The role of biomarkers as an alternative and completion of the diagnostic and therapeutic pathway in patients with aortic stenosis (RCD code: VIII)

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Abstract

Aortic stenosis (AS) is the most frequent type of valvular heart disease. Clinically, it presents as calcific and congenital AS. Calcific AS is often age dependent and affects 2–7% of people over 65 years of age. Many clinical studies proved high correlation between age and the prevalence of calcific aortic stenosis. According to todays' knowledge, AS presents not only as simple degenerative disease of the valve, but as an active inflammatory and proliferative process. Better control and evaluation of risk factors might decelerate progression of the disease. It is necessary to increase the knowledge about risk factors and early markers of AS. Echocardiography is the method of choice in the diagnostic course and evaluation of stenosis grade and disease progression, but the role of biomarkers is becoming more and more significant among the clinical evaluation of patients and has been already mentioned in The European Society of Cardiology (ESC) guidelines on the management of valvular heart disease in patients qualified for Aortic Valve Replacement (AVR) with severe, asymptomatic AS, preserved ejection fraction and normal exercise stress test results. The natriuretic peptides level increase at the follow-up measurements is an important co-factor in decision-making. This review article analyses and summarizes the most important research and correlation between calcific aortic valve disease and the biomarkers. The potential clinical implementation of fourteen biomarkers has been reviewed. Echocardiography depends on the operator experience and imaging quality, therefore biomarkers could contribute important information to patients' diagnosis and follow-up. JRCD 2016; 2 (7): 1–1

Key words: echocardiography, aortic valve replacement, calcific aortic valve disease

Introduction

Aortic stenosis (AS) is the most frequent type of valvular heart disease. Clinically, it presents as calcific and congenital AS. Calcific AS is often age dependent and affects 2–7% of people over 65 years of age. Congenital AS is usually diagnosed in younger patients although rheumatic AS is becoming less frequent [1]. Many clinical studies proved high correlation between age and the prevalence of calcific aortic stenosis. Progression of the population's aging will result in increasing numbers of new cases in the nearest future [2,3,4]. Clinical presentation and the course of the disease was primarily proposed by Ross and Braunwald in 1968. In general, during the asymptomatic period, grade of valvular stenosis and the left ventricle overload increase and is often found during routine echocardiographic examination. Symptoms onset significantly increase mortality among patients with AS [5]. According to todays' knowledge, AS presents not only as simple degenerative disease of the valve, but as an active inflammatory and proliferative process with risk factors in high relation to atherosclerosis [6,7]. Better control and evaluation of risk factors might decelerate the progression of the disease. Therefore, modification of risk factors, surgical and minimally invasive intervention with transcatheter aortic valve implantation (TAVI) in an appropriate time should decrease morbidity and mortality, as well as improve Quality of Life among these patients [8]. It is necessary to increase knowledge about the risk factors and early markers of AS.

The role of biomarkers in the European Society of Cardiology (ESC) guidelines

Surgical Aortic Valve Replacement (AVR) is nowadays in most cases a therapy of choice in severe AS and several studies concerning new surgical methods are being conducted [9,10,11] TAVI may be considered in selected patients only in hospitals with cardiac surgery on-site and with a heart team available to assess individual patient risk. Based on heart team decision TAVI is indicated in patients with severe symptomatic aortic stenosis who are unsuitable for surgery but have sufficient life expectancy. TAVI should be considered for high-risk patients with severe symptomatic aortic stenosis based on the individual risk profile as assessed by the heart team. It is recommended not to perform TAVI in patients at low or intermediate risk for surgery. Echocardiography is the method of choice in the diagnostic course and evaluation of stenosis grade and disease progression. The role of biomarkers is mentioned in evaluation of patients qualified for AVR with severe, asymptomatic AS with preserved ejection fraction and normal exercise test results if the natriuretic peptides level increase in follow-up measurements (level of evidence II B) [1]. Echocardiography depends on the operator experience and imaging quality, therefore biomarkers could be a great complement to patients' diagnosis and follow-up.

Methodology

This review article analyzes and summarizes the most important research and correlation between calcific aortic valve disease and blood biomarkers. The potential clinical usage was marked.

