EDITORIAL

Remodeling of the heart: so much is known, so much remains to be discovered

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Cardiac remodeling is a process leading to changes in size, architecture, and histology of the heart. It occurs in myocardial infarction, valvular disease, arrhythmias, acute and chronic myocarditis, and other conditions. It can be eccentric or concentric, local or global, progressive or reverse, and adverse or beneficial.

Although remodeling may affect all cardiac chambers, the most attention has been paid to dilatation of the left ventricle (LV). It results from physical tension of the myocardium which, according to Laplace's law, is proportional to the product of intracavitary pressure times the radius of wall curvature, and inversely related to the thickness of the wall. The bigger the radius, and the thinner the wall, the more the tension increases, leading to a vicious circle causing an uncontrolled increase in LV volume and sphericity, and progressive systolic and diastolic dysfunction.

Although physics plays an important role, biological mechanisms of cardiac remodeling are even more important and complex. LV remodeling was studied the most extensively in patients with myocardial infarction.[1] In this clinical scenario, substantial acute necrosis and regional dysfunction must be acutely compensated by the noninfarcted myocardium. The necrosis induces an inflammatory process, followed by healing. Ideally, it may lead to replacement of the necrotic tissue with fibrous tissue, preserving the remaining viable cells, with at least partial restoration of their function. Removal of the necrotic elements usually requires degradation of the intercellular matrix, which may facilitate changes in the wall shape. This may continue in the late phase of the remodeling process. In the worst-case scenario, also the remote, noninfarcted but overstimulated myocardium may become thinner and dysfunctional, and the entire LV may become spherical, causing global LV dysfunction and heart failure. Numerous factors are linked to adverse remodeling, including vasoconstriction, neurohumoral activation, apoptosis, intensity of inflammatory response, intracellular matrix degradation, fibrosis, and others.[1] Activation of the inflammatory cells and matrix metalloproteinases (MMPs) plays an important role in the degradation of extracellular matrix proteins. On the other hand, there are counterbalancing mechanisms, including tissue inhibitors of matrix metalloproteinases (TIMPs) and natriuretic peptides that unload the ventricle.[2-4] Prompt and effective revascularization, early inhibition of the overstimulated adrenergic and renin-angiotensin-aldosterone systems, and resynchronization therapy are beneficial, and in some patients may even lead to reverse remodeling.[5] However, there are still patients in whom adverse remodeling progresses despite the use of all currently available conventional strategies.

Although the main mechanisms of myocardial remodeling in myocarditis are similar, they may substantially differ in comparison with the myocardial infarction model. The myocardial injury that initiates the process is usually caused by a viral infection. Cell damage may be global, massive, and quick (leading, in rare cases, to fulminant myocarditis), or patchy, minimal, and clinically silent.[6,7] The induced inflammatory process may be beneficial (pathogen elimination and full recovery in the vast majority of patients), but it may also become deleterious, causing a continued autoimmune response and chronic remodeling, progressing to the phenotype of dilated cardiomyopathy. Importantly, this is the main cause of heart failure in young patients.[2,3] It is estimated that up to 60% of dilated cardiomyopathy cases are due to previous myocarditis.[3]

It is not fully understood why some patients fully recover, while other develop remodeling and heart failure. It is postulated that the progression or healing may depend on the pathogen type, patient's genetic predisposition, and environmental factors.[3,7]

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Endomyocardial biopsy is a gold-standard tool used to confirm myocarditis. It can be useful in assessing the balance between the viral infection and the immune response, and can help in deciding whether or not to implement antiviral or immunosuppressive treatment in high-risk patients. However, due to invasiveness of this approach and a highly variable clinical course of acute myocarditis, routine biopsy is not recommended.[6,7]

The search for noninvasive predictors of reverse remodeling is very important. A number of substances were found to be associated with different stages of remodeling, including markers of 1) cardiac injury and necrosis (troponins, heart-type fatty acid–binding protein, ischemia-modified albumin), 2) inflammation (tumor necrosis factor, interleukin (IL)-1, IL-6, soluble suppression of tumorigenicity-2, growth differentiation factor-15, myeloperoxidase), 3) cardiac fibrosis (galectin-3), 4) collagen turnover (amino-terminal propeptide of type III procollagen, MMPs, TIMPs), or 5) myocardial wall stress (B-type natriuretic peptide, N-terminal pro–B-type natriuretic peptide, copeptin, mid-regional proadrenomedullin, circulating ribonucleic acids, and others).[8] Yet, none of them has been found good enough to precisely predict adverse remodeling.[8] Combining multiple biomarkers with imaging data may be more helpful, and such an approach is currently under investigation.[9]

Progress in imaging, including echocardiography, and particularly cardiac magnetic resonance (CMR), allows for assessing not only the cardiac structure and mechanics but also myocardial extracellular volume and fibrosis, as well as for precisely measuring the remodeling indices in time.[7,10] It is also becoming an important tool for identifying myocarditis among patients with elevated necrosis markers, and those with normal coronary arteries (MINOCA).[8] CMR has shown an early increase in chamber volumes in biopsy-proven acute myocarditis.[11] Some studies reported promising results regarding the long-term prediction of further remodeling, but they were not fully confirmed by others.[11]

The paper by Kozieł-Siołkowska et al[12] published in this issue of *Polish Archives of Internal Medicine* is an example of a study searching for indices predicting reverse LV remodeling in patients with a clinical diagnosis of myocarditis. The authors found that echocardiographically assessed mechanical dispersion (MD) was an independent predictor of LV volume decrease at follow-up; however, no precise cutoff value of this parameter was determined. Regional mechanical delay may be a result of inflammatory infiltration and fibrosis.[13] An additional independent predictor was QRS duration, while many other parameters investigated by the authors did not have any significance. Similarly to other studies, global longitudinal strain (GLS) detected LV dysfunction with higher sensitivity than the commonly used LV ejection fraction.[14] GLS was associated with the study end point; however, it did not reach statictical significance in the multivariate analysis. The study suggests that MD could be a valuable risk marker in acute myocarditis, and this interesting concept needs confirmation in a larger population.

Due to high variability of the acute myocarditis course, treatment strategies are currently not well established, apart from general supportive therapy and neurohormonal inhibition aiming for prevention of heart failure.[6,7] Influencing any of the remodeling mechanisms (eg, inflammatory cytokines or MMPs) may be either helpful or harmful due to the complex pathophysiology of the condition. Research continues to enable early identification of patients at a high risk of remodeling.[15] Identification of the main mechanism and the phase of the process taking place in the myocardium of individual patients may allow for tailored treatment. Such an approach may make it possible to modulate these processes and stop the adverse remodeling, thus preventing heart failure in different clinical scenarios, including myocarditis.[15]

ARTICLE INFORMATION

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