Cardiac hypertrophy is defined as an abnormal increase in heart muscle mass and is functionally, mechanistically, and histologically distinguished from normal embryonic and postnatal myocardial growth by characteristic changes in cardiac myocyte shape and volume. Reactive hypertrophy, that is, hypertrophy that occurs in response to an extrinsic increase in cardiac work, is distinguished from genetic familial hypertrophic cardiomyopathy mutations in which the stimulus for hypertrophy is intrinsic to the cardiomyocyte. In the prototypical reactive hypertrophic response to pressure overload, decreased wall stress (estimated as the ratio of ventricular radius to wall thickness; Figure 1) resulting from “compensatory” cardiac hypertrophy provides mechanical advantages that help normalize ejection performance in the face of increased workload as originally described by Grossman et al (Figure 1). These mechanical benefits accrue whether the stimulus for hypertrophy is intermittent, as with exercise training that produces “physiological hypertrophy,” or sustained, as with hypertension or aortic stenosis that produce “pathological hypertrophy.” With sustained hemodynamic overload, however, progressive systolic dysfunction ultimately occurs that leads to heart failure (Figure 1). The realization that prolonged, continuous hemodynamic stress will ultimately lead to hypertrophy decompensation, together with accumulating information that the hypertrophied myocardium is transcriptionally and biochemically distinct from normal myocardium, lead Katz to derive the concept of a “cardiomyopathy of pressure overload,” which is a specific contextual application of the notion of pathological hypertrophy.

Whether it is compensatory or decompensated, hypertrophy is associated with alterations in cardiac geometry (size and shape) collectively referred to as “ventricular remodeling.” Importantly, although they are related to each other, cardiac architecture (remodeled or not), function (failing or not), and mass (hypertrophied or not) are independent variables. For example, a concentrically hypertrophied (thick walled) pressure-overloaded ventricle can have normal or enlarged diastolic dimension with either normal or diminished ejection performance. Likewise, whereas eccentrically hypertrophied (normal wall thickness) volume-overloaded hearts are enlarged at end diastole and more spherical in shape, they can exhibit normal, supernormal, or diminished ejection performance.

The standard approaches to categorize hypertrophy have tended to overlap with designations of cardiac architecture and function. For example, hypertrophy can be classified on the basis of chamber morphometrics as concentric or eccentric, on the basis of functional outcome as adaptive or maladaptive, and on the basis of whether it progresses to an outright disease state as physiological or pathological. Although each of these classification schemes has strengths and weaknesses, the label of “physiological” versus “pathological” generates confusion in part because the simplicity of the labels belies the complexity of the conditions. Certainly, it is an appealing notion that physiological hypertrophy should be distinguished from pathological forms strictly on the basis of it being a favorable adaptation. However, a useful operative definition of “physiological hypertrophy” has been difficult to achieve. As with Justice Potter Stewart’s explanation of obscenity for the 1964 United States Supreme Court (“I know it when I see it”), in a world of black and white, physiological hypertrophy can simply be considered as cardiac hypertrophy that is not pathological, that is, that does not cause or contribute to disease. This probabilistic approach relies on a binary or “crisp” presupposition that nonfailing hypertrophy and decompensated hypertrophy are precise and distinct, such that progression from one to the other can be determined with certainty. However, the distinctions are blurred in reality, where heart failure rarely exists without cardiac enlargement at the organ and cellular level and where a hypertrophied, pressure-overloaded heart with normal ejection performance characteristically exhibits abnormal contractile function measured at the cellular or myofibrillar level. Furthermore, it has been noted that the hypertrophy of cardiac conditioning may actually reverse heart failure.

Thus, intermediate condition(s) between the ideals of normal and pathologically hypertrophied hearts are predominant and may best be characterized within a range of more or less physiological in nature (Figure 2). Here, an overview is presented to help the interested academic and clinician better understand the factors that contribute to hypertrophy being “more or less” physiological in nature, to recognize the adaptive and potentially maladaptive features of “physiological” hypertrophies, and to better appreciate the possibilities of harnessing various aspects of physiological hypertrophy as therapeutic modalities in heart failure.

Fuzzy-o-Logical Hypertrophy?

