Tachycardia-induced remodeling: atria and ventricles take a different route

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See article by Hanna et al. [7] (pages 236–244) in this issue.

Myocardial remodeling is a common cardiac response to various pathological stimuli and may refer to changes in structure and function (structural remodeling) or electro-physiologic properties (electrical or ionic remodeling) [1–3]. Such disease-induced changes of tissue composition and architecture or function occur in both the atrium and/or the ventricle, and appear to progress steadily in a vicious cycle that, if not halted, eventually causes death of the patient [1]. Structural remodeling itself has a substantial influence on cardiac conduction properties [4]. In particular, the development of conduction inhomogeneities, including areas of slow conduction and conduction block, is associated with the occurrence of re-entrant arrhythmias in the atria and ventricles. Ventricular remodeling in the setting of volume or pressure overload contributes significantly to LV dilatation and dysfunction and, thereby, to the progression of heart failure, and is associated with increased morbidity and mortality [1,5]. Atrial remodeling and its relationship to atrial fibrillation (AF) have gained much interest during recent years since AF is the most common arrhythmia in clinical practice [2–4,6]. The high incidence of AF in the general population and the associated risk of stroke/heart failure make the identification of the underlying molecular and cellular mechanisms important goals towards alternate causal therapeutic concepts.

Recent studies have provided first insights into the molecular mechanisms that are involved in the development of cellular and subcellular structural changes [1–6]. Prominent features of disease-induced myocardial remodeling include fibrosis, hypertrophy, and apoptosis. Some of these alterations are due to the temporary or persistent activation of cellular signal transduction systems. Activation of the local angiotensin II system is paralleled by activation of the MAP kinases Erk1/2 and JNK. In a healthy heart, the majority of the cells are fibroblasts. The fraction of fibroblasts is even further increased under pathological conditions. Myocardial cells are supported by a three-dimensional network of extracellular matrix (ECM) that largely determines the structural and functional integrity of the heart. As changes in the ECM require the activity of matrix-degrading enzymes, a number of recent studies were devoted to the role of matrix metalloproteinases (MMPs) and their endogenous inhibitors, the tissue inhibitors of matrix metalloproteinase (TIMPs). However, as MMP activity and overall collagen content of the tissue do not always correlate with each other, it is rather the collagen quality and orientation that defines the ECM remodeling. Furthermore, the expression of MMPs as well as other molecular changes appear to occur in a regionally and timely well-balanced fashion. Early changes may even oppose those seen in later stages of disease. Therefore, experimental studies performed with different models and at different time points after the induction of disease have yielded partly conflicting results. Accumulating evidence points to the existence of local and temporary differences in the molecular and cellular mechanisms underlying atrial and ventricular remodeling. However, no direct comparative analyses of changes at both the ventricular and atrial tissue level have been performed systematically thus far.

In this context, the report by Hanna et al. [7] in this issue of the Journal is of particular interest. They compared details of tissue remodeling in atria and ventricles using a canine tachypacing-induced congestive heart failure (CHF) model. Of note, the time course of cellular and molecular changes was clearly presented. The authors confirm that the process of tissue remodeling is substantially different in the atria compared to ventricular myocardium. Leukocyte infiltration, cell death, and apoptosis appear to be transient early
phenomena in the atria, whereas these processes occur more gradually in the ventricles, reaching the highest levels after 5 weeks. The induction of MAP kinases and angiotensin II levels show also substantial chamber-specific differences. The expression of JNK parallels the occurrence of leukocyte infiltration and apoptosis. In contrast to ventricular myocardium, ERK1/2 is rapidly induced in the atria, corresponding to atrial angiotensin II levels. Whereas some alterations appear to be temporary and reversible, the developed interstitial fibrosis persists and may even further progress in the absence of the initial trigger. In this regard, it is reported that the atrium is particularly prone to fibrosis, the extent of which exceeds that of the left ventricle by more than 20-fold. Mean P wave duration correlated with mean percentage of atrial fibrosis, clearly confirming the established impact of fibrosis on atrial conduction. Thus, with respect to previously published data showing the interactions between atrial fibrosis and inducibility of atrial fibrillation, Hanna et al. give more molecular insights into the development of an arrhythmogenic atrial remodeling in CHF. This is in full accordance with previous reports showing that structural atrial remodeling begets AF. Such early events include the angiotensin II system and MAP kinase activation and, in the long run, dysregulation of the delicate MMP/TIMP balance, and the pro-fibrotic cytokine TGF-β1 are clearly involved.

An interesting finding of Hanna et al. is the considerably higher resistance of ventricular myocardium to structural remodeling compared to the atria. However, a self-perpetuation process of myocyte degeneration, cell death (autophagy/oncosis), and replacement fibrosis may occur later on in the progression of LV failure [1]. In addition, as a model of rapid right ventricular pacing was used, the described ventricular molecular changes appear to be useful to study alterations during left ventricular dyssynchrony, since a complete left bundle branch block was induced and maintained during 5 weeks of RV pacing. Thus, the results contribute also to our basic knowledge about the molecular biology of left ventricular dyssynchrony, and, therefore, the study by Hanna et al. may have clinical implications for left ventricular resynchronization therapy.

However, the present study, as all pioneer studies do, raises several questions. For example, which pro-apoptotic molecular mechanisms are activated transiently in the atria, and what is the effect of apoptosis and cell death on atrial electrophysiology and function? Are there regional differences in ventricular molecular alterations during rapid dyssynchronous pacing? How do ventricular changes correspond to inducibility of arrhythmias? Nevertheless, the study will stimulate further research, and, therefore, the presented data will have a significant impact on the field. Furthermore, the data underscore the importance of a rapid therapeutic interruption of tachyarrhythmias to prevent the initiation of irreversible tissue remodeling processes, especially in the atria. An anti-inflammatory, anti-apoptotic therapy may only have a potential benefit in the very early phase of atrial remodeling. An “anti-remodeling” therapy currently employs the anti-fibrotic activity of ACE-inhibitors and angiotensin II type 1 receptor antagonists [2,6]. Results from the study of Hanna et al. confirm these pharmacological strategies as reasonable and mechanism-based options to attenuate tissue remodeling in the setting of heart failure.

References