Cardiac hypertrophy is the common myocardial response to chronic hemodynamic overload. It currently affects nearly 5 million Americans and is responsible for ≈50,000 deaths annually.

Why Is a Big Heart a Bad Thing?
From the perspective of cardiac mechanics, it seems surprising that cardiac hypertrophy is a killer. The physics of reactive hypertrophy date to the 19th century and predict that hypertrophy will compensate for increased hemodynamic loading through normalization of ventricular wall stress, the phylogenetically conserved set point for cardiac load.

The Laplace relationship (stress = \(\frac{1}{2}prh\)), describes wall stress increasing in direct proportion with intraluminal pressure (p) and chamber radius (r), but decreasing as wall thickness (h) grows. Accordingly, whether the ventricle dilates or is subjected to increased pressure, hypertrophic thickening of its walls should compensate. And it does. However, long-term functional compensation relies on the quality of hypertrophied myocardium being invariant as quantity increases, which is not the case. Multiple studies have defined molecular, cellular, and functional characteristics of reactive hypertrophy that differentiate it from normal myocardium and from cardiac enlargement caused by physiological conditioning.

Such findings gave rise to the notion of pathological and physiological hypertrophies and provide a mechanistic framework for why reactive hypertrophy ultimately fails, whereas physiological conditioning of the heart does not.

Cardiac hypertrophy also has effects unrelated to contractility and ventricular ejection performance. To quote Joseph Stalin out of context, “Quantity has a quality all its own”, meaning that a steady quantitative change can create a sudden qualitative shift. The heart aptly demonstrates this principle because reactive hypertrophy and wall thickening increase ventricular stiffness, which leads to diastolic dysfunction and heart failure with preserved ejection fraction.

Moreover, a number of studies have suggested that cardiac hypertrophy is not essential to functional compensation after pressure overload. When genetic techniques were employed to inhibit critical hypertrophy signaling pathways after pressure overload of mice, the absence of reactive hypertrophy was not associated with functional deterioration.

Although the long-term efficacy of hypertrophy inhibition and its chronic consequences on ventricular function have not been completely defined, these results demonstrate that it is possible to suppress reactive hypertrophy without catastrophic functional decompensation. Thus, cardiac hypertrophy appears to be both undesirable and dispensable.

Containing the Enemy
If the stimulus for hypertrophy cannot be eliminated, what approach for controlling hypertrophy will best translate to the clinic? Hypertrophy signaling might be inhibited, and myocardial angiotensin II, α-adrenergic, and endothelin pathways that stimulate Gq signaling have been identified as attractive targets. Indeed, clinical hypertrophy regression has been achieved by targeting angiotensin signaling, but it is likely that regression is caused by not only attenuation of hypertrophy signaling, but by decreased ventricular loading as well. In theory, it may also be undesirable to inhibit one hypertrophy-stimulating agonist pathway while leaving intact other receptor systems that can activate the same downstream signaling events.

A complementary approach would be to mimic or enhance the activity of endogenous hypertrophy inhibitors. In this issue of Circulation Research, Jeong et al searched for such inhibitors using PCR-based subtractive RNA profiling of differentially regulated genes in aortic banded rats, thus identifying protein kinase C (PKC)-interacting cousin of thioredoxin, or PICOT. Confirmatory Northern analyses showed that PICOT RNA was increased in vitro by treatment of cultured neonatal rat cardiomyocytes with hypertrophic agonists and in vivo in cardiac myocytes of transverse aortic banded rats, demonstrating that it is a cardiomyocyte-specific hypertrophy-inducible factor. Adenoviral overexpression of PICOT in neonatal rat cardiomyocytes attenuated phenylephrine- and endothelin-stimulated cell enlargement, sarcomeric organization, atrial natriuretic factor expression, and protein incorporation. Antihypertrophic properties were also observed with in vivo transgenic overexpression of PICOT, which inhibited by 50% pressure overload hypertrophy measured 2 weeks after transverse aortic banding. Importantly, PICOT overexpression was also associated with improved left ventricular contractile performance in unbanded mice, suggesting that it may have dual benefits.

