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A Change of Heart: Heterogeneous Remodeling in Heart Failure

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Heart failure is a culmination of a heart's failed attempt at adapting to undue stress, injury or disease. It is a complex constellation of adaptations involving environmental influences; genetic, developmental and neurohumoral factors; inflammatory cell responses; remodeling of extracellular matrix, ion channels and gap junctions; activation of stress receptors and intracellular signaling pathways; and reversion to adaptive but ultimately detrimental transcriptional programs. Over the past two decades, the molecular determinants of structural and electrical remodeling of the failing heart have not only been identified, but targeted in the design of efficacious therapy used in patients with heart failure to ameliorate symptoms, reverse ventricular remodeling and reduce mortality.¹

One recent study even found a modest decline in the incidence of heart failure in elderly persons in recent years; however, the authors noted that the "absolute numbers will continue to increase as the Medicare population grows".² Despite offerings of combined neurohormonal blockade, cardiac resynchronization therapy and implantable cardioverter-defibrillators (ICDs), and despite declining death rates from cardiovascular disease, the mortality from heart failure remains high as an estimated 550,000 newly diagnosed cases are added each year to an already staggering prevalence of 5.3 million people affected in the US alone.³ Thus, research designed to clarify the underlying mechanisms responsible for lethal ventricular arrhythmias and sudden cardiac death in heart failure are indeed crucial for advancing the treatment strategies aimed at preventing, not just treating, arrhythmogenesis and sudden death in this patient population.

Effective therapies for heart failure include neurohormonal blockade,¹ mechanical unloading^{4,5} and cardiac resynchronization.^{6–8} Therapeutic approaches to managing heart failure that are most beneficial in ameliorating symptoms or reducing mortality generally reverse, even if only partially, some aspect of structural remodeling.^{1,4,5,9} For example, ACE inhibitors, β -blockers and angiotensin II receptor antagonists have each been shown to attenuate ventricular remodeling. In contrast, less emphasis has been placed on developing pharmaceuticals that would reverse electrical remodeling. This is not surprising, as drug development for the treatment of ventricular arrhythmias has fallen somewhat into disfavor since demonstration of increased mortality reported in the Cardiac Arrhythmia Suppression Trial¹⁰ and concerns of pro-arrhythmia¹¹ and drug-induced Torsades de Pointes¹² on one hand, and efficacy of ICDs^{7,13} on the other. Nevertheless, there are compelling arguments for pursuing development of antiarrhythmic drugs that would treat electrical remodeling,

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None.

particularly if electrical remodeling might also exacerbate structural remodeling. Devices neither prevent lethal arrhythmias nor cure the diseases that cause them. Clearly, however, before one can design safe, effective and novel drugs to treat arrhythmias in the setting of heart failure, greater understanding of the substrates for and mechanisms of those arrhythmias is a necessity.

Gap junctions comprise the major intercellular coupling protein expressed in ventricular myocardium, connexin43 (Cx43), and are critical determinants of impulse propagation in the heart.¹⁴ Alterations in the structure or function of gap junctions that occur in heart failure^{15–19} may result in conduction abnormalities leading to induction of arrhythmias.^{16,20,21} In this issue of *Heart Rhythm*, Wiegerinck et al.²² report an association between transmural dispersions of refractoriness and of conduction and heterogeneous remodeling of Cx43 in a combined pressure and volume overload model of heart failure in rabbits. They show convincingly that, in the absence of fibrosis or changes in action potential duration, transmural dispersion of refractoriness was increased significantly in failing hearts compared to controls. Refractory periods were increased in both sub-epicardial and midmyocardial regions of the failing hearts, but the dispersion of refractoriness within each respective region was not different in failing hearts compared to controls; that the transmural dispersion of refractoriness was different suggested a mechanism involving differential remodeling within the layers of the free wall in the failing hearts. Interestingly, unipolar electrogram recordings from a 16 × 15 epicardial electrode grid and 32 intramural needle electrodes demonstrated that although average transmural conduction velocity was not different between failing and control hearts, the heterogeneity in transmural conduction velocity was increased significantly in failing hearts. Furthermore, ventricular arrhythmias were induced by programmed electrical stimulation from sub-epicardial and midmyocardial electrodes in failing and control hearts. However, not only were arrhythmias more readily inducible in failing hearts, the severity of arrhythmias was greater when induced from intramural as opposed to sub-epicardial sites.

Finally, total Cx43 protein expression by immunoblot analysis and quantification of immunohistochemistry revealed that heterogeneity of Cx43 expression was significantly greater in the midmyocardium of failing hearts compared to the sub-epicardium of failing hearts or either region of control hearts,²² suggesting that heterogeneous reduction of Cx43 in the midmyocardial layers of the failing heart is a likely source of differential transmural conduction, dispersion of refractoriness and enhanced inducibility and severity of arrhythmia. These results raise several intriguing possibilities. Might the reduction in Cx43 be a potential target for treatments to effect reverse remodeling? As alluded to above, electrical remodeling, in this case heterogeneously reduced intramural Cx43 expression and transmural discontinuities in conduction, could potentially contribute to mechanical dysfunction and further electrical remodeling. Might reverse remodeling of the downregulation in Cx43 produce multiple beneficial effects (antiarrhythmic and antidysynchrony)? It would be worthwhile to test rotigaptide, a hexapeptide that augments gap junctional conductance and has been shown to be effective in suppressing both atrial and ventricular arrhythmias,²³ in this model of heart failure. Such an experiment would provide additional evidence that decreased Cx43 expression actually results in reduced or heterogeneously reduced coupling; the present data can only suggest that the mechanism involves disrupted intercellular coupling.

As with any good study, more questions are raised than answered. What is the cause of the patchy reduction in Cx43? N-cadherin and β -catenin were not similarly remodeled, suggesting that the adhesion junctions were not altered in this model.²² This result might suggest that enhanced degradation rather than defects in trafficking or assembly of Cx43 may have occurred. However, the molecular crosstalk between mechanical and electrical junctions is critical not only for assembly and degradation, but also for function.^{24–25} Remodeling of other interacting proteins, such as zonula occludens-1,²⁶ in the larger macromolecular complex to

which connexins are bound²⁷ is also likely to be an important determinant of altered Cx43 protein expression and function in the failing heart. In addition, an important regulator of both turnover and function of Cx43 is phosphorylation. The magnitude, timing and consequences of changes in the phosphorylation status of potentially 13 or more amino acid residues in the C-terminal tail of Cx43 during progression of heart failure,^{18,19,21} just as during ischemia,²⁸ are complex. Which kinases and signaling pathways are activated during the early development of failure in this model, and how do those pathways interact with parallel or intersecting pathways that are activated with advanced disease or aging?

Finally, as with many experimental studies, inconsistencies between the present results and other published work exist.^{18,20} However, differences in reported results due to differences in species, creation of the models and experimental endpoints should only motivate investigators to examine the findings more closely to determine which observations are most important and consistent, and to ascertain how to apply new experimental data to investigations that will advance our understanding of the mechanisms that function in patients with heart failure. Future studies will be required to determine whether enhancing gap junctional intercellular communication or engrafting Cx43-expressing myocytes²⁹ may ultimately prevent lethal ventricular arrhythmias in patients. Wiegerinck et al.²² have provided evidence that targeting Cx43 remodeling in heart failure is worth continuing efforts to do so.

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