Is there any condition where hypertrophy is truly physiological? Based on the simple criterion that physiological hyper-
troph is cardiac and/or cardiac myocyte enlargement that neither causes nor contributes to heart failure, the answer is "yes." The most striking example of physiological hypertrophy in nature may be the recently described postprandial cardiac hypertrophy in Burmese pythons.\(^\text{12}\) These snakes are a dramatic model of physiological extremes in that they are cold blooded and normally inactive in the fasting state but increase their metabolic rate 40-fold while digesting a large meal. Oxygen consumption (metabolic work) in pythons increased 7-fold when measured 48 hours after ingesting a meal equal to 25% of their body mass, which was accompanied by a 40% increase in ventricular mass and an increase in stroke volume half-again greater than that achieved by fasting animals at peak exercise (ie, in maximally stressed nonhypertrophied hearts).\(^\text{13}\) Cardiac muscle-specific mRNA was increased in postprandial snake hearts, and the ratio of DNA to protein decreased, reflecting increased protein content per myocyte. Most remarkably, ventricular mass returned to normal 28 days after the meal. Thus, postprandial cardiac hypertrophy in pythons exhibits all of the prerequisites of a physiological hypertrophy: it is a functionally adaptive response to increased cardiac load characterized by an abnormal increase in organ and cardiomyocyte protein mass and enhanced cardiac gene expression that is completely reversible and without pathological sequelae. If one accepts this as a reasonable definition of physiological hypertrophy, the next question is, "Does it occur in humans?"

In fact, postprandial cardiac hypertrophy is not known to occur in humans, although occasional reports of postprandial angina pectoris reveal a qualitatively similar, if smaller, increase in cardiac workload during human digestion.\(^\text{14,15}\) Digestion in mammals does not increase the metabolic rate for as long or proportionally as much as it does in reptiles, and it takes weeks rather than days of sustained hemodynamic overload to develop a full, stable cardiac hypertrophic response in mammals. However, there is an analogous condition in humans in which a prolonged but reversible increase in cardiac workload produces reversible cardiac hypertrophy: pregnancy.

During the second and third trimesters of pregnancy, cardiac output increases to match placental blood flow, resulting in a condition of sustained volume overload. The heart responds by undergoing modest eccentric cardiac hypertrophy.\(^\text{16–18}\) Each of these changes is fully reversible after delivery, when cardiac load returns to normal. Furthermore, the hallmark pattern of increased fetal gene expression that is prototypical for human and experimental pressure or volume overload (ie, pathological) hypertrophy was not observed in a recent study of pregnancy-induced hypertrophy in mouse hearts.\(^\text{19}\) Thus, hypertrophy of pregnancy also fulfills the neces-
sary criteria for a physiological hypertrophy, although the hormonal changes of pregnancy and possible consequences on cardiac gene expression complicate this classification, and may make it “less-than-completely physiological.” Indeed, for unknown reasons, a very small percentage of patients develop dilated cardiomyopathy after pregnancy, a condition designated “peripartum cardiomyopathy.” Some genetically manipulated mice recapitulate this association of pregnancy and heart failure, which mechanistically has been attributed to peripartal cardiomyocyte apoptosis. However, the cellular and molecular events that cause human peripartum cardiomyopathy remain unknown at this time.

The Athlete’s Heart and Cardiac Remodeling

The traditional view of exercised-induced cardiac adaptations is that they are favorable, or at least benign, and include increased cardiac mass (hypertrophy), enhanced aerobic capacity, and diastolic cardiac enlargement (remodeling), resulting in increased ventricular stroke volume and cardiac output. However, these are largely the consequences of endurance exercise training, such as long distance running or swimming, and are associated with eccentric remodeling of the heart. Physical conditioning that emphasizes strength training, such as weight lifting and wrestling, only modestly increases cardiac output but causes concentric cardiac hypertrophy without chamber dilation and an increase in peripheral vascular resistance. The different patterns of hypertrophy and their associated changes in ventricular architecture reflect differences in the ratio of ventricular internal dimension to wall thickness and recapitulate the geometric changes seen with different stimuli for pathological hypertrophy. For example, during the early, functionally compensated stage of pure chronic volume overload because of mitral valvular regurgitation, the heart undergoes eccentric hypertrophy where left ventricular chamber dimension and wall thickness increase proportionally. This form of hypertrophy is typically “adaptive” for long periods of time before undergoing functional decompensation and progression to dilated cardiomyopathy. In contrast, chronic pressure overload, as in aortic stenosis or systemic hypertension, results in concentric hypertrophy with a small, thick-walled left ventricle. This form of hypertrophy is more maladaptive, undergoing predictable and comparatively rapid functional decompensation.

For the physiological stimulus of exercise, endurance training diminishes vascular resistance, producing increased cardiac flow at normal pressures (volume overload) and a form of eccentric hypertrophy that is considered to be generally favorable. On the other hand, strength training increases vascular resistance, producing an intermittent pressure-overload state and concentric hypertrophy that may not have the same benefits as endurance training. Indeed, recent experimental studies have shown that it is the nature of the stimulus (physiological exercise versus pathological pressure overload), not whether it is intermittent or sustained, that determines the outcome of hypertrophic remodeling (see below). The paradigm that stimulus is the primary determinant of response may also apply to subtypes of exercise-induced hypertrophy. Not only do endurance and strength training produce different cardiac morphologies and metabolic activities, but there is accumulating evidence that prolonged exercise conditioning, at least with those activities that include a strength component (ie, cycling and rowing, which combine strength and endurance), can mimic pathological hypertrophy and potentially lead to myocardial disease or sudden cardiac death. Accordingly, there are reports that ventricular dilation does not completely reverse even after 5 years in a substantial number (≈20%) of deconditioned athletes, suggesting that permanent myocardial damage can occur as a consequence of prolonged conditioning. This has particular relevance to professional athletes and has propelled efforts to use available clinical diagnostics to differentiate between benign or favorable cardiovascular changes associated with athletic conditioning and potentially pathological conditions that can lead to death or disability. These findings and the diagnostic and therapeutic dilemmas they pose have been reviewed recently.