Are the antihypertrophic and positive inotropic effects of PICOT a consequence of its interaction with, and inhibition of, PKC? Earlier studies have demonstrated hypertrophic effects of PKCe and PKCd and negatively inotropic effects of PKCa. Therefore, inhibition of these cardiac PKCs by PICOT might diminish hypertrophy and enhance contractility. However, caution is warranted before concluding that this is the only operant mechanism. Jeong et al show that total PKC activity in endothelin-1 and phenylephrine-stimulated neona-
tal rat cardiac myocytes is diminished by adenoviral overexpression of PICOT, as is phosphorylation of PKCβ, PKCε, and PKCζ. It is important to note that the data do not show that PICOT interacts with these PKC isoforms in cardiac myocytes, and that the original description of PICOT as a PKCβ-interacting protein found no interaction with PKCζ in Jurkat cells. Thus, PICOT exhibits interactive specificity for PKC isoforms, and the details of its physical association with, and inhibition of, different PKCs in the heart await further investigation.

As with all newly described hypertrophy modulating factors, questions arise. First, is there a relationship between positive inotropy and hypertrophy inhibition by PICOT? Improved performance tends to move the heart to the left in the pressure-volume plane. Under consistent loading conditions a smaller heart would be expected to have less wall stress and thus less stimulus to hypertrophy. Second, can the inotropic and antihypertrophic effects of PICOT be dissociated? A number of biochemical sequelae of PICOT expression in cardiomyocytes that may relate to one or the other response were observed: inhibition of PKC, inhibition of mitogen-activated protein kinases, increased calcium sensitivity of the contractile apparatus, and enhanced sarcoplasmic reticulum calcium reuptake. Because there is considerable cross-talk between hypertrophy-signaling pathways it is possible that each of these effects is caused by PKC inhibition.

As presented, the data do not establish a causal relation between these events and either in vivo hypertrophy inhibition or positive inotropism because the mechanistic studies were performed in adenoviral-transfected adult rat cardiac myocytes rather than myocytes obtained from PICOT transgenic mice. Levels of PICOT expression differed substantially between the 2 systems, as did time of expression. To more clearly relate the cellular and in vivo effects of PICOT will require isolated cardiomyocyte and signaling studies from the transgenic mouse. Even then, functional promiscuity seen with overexpressed signaling factors may confound the results.

PICOT joins an expanding list of endogenous factors that inhibit specific hypertrophy signaling pathways in the heart, some of which are shown in the Figure. Sadoshima has classified endogenous negative regulators of hypertrophy as either constitutively expressed or inducible. Constitutive inhibitors include glycogen synthase kinase 3β, peroxisome proliferator-activated receptors, and class II histone deacetylases. Hypertrophy-inducible negative regulators, of which PICOT appears to be one, include atrial and brain natriuretic peptides, the calcium binding S100β protein, and myocardium-enriched calcineurin-interacting protein (MCIP1). Interestingly, recent studies using gene ablation have indicated that MCIP1 effects can vary with physiological context. Likewise, PICOT gene ablation will ultimately be required to determine whether its absence will affect baseline cardiac mass.

The study by Jeong and colleagues represents a significant step in delineating endogenous inhibitors of critical hypertrophy signaling pathways and emphasizes the potential of pursuing strategies to augment or mimic their effects. Will PICOT have therapeutic utility in hypertrophy and/or heart failure? At present, it is impossible to tell. Certainly, other candidate inhibitors have been difficult to modulate in a manner that is readily translatable to the clinic. However, the existence of a hypertrophy-inducible, PKC-inhibiting negative regulator of hypertrophy lends support for targeting PKCs. Toward this end, small molecule inhibitors of PKCs show promise as inotropic agents that can ameliorate heart failure in experimental models. In the future, with so many hypertrophy-inhibiting factors from which therapeutics could potentially be developed, we may be containing hypertrophy with a “pick it” fence.

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References


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