Plasma B-type natriuretic peptide (BNP) and its N-terminal pro-form, NT-proBNP

BNP is a hormone secreted from atrial and ventricular myocardium during intracardiac pressure increase. Pro-BNP is stored in cardiomyocytes and splited to NT-pro-BNP and BNP which are released to blood [12]. NT-pro-BNP level measured in peripheral blood correlates with ageing and renal function. It is important to estimate baseline level and monitor its increase over time [13,14].

In patients with heart failure the blood concentration of natriuretic peptides is considered to be an important decision making factor. Untreated patient with normal natriuretic peptide level has no significant heart failure. Depending on heart failure symptoms onset two different threshold levels of NT-pro-BNP and BNP are being used. In acute heart failure the recommended level is 300 pg/mL for NT-proBNP and 100 pg/mL for BNP. Chronic heart failure may be diagnosed if the level is 125 pg/mL for NT-proBNP and 35 pg/mL for BNP[15].

Pressure stress observed in AS also causes secretion of BNP peptides. Level of BNP depends on AS severity and higher level is observed in symptomatic patients [16,17]. Significantly, the increase of serial follow-up measurements of BNP is a symptom predictor and risk monitor of severe asymptomatic AS [18]. Patients with high level of BNP before AVR have poorer outcome, so the careful follow-up should be performed [19]. Interestingly, BNP is better postoperative predictor as the EuroScore [20]. For example, Canadian Cardiovascular Society recommends assessment of BNP before TAVI [21]. Monin JL et al proposed a mathematical formula (peak aortic velocity (m/s) × 2)+(natural logarithm of BNP × 1.5)+1.5 if female sex) for asymptomatic AS which shows the correlation between LV function and stenosis severity and it is outcome predictor [22]. A new risk calculation parameter in AS is BNP ratio (BNP level to baseline value for age and sex) which represents BNP activation. Clavel MA et al analyzed 1953 patients with moderate to severe AS were examined regarding BNP ratio. It was independent survival predictor of disease. In the same study in subgroup of patients with asymptomatic AS, normal EF, and no history of myocardial infarction, BNP activation was not only an independent survival but also a prognosis predictor [23]. What is also important, the correlation of BNP levels and myocardial fibrosis was proved, thus BNP as a simple and standardised test could reveal the beginning of myocardium remodelling [24,25].

Troponin I (TnI)

Troponin I as a cardiac protein is released to blood in myocardium damage. Nowadays the progress of assay technology enables to measure even very low level of troponin [26,27]. Chin CW et al analyzed two cohorts of patients. "Mechanism cohort" of 122 patients with mild to severe aortic stenosis without other significant valvular heart disease or cardiomyopathy and "Outcome cohort" of 131 patients from the "Scottish Aortic Stenosis and Lipid Lowering Trial, Impact of Regression (SALTIRE)" study were analyzed. Both groups were compared to well matched thirteen healthy volunteers in terms of age and sex. In "Mechanism cohort" the correlation between TnI concentration, stenosis parameters and myocardial alteration was obtained. Ventricular remodelling was measured by focal myocardial fibrosis assessed by CMR late gadolinium enhancement (LGE). In "Outcome Cohort" the role of plasma TnI level in prognosis of AS patients was assessed. In "Mechanism cohort" the independent correlation with cTnI concentration was only proved in age, LV mass index, and%LGE. Interestingly, in population with aortic stenosis and mid-wall LGE TnI level was twice higher comparing to the population without mid-wall LGE. In "Outcome Cohort" TnI level was proportionally correlated with increased risk of AVR or cardiovascular deaths. As the conclusion, plasma TnI concentration has a high potential to be a marker of LV dysfunction in patients with AS, also without symptoms. In this study BNP markers were measured in both cohorts but without evidence of prognostic issue and it was suggested that BNP is released in case of LV failure. In opposition to the increase of BNP, TnI concentration corresponds with myocardial fibrosis which foreruns LV decompensation[28].

