Adverse Cardiac Remodeling
Phosphoinositide 3-Kinase, Another Unique Factor in a Multifactorial Condition

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Left ventricular remodeling has originally been defined as enlargement attributable to “alterations in the topography of both the infarcted and noninfarcted regions of the ventricle.”1 Similar remodeling processes appear to follow other types of stress, like pressure overload (aortic constriction). In contrast, physiological hypertrophy represents the response of the healthy heart to exercise. Three decades of research have added comprehensive information beyond the organ level. Wound healing of the infarcted zone has become its own field of research,2 and the role of inflammatory cells has been stressed recently.3 Remodeling of various myocardial cell types includes myocyte concentric and eccentric hypertrophy, slippage, accumulation of interstitial tissue, and rarefaction of coronary vasculature in the noninfarcted myocardium.4–6 Early observations on molecular changes include a shift of myocardial proteins and enzymes toward an embryonic pattern and a loss of cardiac energy reserve.7 Changes of proteins result in impairment of excitation-contraction coupling and apoptosis.8 More recently, a crucial role of microRNA in regulation of these and many other processes has been suggested.9

Recent investigation has discovered several growth factor effector pathways important for the progression of cardiac hypertrophy and heart failure, including phosphoinositide 3-kinase–Akt, and mammalian target of rapamycin (mTOR). The phosphoinositide 3-kinase–Akt pathway is of central importance regulating cardiomyocyte size, survival, angiogenesis, and inflammation under both physiological and pathological conditions. The current study by Das and coworkers10 in this issue of Circulation investigates the role of serum and glucocorticoid-regulated kinase-1 (SGK1), a phosphoinositide 3-kinase–dependent serine-threonine kinase structurally similar to Akt. Indeed, SGK1 seems to be an attractive target for heart failure research: it is activated in failing hearts, regulates sodium transporters and could thereby be important for the development of arrhythmias, and is regulated by a pathway relevant for heart failure development, the mineralocorticoid system. In their study, Das et al provide evidence for the importance of SGK1 in both cardiac dysfunction and arrhythmias and for mechanisms that work through the cardiac sodium channel. It includes an ischemia and a hypertrophy model, a model of physiological exercise–induced hypertrophy and human tissue samples. A gain of function approach with SGK1 activation levels observed under heart failure conditions led to an exaggerated development of heart failure after transverse aortic constriction, whereas loss of function conferred protection. It is most appreciated that animal phenotyping includes left ventricular pressure volume curves as well as in vivo electrophysiology (ie, a complete physiological and molecular characterization). Experimental methods for the study of remodeling in rodents, which has started with the meticulous in vivo hemodynamics and passive pressure volume curves, have undergone an impressive development toward sophistication.11

Molecular pathways underlying physiological and pathophysiologic, concentric, and eccentric hypertrophy differ and appear to be at least in part redundant.12 Multiple regulator systems have been identified and may not be discussed here individually. Only a few have resulted in therapeutic concepts and clinical testing. Pharmacological interventions in neurohormonal systems like the renin-angiotensin-aldosterone system and the sympathoadrenal system have so far been successful, which control remodeling of the cardiac cellular and extracellular compartments. But the drugs used there are rather dirty and not very specific. Clinical studies failed to prove beneficial effects of endothelin inhibitors13 or cytokine antagonists,14 whereas experimental studies were highly suggestive of an important role of the respective systems in remodeling. Clinical studies adding further inhibitory principles of the renin-angiotensin-aldosterone system were also unsuccessful, at least in heart failure. Completely novel concepts are therefore urgently required for the prevention of remodeling, heart failure, and sudden death. SGK1 inhibition may be such a promising new target.

Cardiac arrhythmias and contractile dysfunction represent common consequences of remodeling and most serious complications in patients with heart failure.15 It is essential to recognize that the clinical situation is a complex process of morphological, mechanical, molecular, and electric remodeling, including the various cell types of the heart, the interstitial tissue, and their interplay. The present study is persuading in supporting one important link between morphological and electric remodeling, but the clinical importance of other modulators of sodium channel expression and other mecha-
nisms, like reentrance circuits attributable to left ventricular scarring or recurrent or persistent ischemia, need to be appreciated.

Last but not least, cardiac remodeling triggers systemic alterations even in the absence of symptoms and overt heart failure. Bone marrow molecular alterations after myocardial infarction have been reported with potential impact on remodeling. Remodeling of the heart results in activation of brain nuclei, which are responsible for fluid and blood pressure regulation. Thus, the systemic disease heart failure starts before clinical manifestation with impact on therapeutic concepts.

Disclosures
None.

References
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