Molecular Studies of Exercise-Induced Cardiac Hypertrophy

Recently, there has been an explosion of data exploring the biochemical and molecular differences between physiological and pathological hypertrophy based on comparisons between some form of exercise as a physiological stimulus and some form of pressure overload as a pathological stimulus. The likely biochemical signaling pathways that transduce physiological and pathological hypertrophies are reviewed in detail below, but it is important to note here that neurohormonal signaling pathways mediated through 7 transmembrane spanning receptors, especially those coupled to the Gq heterotrimeric G protein, are largely associated with pathological hypertrophy, whereas peptide growth factors, such as insulin-like growth factor (IGF) and epidermal growth factor, coupled to the phosphatidylinositol 3-kinase (PI3K)/Akt pathway are more associated with physiological hypertrophy.

Specific alterations in cardiac gene expression observed in pathological hypertrophy are sufficiently characteristic so that they have become important criteria for its detection and diagnosis. Our laboratory performed one of the first attempts to delineate the molecular signatures of physiological and pathological forms of cardiac hypertrophy using early murine microarrays and 5 different mouse genetic hypertrophy models. In these experiments, more physiological hypertrophy was represented by a mouse in which protein kinase C ε was specifically activated through transgenic translocation facilitation. Pathological hypertrophy was represented by a mouse overexpressing the α subunit of Gq, and pathological hypertrophy in transition to heart failure was represented by a mouse overexpressing calcineurin. Although the study was limited by lack of comprehensive representation of the mouse genome on the Incyte microarrays and by use of specific genetic perturbations rather than physiological stress to create a spectrum of hypertrophy, the results are noteworthy in that they revealed nonoverlap of gene expression between the physiological and pathological hypertrophy phenotypes and described an apoptosis gene expression program in pathological hypertrophy. Both of these findings have subsequently been validated and support not only the existence of different transcriptional programs for various forms of hypertrophy, but also relevance of gene expression as a determinant of disease outcome.
Recent microarray studies of murine pressure-overload hypertrophy have revealed increased expression of extracellular matrix genes and downregulation of metabolic genes, especially those involved in fatty acid metabolism. Because each of these pathways may contribute to deterioration of hypertrophy to heart failure and would, therefore, not be expected to occur in true physiological hypertrophy, it was useful to perform direct comparisons of the molecular phenotypes for physiological and pathological hypertrophy, thus defining their individual genetic “fingerprints” and delineating any of the hypothetically distinct pathophysiological mechanisms. These types of studies have recently become more practical with the availability and affordability of comprehensive gene microarrays for mice, rats, and humans. However, proper interpretation of these data, especially when comparing different studies, does require careful attention to the specifics of physiological stimuli (voluntary or forced running or forced swimming) and pathological stimuli (typically genetic hypertension, surgical aortic coarctation, or myocardial infarction) used.

One of the first studies to directly compare cardiac gene expression in physiological (swimming rats) and pathological (spontaneous hypertensive rats) hypertrophy described several genes that were upregulated in pathological hypertrophy, but not with exercise, despite similar increases in left ventricular mass. These genes include brain natriuretic peptide, angiotensin-converting enzyme, the endothelin receptor, and the β-adrenergic receptor kinase. These pathological genes belong to a group of signaling effectors or regulators for neurohormonal pathways that have been implicated in pathological hypertrophy by translating the mechanical stress stimulus into a hormonal signaling event. Interestingly, β-adrenergic receptor mRNA was similarly increased in both physiological and pathological hypertrophy, suggesting that there can be molecular overlap between hypertrophies stimulated by exercise and hypertension. Whether these regulated genes represent events that contribute to the hypertrophic response or that are a consequence of hypertrophy, the different expression patterns helped to establish that pathological and physiological hypertrophy could have individual molecular fingerprints.