Table 1. Table summarizes results of main trials with brain natriuretic peptide

The first author of the study and year of publication	Number of patients	Clinical implication
Bergler-Klein Circulation 2004	130 (severe AS)	NT-proBNP predict symptom free-survival and postoperative outcome in severe aortic stenosis
Gerber IL, Am J Cardiol 2005	29 (asymptomatic patients with AS)	Serial BNP measurements are symptom predictor and risk monitor in asymptomatic AS
Gerber IL, Circulation 2003	74 (mild to severe AS)	BNP level is proportional related with symptoms and NYHA scale thus plays a additional role in patients evaluation
Clavel MA, J Am Coll Cardiol 2014	1953 (moderate to severe AS)	BNP ratio is long-term mortality predictor also in asymptomatic population
Monin JL, Circulation 2009	107 (asymptomatic moderate to severe AS)	BNP level, peak valve velocity and female sex combined in formula predict poor outcome and event free survival
Weidemann F, Circulation. 2009	58 (symptomatic severe AS)	Positive correlation between grade of myocardial fibrosis and level of BNP

Chemokines PF-4 and RANTES

Motovska Z et al analyzed 124 patients with diagnosed severe AS. Subjects were divided into two groups depending on coronary artery disease presence. The groups were compared to the control group without CAD and valve disease. In both groups serum level of PF-4 was significantly higher than in patients' control group but the rate of RANTES was increased only in patients with AS without CAD in comparison to the control group. Interestingly, there was no correlation between chemokines and mean pressure gradient [29].

The first plaque of coronary artery disease and AS is comparable. The role of chemokine RANTES in coronary artery disease was proved [30] and the negative correlation between RANTES level and the atherosclerosis dissemination measure [31]. By analogy it could be a marker of active process of valve degeneration in AS (comparison between moderate and severe AS).

microRNAs

Pressure overload in aortic stenosis leads to remodelling of ventricle. That alteration of myocardium is related to increase of extracellular matrix. It is well-known that microRNAs (miRNAs) has influence on mRNA. The role of miRNAs was proved also in heart diseases and one of them – miR-21 – plays the role in remodelling of the myocardium [32].

Villar AV et al have measured the myocardial and plasma level of miR-21 in patients with severe aortic stenosis qualified to AVR. Both myocardial and plasma level were significantly higher in aortic stenosis than in the control group. The correlation between miR-21 concentration and mean transvalvular pressure was revealed. Also the level of serum and myocardial miR-21 was proportional [33].

Chemokine CCL21

The chemokine CCL21 plays the role in homeostasis through leukocytes regulation. In the studies the influence of the chemokine on fibroblasts, endothelial cells and vascular smooth cells has been proved. Moreover, CCL21 expression was higher in patients with postinfarction heart failure and the level was corresponded to the patients' total mortality of heart failure [34].

Finsen AV et al analyzed 136 patients with symptomatic AS referred for AVR. The correlation between the level of chemokine CCL21 and the outcome in patients with symptomatic AS has been proved. CCL21 concentration was higher in AS group comparing to the control group and it corresponds to decreased aortic valve area and cardiac output [35].

Copeptin

Copeptin is a part of bigger particle – arginine vasopressin precursor peptide secreted from pituitary gland. Stress and blood pressure decrease trigger the release of copeptin. It is a marker of cardiovascular diseases and the potential role of that was proved in coronary artery disease and heart failure [36,37]. Mizia-Stec K et al recruited 64 patients with aortic stenosis without heart failure and divided them into two groups: with moderate and severe stenosis. The serum level of copeptin and NT pro-BNP was assessed and compared. The levels of copeptin were higher in both: aortic stenosis groups comparing to the control group, as well as in the group with severe AS in comparison to moderate AS. The correlation between copeptin concentration and stenosis severity has been proved. The same correlations were found in NT pro- BNP. Both investigated markers revealed no correlation. Surprisingly, there was no significant increase of copeptin level in both groups in the presence of coronary artery disease [38].

Uric acid

Serum uric acid level (SUA) is associated with cardiovascular risk. The correlation between SUA concentration and markers of atherosclerosis has been proved [39,40].

Demir B et al recruited 64 patients with mild to severe aortic stenosis. The positive and statistic significant correlation between maximal and mean transvalvular gradient and SUA was proved. Valve area was found in negative correlation to SUA. Unfortunately, the study has limitations: population number, lack of additional oxidative stress markers estimation as well as no standardisation in data of dietary and physical exertion [41].

