalvular aortic stenosis, Kadem et al. showed that an increase of the systemic pressure resulted in a decrease of the pressure gradient and an increase of the aortic valve area. This area increase remained unclear and it could only be explained by the modality of inducing supravalvular stenosis. Namely, in this study, AS has been induced by banding the ascendant aorta. In such conditions, the extension of that aorta segment induced by an increased pressure might lead to an increase of the effective valve area.

In contrast to these findings, Razzolini et al. proved, using an in vitro study, that an increase of a systemic pressure led to a small linear increase of the pressure gradient through bioprosthesis. The basic limitation of this study was in dealing with non-stenotic valve.

Little et al. used a handgrip test or phenylephrine infusion in order to increase pressure in patients with AS. They found that the increase of blood pressure and the
peripheral vascular resistance at the end of the intervention resulted in a decrease in transvalvular flow. On the other hand, they found that the aortic valve area was decreased without a change in the mean transvalvular pressure gradient. The changes in blood pressure level inversely correlated with the aortic valve area; although the only independent predictor of the aortic valve area was the change in cardiac output. They showed that an acute increase of blood pressure compromised the assessment of severity of AS. They concluded that the impact of arterial hypertension in the assessment of aortic stenosis severity was mostly based on a cardiac output change, and less on a peripheral vascular resistance increase and a change in artery compliance.

Mascherbauer et al. used a circulation model in determination impact of the systolic pressure level on the determination of the aortic valve area and transvalvular gradient. Similar results were obtained with the application of Doppler and catheter measurements. They did not find that the level of the systemic pressure change the aortic valve area and transvalvular gradient. Their result has been supported by a computer analysis of fluid dynamics, which excludes the impact of the systemic blood pressure on the assessment of AS severity. As all experimental models, this model also tried to achieve a corresponding in vivo condition. However, the limitation that cannot be surpassed is that a rigid system cannot match the vascular bed, and a stenosis model does not correspond to the three-dimensional model in vivo.

The basic limitation of the above studies is in the fact that they dealt with determination the impact of an acute increase in arterial pressure on the assessment of AS severity. Due to the fact that a chronic increase of arterial blood pressure affects the vascular system differently, and due to the fact that calcified aortic stenosis may not be considered an isolated valvular disease, but the manifestation of atherosclerosis processes affecting various components of the vascular bed, Pibarot et al. proposed determination of a total afterload of the left ventricle. Namely, they calculated a valvular-arterial impedance according to the formula $Z_{VA} = (SAP + MG) / SVi$, where SAP is the systolic arterial pressure, MG the mean transvalvular gradient and SVi the stroke volume index. They showed that this measure of the global left ventricle afterload may be used for predicting the left ventricle systolic dysfunction and death outcome in patients with AS.

Despite the controversial findings it is clear that arterial hypertension may mask severity of AS. It is recommended to measure arterial blood pressure with all patients with AS before echocardiographic Doppler assessment of AS severity. In terms of increased value we should try to reduce the arterial pressure to normal value with the use of ACE inhibitors (captopril in the dose adjusted to arterial blood pressure level). In situations when it is impossible to achieve normalization of blood pressure in patients with AS it is advisable to write down a value of the blood pressure in the echocardiographic report. This data would reduce the number of errors in the assessment whether there is a progression of disease or not, regarding echocardiographic observing. Namely, it is recommended that echocardiographic controls of AS severity should be conducted in the same conditions with nearly the same values of arterial blood pressure and, if possible, with normal blood pressure.

**Treatment of arterial hypertension in patients with aortic stenosis**

Assessment of AS severity in patients with arterial hypertension is regarded as a challenge, but the treatment of hypertensive asymptomatic patients with AS is even more difficult. Treatment of arterial hypertension is limited only to asymptomatic patients with AS, because the occurrence of symptoms represents an indication for surgical replacement of the aortic valve.

Due to complex adaptation of the cardiovascular system to an obstruction of the left ventricle output tract, antihypertensives (diuretics, beta and alpha blockers, blockers of calcium channels and inhibitors of the renin-angiotensin-aldosterone system) should be used with caution. Patients suffering from AS are very sensitive to changes in preload, contractility and vasomotor tone. Thus, diuretics whose application refers primarily to the correction of abnormal fluid retention and exceptionally to the treatment of arterial hypertension should be used with caution because having caused hypovolemia with reduction of enddiastolic pressure could lead to decrease of stroke volume. It is not recommended to give beta blockers nor calcium channel blockers due to depression of the myocardial function with possible induction of heart failure. The usage of vasodilators increases the reduction risk of coronary pressure perfusion (Table 2).

