Editorial

Still Stressed Out but Doing Fine
Normalization of Wall Stress Is Superfluous to Maintaining Cardiac Function in Chronic Pressure Overload

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Classically, myocardial hypertrophy is viewed as a long-term adaptive response of cardiac muscle to altered mechanical loading conditions, in which increasing wall thickness serves as the means to restore wall stress to normal, obedient to the law of Laplace. The concept of local biomechanical stress as an instigator for this has been made clear through animal models, studies of cardiac muscle cells stretched in tissue culture, and long-standing clinical wisdom as with obstruction to right versus left ventricular outflow, respectively. Perhaps the most nebulous aspect of load-induced hypertrophy remains the exact identity of the initial mechanoreceptors—mechanical sensor(s) that become activated by a hemodynamic burden — although molecules that physically connect the cytoskeleton to the cell’s extracellular environment are among the prime candidates, including integrins and focal adhesion kinases. Much more is known of the intracellular signaling pathways that lie biochemically and genetically downstream from these initiating events, such as the secretion of preformed growth factors and cytokines, acting in autocrine or paracrine fashion, as well as the upregulation of the production of such proteins locally within the heart. In the context of whole-animal and clinical physiology, systemic effects, including an increase in catecholamines, also come into play. These multiple signals (ligand-dependent and overlaid on those induced by load itself) are transmitted to the cell nucleus via an intricate web of interlinked protein kinases, phospholipid kinases, and protein phosphatases. Beyond just increased mass, the specific long-term transcriptional responses to load entail a myriad of quantitative and qualitative changes in cardiac gene expression that are reminiscent of fetal cardiac myocytes, and are now understood to encompass contractile proteins, ion pumps and channels, secreted proteins, signaling proteins, enzymes involved in cardiac energetics, components of the extracellular matrix, and even regulators of cell survival. The list of such changes in cardiac hypertrophy is now growing rapidly as the fruit of high-throughput gene chip technology and other methods of expression profiling.

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With greater insight into the particulars of the hypertrophic phenotype has come the recognition that changes once viewed simplistically as homeostatic (linked by their shared teleological value) demand a more nuanced interpretation in which beneficial and adverse responses are comingled. Ventricular hypertrophy is demonstrably a risk factor for cardiovascular mortality in humans, which has spurred efforts to antagonize ligands, receptors, cytoplasmic transducers, and even nuclear mediators that act in the hypertrophic cascade. However, the nominally adaptive value of hypertrophy in response to load has remained a point of controversy in understanding progression to heart failure, and with the advent of left ventricular assist devices and other recent therapies for reverse remodeling, has become even more important than in the past.

In the present issue of Circulation, Esposito et al add striking and important new evidence on this matter: Using genetically engineered mice that have markedly blunted growth responses to pressure overload, they demonstrate that cardiac function was well maintained after loading (using a partial aortic constriction), despite the failure to correct wall stress. Indeed, function was even better maintained than in wild-type mice where hypertrophy ensued. Hence, this investigation casts doubt on the assumption that load-induced hypertrophy has adaptive value.

Two specific, intriguing genetic models were used to explore this view. Angiotensin II and endothelin are, clinically, among the most convincingly important hypertrophic agonists, with direct effects on cardiac muscle in addition to their systemic ones. Their receptors signal obligatorily through the GTP-binding protein Gaq, as also do the receptors for α1-adrenergic agonists. Expressing a carboxy-terminal fragment of this protein in the hearts of transgenic mice interferes with the endogenous protein’s function (as a dominant-inhibitory peptide, to use the jargon of the trade) and blocks hypertrophy induced by load. As a second and independent test of the hypothesis, the authors used mice in which both alleles for dopamine β-hydroxylase have been disrupted: such mice lack the ability to make norepinephrine or epinephrine and likewise have attenuated growth responses to load. The authors’ experimental strategy was technically daunting, including pressure-volume and stress-strain analysis in mice.