C-reactive protein (CRP)

The role of CRP in atherosclerosis is well known [42,43]. Imai K et al analyzed the CRP level in 135 patients with asymptomatic (at the begging of the study) mild, moderate and severe aortic stenosis. C-reactive protein level was significantly higher in severe than in mild and moderate aortic stenosis. Also positive correlation between CRP level and AVA has been proved. The acceleration of stenosis progression was faster in the group with higher baseline CRP level. Ultimately, both long-term survival and event free survival correspond to CRP [44].

Sanchez PL et al recruited 43 patients with asymptomatic mild to severe AS. Depending on the AS progression in 6 month follow up patients were divided into two groups. The level of High-sensitivity CRP (hs-CRP) was statistically higher in fast progression group than in the control and slow progression group but there was no correlation between AS severity and hs-CRP level[45].

Jeevanantham et al enrolled 110 patients and found that the level of hs-CRP was significantly higher in patients with aortic stenosis and aortic sclerosis than in control group. There was no statistical difference between both calcific aortic valve disease groups. Thus they suggested that hs-CRP could not play a role as progression marker but a potential valve degeneration onset marker [46].

Von Willebrand factor (vWF) activity

Blackshear JL et al analyzed vWF activity indices and BNP in 66 patients with mild to severe AS. The mean gradient and other echocardiographical parameters were associated with VWF multimer ratio, BNP and VWF latex agglutination immunoturbidic activity/ VWF antigen.

The best severe AS detection marker was the VWF: multimer ratio. In opposition to the BNP VWF indices had no correlation with symptoms severity. VWF:Ltx/VWF:Ag ratio was correlated with increased risk of death or aortic valve replacement and BNP had no statistical correlation[47].

Homocysteine

Homocysteine is correlated with endothelium dysfunction and is a cardiovascular risk factor [48]. Navaro et al analyzed plasma level of homocysteine in 17 patients with AS, 32 with aortic sclerosis and 27 without valve disease. Concentration levels were significantly higher in AS group comparing to ASc and control group, but further analysis revealed that homocysteine was not a predictor of AS [49]. Gunduz et al compared 58 patients with moderate to severe AS to 47 healthy subject. The level of homocysteine was higher in AS group but with no statistical difference. Interestingly in AS group homocysteine was significantly higher in the subgroup with coronary artery disease [50].

Tissue plasminogen activator (t-PA)

t-PA is released by endothelium and has influence on fibrinolysis. It was proved that it plays an important role in cardiovascular disease [50]. Glader et al compared the plasma t-PA of 101 patients with severe AS and 101 controls. t-PA level was significantly higher in AS group[51]. Kochtebane et al analyzed concentrations of t-PA in the valve-conditioned media from 65 aortic stenosis valves. t-Pa concentration revealed no significant difference to the normal human plasma range as well as no correlation to valve calcium content was found[52].

Calcium-phosphorus product.

Mills et al analyzed 107 patients without kidney disease for their calcium, phosphorus and calcium-phosphorus product (CaxP) serum concentration. For phosphorus and CaxP statistical correlation with peak/mean aortic valve gradient and inversely association with AVA has been proved[52]. Linefsky et al measured serum level of mineral metabolism markers(phosphate, calcium, parathyroid hormone and 25-hydroxyvitamin D) and analyzed echocardiography data (aortic valve sclerosis and aortic annular calcification) in 1938 patients. The higher serum phosphate level was well correlated with aortic valve sclerosis [53]. Akat et al compared 38 patients with severe AS to matched 38 control group. In AS cohort levels of serum calcium phosphate and CaxP were statistically higher[54].

Summary

Aortic stenosis is a complex disease, which affects not only valve, but being a pressure overload consequence- also the left ventricle muscle. Due to the disease complexity, the assessment of the different stages of AS may not be dependent on one condition. Importantly asymptomatic severe AS and symptomatic moderate AS are controversial and the decision to perform a surgery is often made in terms of the symptom onset or left ventricular function degradation, when prognosis is poorer. Due to ageing of the population many patients complain about comorbidities. In conse-

quence symptoms of aortic stenosis are very often neglected, so the intervention is delayed. In such situations the use of blood biomarkers could play the great role. Biomarkers in combination with echocardiography and cardiac magnetic resonance could be favourable in the future qualification process to AVR or TAVI. There is a need of future research to combine few biomarkers at different stages of disease.

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