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THE IMPORTANCE OF IMMUNE INFLAMMATION IN THE DEVELOPMENT OF SENILE AORTIC STENOSIS

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Abstract:

Calcific aortic stenosis is the most common organic valvular heart disease in the elderly. Its prevalence is steadily increasing in the general population worldwide. The most frequently discussed cause of this defect is subclinical inflammation, the signs of which are clearly visible when examining sections of altered aortic valves. At the same time, the study of classical inflammation biomarkers in older people faces certain difficulties in standardization of studies, qualitative assessment and predictive value of the detected changes, which is especially relevant for patients with this heart defect.

Keywords: Calcific aortic stenosis, method, inflammation, treatment, biomarkers, old age.

INTRODUCTION

Calcific aortic stenosis (synonyms: degenerative, senile) accounts for 25% or more in the structure of aortic heart defects [1]. Population aging leads to an increase in its incidence in the population to 7–8% among individuals over 70 years of age [2]. According to leading cardiac surgery clinics, the proportion of calcific aortic stenosis (CAS) among aortic valve replacement (AVR) surgeries in individuals under 70 years of age reaches 33%, bicuspid aortic valve – 38%, and rheumatic aortic stenosis – 24% [3]. At older ages, the proportion of CAS increases to 48%, which leads to an increase in the costs of AVR (for example, in the USA – up to $1 billion per year) [4].

MATERIALS AND METHODS

To date, CAS remains a disease with an unspecified etiology. The detection of subclinical inflammation (SI) markers in the aortic valve (AV) leaflets in CAS, along with oxidized LDL surrounded by inflammatory cellular infiltration of lymphocytes, macrophages, and mast cells against the background of severe fibrosis and dystrophic changes in the endothelium, served as the basis for the inflammatory and atherosclerotic theories of the occurrence and progression of the defect [1, 2, 5].

RESULTS AND DISCUSSION

In old age, the determination of cytokines is associated with some features: 1) the presence of age-related dysfunction of the immune system (immunosenescence); 2) a high frequency of comorbid conditions that play their own role in modifying the immunological response (atherosclerosis, vascular and senile dementia, sarcopenia) [2]. The most studied cytokine in the elderly is interleukin-6, which is not accidentally given the unofficial name of "gerontologists' cytokine". A number of studies have shown both elevated and normal values of interleukin-6 (IL-6) with increasing age [3]. Such a range of values could be due to different sensitivity of the tests used, small volume of studies, as well as the health status of the subjects. However, similar data were obtained for tumor necrosis factor alpha (TNF-) [4]. The ability of the above inflammatory mediators to act as markers of individual diseases was demonstrated. It was later established that cytokine values are usually higher in "random groups" compared to relatively healthy elderly individuals, and "favorable" aging (aging without comorbid conditions) is always associated with a certain degree of inflammatory activity [5]. Despite the fact that an increase in the concentration of IL-6 in domestic and foreign literature is often considered as a marker of subclinical coronary sclerosis, it is quite difficult to determine the true cause of its increase in elderly individuals. As a rule, elderly individuals show a 2-4-fold increase in the level of SV markers, which is significantly lower than in acute infections. At the same time, such an "insignificant" increase was associated with an increase in overall patient mortality in a number of prospective studies [2]. In these studies, the concentration of SV parameters was not affected by the presence of concomitant diseases and/or traditional risk factors for death (smoking, blood pressure, physical activity, total cholesterol, body mass index, and intake of nonsteroidal anti-inflammatory drugs), and the results of survival analysis suggest specific biological activity of individual cytokines [3].

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A few studies have shown differences in the associative relationship of individual cytokines with mortality in the elderly. TNF-α was associated with an increase in mortality in patients in nursing homes, and IL-6 in 80-year-old patients turned out to be a significant predictor of death within 6 years. The predictive value of elevated TNF-α values in relation to mortality in males during survival analysis turned out to be higher than that of C-reactive protein (CRP). In a population of relatively healthy elderly Americans, IL-6 was also a more significant predictor of mortality than CRP. These results suggest that TNF-α and IL-6 are independent risk factors with different biological effects in elderly populations, and CRP may serve as a surrogate marker for these two cytokines.

One of the most important features of CAS is the severity of aortic valve calcification, which changes depending on the stage of the disease. It is no coincidence that later researchers tried to clarify the role of CRP in the occurrence and progression of calcification of the aortic valve cusps. One of such studies was the experimental work of Warrier B. et al. [2], which simulated a model of aortic wall calcification under the influence of an excess concentration of CRP. It was shown that the rate of calcification of the aortic wall was directly dependent on the concentration of CRP. Similar data were established for chronic renal failure (CRF), where activation of subclinical inflammation (increased CRP concentration) and an increase in the concentration of calcium phosphates significantly accelerated calcification of the heart valves. However, these and other experimental findings were not confirmed in one-stage clinical studies. Thus, the assertion about the presence of a direct link between the concentration of CRP and aortic valve calcification in CAS outside of CRF remains controversial. The expression of CRP in the cusps of both natural and artificial (biological) valves in patients with CAS, established in a number of histomorphological studies by D. Skowash et al., as well as a significant correlation between serum and tissue levels of CRP, allowed us to assume a dystrophic effect of this marker of SV on the endothelial cells of the aortic valves with their subsequent damage and increased local inflammatory response, which has many common features with the processes occurring in atherosclerosis [3].

Data on the state of other inflammation markers in patients with CAS were obtained mainly from pathomorphological studies. In the cusps of stenotic aortic valves, or more precisely in the zones with maximum leukocyte-macrophage infiltration, increased expression of interleukin-1-beta (IL-1), TNF-, IL-6 along with matrix metalloproteinases (MMP) was established. Presumably, possible sources of cytokines in CAS may be leukocytes, fibroblasts, and single smooth muscle cells in the aortic valve cusps. Previously, expression of the above markers was associated with a number of cardiovascular diseases, including atherosclerosis, aortic aneurysm, postischemic left ventricular (LV) remodeling, and myxomatous degeneration of the mitral valve. Most likely, the primary activation of IL-1β creates a "proinflammatory background" in the aortic valve cusps, which in turn leads to the activation of local interstitial cells, including myofibroblasts, with subsequent expression of other cytokines that modulate cellular proliferation and accumulation of extracellular matrix [5].

In other pathophysiological models, it has been shown that severe hemodynamic overload of the myocardium by pressure or volume is accompanied by an avalanche-like increase in the above-mentioned cytokines. Expression of the TNF-α gene has been studied in ischemic and idiopathic dilated cardiomyopathy (CMP), in which TNF-α values correlated with the severity of disease symptoms. According to L.P. Fried et al., such a variation in TNF- values is more closely related to sarcopenia or the "syndrome of frailty" in elderly individuals than to the presence of specific cardiovascular disease. The essence of the syndrome is a progressive age-related decrease in the volume and strength of muscle mass, leading to gait disturbance, followed by a decrease in the ability to self-care, an increase in the number of falls, hospitalizations, and mortality.

CONCLUSION

In addition, all patients included in the study suffered from critical aortic stenosis and were awaiting surgical correction of the defect, which also could not but affect the results obtained. The cytokine profile in elderly patients with aortic stenosis remains not fully described. Its retro- and prospective role in relation to symptoms and outcomes of the disease, the relationship with intracardiac hemodynamic parameters, and other classic risk factors for cardiovascular diseases are unknown, which makes it difficult to determine the role of SV markers in diagnosis, severity assessment, and prognosis in CAS.

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