Measured in this fashion one week after banding, end-systolic wall stress was found to be corrected to control levels in wild-type mice but not in mice expressing the Gaq inhibitor, where wall stress was roughly 2-fold greater. Nonetheless,
wild-type mice ultimately fared worse in response to long-term load, as shown by progressive LV dilatation and dysfunction on serial echocardiography. In short, cardiac function was preserved by the genetic alteration, despite high wall stress, whereas wild-type mice deteriorated progressively, despite the early correction of wall stress by means of hypertrophic growth. Hence, from these paired observations, the article’s “take-home” message is that normalizing wall stress is dispensable to preserve cardiac function in the face of a long-term hemodynamic burden. Similarly, wild-type mice fared worse than those lacking dopamine β-hydroxylase, with the caveat that wall stress was not measured in this latter case.

Apart from their suggestive pathophysiological importance, the long-term findings reported in this manuscript also add credibly to the evolving notion of Gαq as a therapeutic target in heart failure. Whether Gαq itself is more workable or advantageous a target than its effectors is not yet clear, of course, and such answers often come empirically, rather than from conceptual principles. The 2 mouse models studied by Esposito et al have biochemical effects that invite speculation, but also counter-speculation. A prominent effect of both genetic interventions is a block to load-induced activation of phosphoinositide 3-kinase (PI3-K), a family of lipid kinases that catalyze phosphorylation at the 3-position of the inositol ring of phosphoinositides. Downstream signaling targets that are activated directly or indirectly by PI3-K lipid products are numerous and ramified: Akt (protein kinase B), protein kinase Ce, phospholipase Cγ, the GTP-binding protein Rac, and p70 S6 kinase among them. Notably, PI3-K and several of these targets are known to cause cardiac hypertrophy at least in mice.8–10 Because a lack of PI3-K activation after aortic banding in the genetically altered mice was associated with preserved ventricular function in the present study, the authors suggest as a logical and conservatively stated inference: that inhibition of PI3-K might prove beneficial in preventing the transition from cardiac hypertrophy to heart failure.5

However, hypertrophy spans the good, the bad, and the global. Notwithstanding hypertrophy as a clinical risk factor, certain specific changes might be likelier than mass per se to predicate the transition from a compensated state to a decompensated one. A priori alterations that impair myocyte contractile function seem more germane, defective β-adrenergic signaling and calcium homeostasis among them, especially where molecular correction of the defect already has proven utility.11,12 Other responses, including signals for cell survival itself, may be essential after increased wall stress.13

In further support of this concept, several genetic models now exist of hypertrophy that is well tolerated or even beneficial. The mitogen-activated protein kinase (MAPK) superfamily culminates in 3 subfamilies of terminal effector kinases: extracellular signal–regulated protein kinase (ERK), c-jun N-terminal kinase (JNK), and p38 MAPKs. Specific activation of ERK by a kinase that lies upstream caused concentric hypertrophy without decompensation accompanied by marked resistance to apoptotic cell death.14 A very similar phenotype can be elicited in myocardium by a very different mechanism, namely preventing the normal down-regulation of telomerase reverse transcriptase after birth15; this RNA-dependent DNA polymerase has an important role not only in senescence but also in DNA repair. By contrast, a catastrophic cardiomyopathy is evoked by selective activators of either p38 or JNK,14,16,17 thus inhibiting these kinases more so than ERK as targets for drug development in heart failure. Mass, in fact, increases far less in these models than where ERK activation predominates. Likewise, the PI3-K/Akt pathway can promote cardiac myocyte growth that is perhaps more physiological and is associated with cardioprotection in cell culture18 and in mice.8,19

For this reason, although the authors’ argument that PI3-K contributes to β-adrenergic receptor desensitization20 and that improvements might result is conceptually sound, on such grounds, from its inhibition, one must append a cautionary note that PI3-K has multiple other effects in the heart, some of which, at least experimentally, may oppose the transition to heart failure. From the same perspective, the fact that normalization of wall stress is superfluous in the present study may be contingent on the absence of specific adverse responses to load, which have been disrupted concomitantly. Answering the question of who is “good” and who is “bad” in heart failure has never seemed so timely as in the present era of new molecular phenotypes and the emerging potential for more rational therapies.

References

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