Cardiac hypertrophy is the common myocardial response to chronic hemodynamic overload. It currently affects nearly 5 million Americans and is responsible for \( \approx 50,000 \) 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.\(^2\) The Laplace relationship (stress = \( \frac{1}{2} \) pr / h), 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.\(^3\) 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 physiological hypertrophies and provide a mechanistic framework for why reactive hypertrophy ultimately fails.\(^8\) Wherephysiological 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.\(^9\)

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.\(^10\)–\(^12\) 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, \( \alpha \)-adrenergic, and endothelin pathways that stimulate \( G_q \) signaling have been identified as attractive targets.\(^13\),\(^14\) Indeed, clinical hypertrophy regression has been achieved by targeting angiotensin signaling,\(^15\) 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\(^16\) 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, sarcormeric organization, atrial natriuretic factor expression, and protein incorporation. Antihypertrophic properties were also observed 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 unbande 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 PKC\( \delta \) and negatively inotropic effects of PKCa.\(^14\),\(^17\),\(^18\) 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-

**The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.**

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*Circulation Research* is available at http://circres.ahajournals.org

DOI: 10.1161/01.RES.0000236795.57759.45
Endogenous Hypertrophy Inhibitors

Dorn

Endogenous inhibitors of major hypertrophy signaling pathways. To the left is the insulin-like growth factor (IGF) pathway, a tyrosine kinase receptor that stimulates hypertrophy via activation of phosphatidylinositol-3 kinase (PI3K). Downstream in this pathway is the constitutively expressed hypertrophy inhibitor glycogen synthase kinase (GSK-3β), which phosphorylates and inhibits DNA binding of GATA4 and NFAT transcription factors. Phosphorylation of GSK-3β by Akt/PKB releases these transcription factors from tonic inhibition. To the right is the neurohormonal signaling pathway mediated by receptors for angiotensin II (Ang II), the α1-adrenergic agonist phenylephrine (PE), and endothelin-1 (ET), which increase intracellular calcium (Ca++) via activation of Gq and phospholipase C (not shown). Calcium can activate calcineurin (CN), PKC, and calmodulin kinase (CaMK).

PKC activation of transcription factor AP1 is inhibited by hypertrophy-induced PICOT. PKC also activates PKD which, along with CaMK, phosphorylates and inactivates the constitutive hypertrophy inhibitors, class II histone deacetylases (HDAC), thus releasing transcription factor MEF-2 from tonic inhibition.

Datasources of Funding
Supported by NHLBI HL59888, HL58010, HL77101, and HL69779.

Disclosures
None.

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Key Words: Protein kinase C ■ hypertrophy regression ■ transgenic mouse
Containing Hypertrophy With a PICOT Fence
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Circ Res. 2006;99:228-230
doi: 10.1161/01.RES.0000236795.57759.45
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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