The risk of negative manifestations of above-mentioned drugs is higher when aortic stenosis is more severe.

However, these reasons are not sufficient for giving up the treatment of arterial hypertension in these patients. The therapy is directed towards a reduction of pressure load on the left ventricle and a possible reduction of additional mechanical stress and valve deformation. In that circumstances, the application of antihypertensives is continued.

In time, ACE inhibitors imposed themselves as the drugs that we use most frequently in treatment of arterial hypertension in patients with AS (Table 3). At the beginning, as other antihypertensives, they were used in individual cases because it was believed that vasodilator treatment is thought to be harmful as the stenotic aortic valve orifice may prevent an adequate increase in cardiac output resulting in coronary hypoperfusion and systemic hypotension. Also, there was a fear that extensive vasodilatation can cause a serious fall of coronary and cerebral perfusion with symptoms and signs of angina pectoris, cerebral insult and sudden death.

In spite of these presumptions, Martinez Sanchez et al. analyzed the effects of application of captopril in 22 patients with a severe AS. By using catheterization of the right heart they discovered that the application of ACE inhibitors led to a decrease in systemic vascular resistance and increased cardiac output.
The reason for further research the efficiency of ACE inhibitors in treating arterial hypertension in patients with AS were the findings of O’ Brien et al. who established that an angiotensin converting enzyme might be found in the leaflets of the aortic valve in patients with AS. At the same time, they eliminated its existence in patients with unchanged aorta leaflets. The assumption on enzyme activity of ACE in the aortic valve was supported by the finding that the leaflets of changed aortic valve also included angiotensin I receptors. Additionally, angiotensin II was found in the changed leaflets of the aortic valve in the calcified AS, and it was presumed that due to the multiple pro-inflammatory effects and influence on the fibrinolytic system, it participated in the creation and development of aortic valve disease. This histochemical finding indicated that the renin-angiotensin system played an important role in the active process of creating “degenerative” aortic stenosis. According to this it was presumed that application of ACE inhibitors, along with arterial pressure reduction might postpone the progress of valvular disease.

O Brien et al. found that treatment with ACE inhibitors in 71% out of the 123 participated patients with AS led to the termination of calcification progress, which was assessed using an electron beam computed tomography.

The results of the study conducted by Rosenhek et al. opposed the above. The study included 211 patients with AS. The half of the patients were treated with an ACE inhibitor, in contrast to the other half who were not treated with this agent. After a six-month therapy there was no postponement in the progression of AS in the patients treated with an ACE inhibitor in comparison with those who did not receive this kind of medical therapy.

Jimenez-Candil et al. confirmed the benefits of the application of ACE inhibitors in hypertensive patients with AS. The study included 20 patients with AS and arterial hypertension. The therapy resulted in a reduction of the value of systolic pressure with unchanged values of diastolic arterial pressure, increased flow velocity through the aortic valve without change in the aortic valve area. The stress test during ACE inhibitor therapy established an increase in the upstroke volume without an increase in the systolic pressure value. The treatment had to be terminated in two patients in the group of patients who were treated with ACE inhibitor and three patients in the group of patients who were not treated with ACE inhibitor. The therapy was terminated in one of the treated patients due to hypotension and due to the upstroke volume drop in the case of other patients. The conclusion of the research was that ACE inhibitors were well toler-
ated and improved the stress hemodynamics in most hypertensive patients with AS.

Prior to wider accepting of ACE inhibitors in treatment of arterial hypertension in patients with AS it is necessary to apply them successfully in a greater number of patients. Since many treatment regimens have changed, for example beta blockers, which had been contraindicated in treatments of heart failure became unavoidable, it may be expected that ACE inhibitors will become the choice medicines for treating arterial hypertension in patients with AS, particularly if there have been more convincing evidence that they play a significant role in the postponement of the progress of AS 37. Such verification would cause their application in normotensive patients with AS. Additionally, since an improvement of the functional class of normotensive symptomatic patients with severe AS with good tolerance and safety has been proved, it may be presumed that they will be accepted more widely for treating patients with symptomatic AS who do not agree with surgical replacement of the valve 38,27.

REFERENCES