Recent studies have used microarrays to perform more extensive, unbiased comparisons of regulated genes in physiological and pathological hypertrophy. Kong et al used Affymetrix Rat Genome U34A microarrays to compare transcript profiles in control rats (sedentary Dahl salt-sensitive rats on low-salt diet), physiologically hypertrophied rats (daily exercise), and compensated pathological hypertrophy (Dahl salt-sensitive rats on high-salt diet). Prolonged high-salt diet resulted in progression to heart failure, providing a fourth group (decompensated pathological hypertrophy) for analysis. Of ~3000 known genes represented on the microarrays, 404 were regulated in 1 of the hypertrophies: 91 were regulated in physiological hypertrophy, 159 were regulated in both physiological and pathological hypertrophy, and 154 were regulated in pathological hypertrophy. Genes largely regulated in physiological hypertrophy were represented by functional clusters for metabolism and cellular growth, including members of the IGF/epidermal growth factor signaling pathway. In contrast, genes identified with pathological hypertrophy were largely from inflammation and stress-response clusters. Genes regulated in both conditions tended to be those identified previously with hypertrophy response and likely represented common or nonspecific factors involved in cardiomyocyte cell growth (Figure 3). Of particular interest, the gene expression profile in decompensated hypertrophy/heart failure was an exaggeration of that seen in compensated pathological hypertrophy and included apoptosis factors. This excellent study provides additional support to the hypothesis that physiological hypertrophy is transduced by IGF signaling pathways, whereas pathological hypertrophy shares a molecular phenotype with heart failure.

The above findings were confirmed and extended in a study of gene expression in cardiac hypertrophy stimulated by treadmill conditioning in rats. Again using Affymetrix Rat Genome U34A microarrays, 267 genes were upregulated and 62 downregulated with exercise. Consistent with the notion that physiological hypertrophy is distinct from pathological hypertrophy, upregulation of hypertrophy-associated fetal cardiac genes, atrial natriuretic factor, brain natriuretic peptide, α-skeletal actin, and β-mysin heavy chain was not observed in treadmill-conditioned rat hearts. Increased collagen gene expression was also not observed, which, along with myocardial fibrosis, is classically associated with the development of pathological hypertrophy. However, as seen in the study by Kong et al, some genes upregulated in pathological hypertrophy were also upregulated in exercised rats, including genes for extracellular matrix and cytoskeletal proteins, ribosomal proteins, and some signaling proteins, that is, genes that are generally required for cardiomyocyte protein synthesis and structural growth. Notably, the gene for G-protein receptor kinase 2, which functionally uncouples β-adrenergic receptors from downstream signaling effectors and is increased in pathological hypertrophy, was downregulated with exercise, suggesting a possible mechanism for exercise benefits in myocardial disease.

An important result of these studies is the insight that they have provided into distinct metabolic changes that occur with physiological and pathological hypertrophy. It has been appreciated for some time that a variety of metabolically or energetically unfavorable events occur in pathological hypertrophy, including contractile protein isoform shifts, a de-
crease in the ratio of mitochondria to the number of cardio-
myocytes,44,45 and a shift away from normal fatty acid use to
glucose as the primary myocardial energy substrate.46–49 In
contrast, physiological hypertrophy typically is not associated
with changes in contractile protein isoforms (see above), and
mitochondrial biogenesis is actually induced in athlete’s
hearts.50,51 The consequences of physiological conditioning
on myocardial metabolism had not been explored in detail,
but Strom et al40 found recently that a number of genes
involved in fatty acid oxidation were upregulated in physio-
logical hypertrophy, whereas they have been reported to be
downregulated in pathological hypertrophy.52,53 Specific an-
tithetically regulated metabolic genes of interest include the
uncoupling protein UCP2, which induces mitochondrial heat
generation by mitochondrial respiration instead of ATP pro-
duction.54 This gene is upregulated in pathological hypertro-
phy55 but was downregulated by chronic treadmill condition-
ing, possibly determining more efficient energy production in
physiological hypertrophy56 but was downregulated by chronic treadmill condition-
ing, possibly determining more efficient energy production in
physiological hypertrophy.56 Interestingly, expression of UCP2 is
normalized by 2 pharmacological treatments for heart
failure,38,60 β-adrenergic receptor blockade and angiotensin-
converting enzyme inhibition.55,56 Another gene of interest is
FAT, or fatty acid translocase, which was upregulated in
exercise-conditioned hearts but not affected by pathological
hypertrophy.40 Insufficiency of this gene, also known as
CD36, has been implicated in defective fatty acid metabolism
seen with hypertensive and postischemic myocardial dis-
ease.57,58 Taken together, these results suggest that different
physiological or pathological hypertrophic stimuli may cause
distinct forms of hypertrophy that are either beneficial or
harmful, based in part on transcriptionally determined alter-
ations in basic metabolic parameters and other factors (see
Figure 3). An emerging picture of specific transcriptional
mechanisms that can modulate myocardial metabolic genes in
pathological cardiac hypertrophy and heart failure has been
reviewed recently in detail.59

**Signaling Pathways in Physiological Hypertrophy**

In understanding physiological hypertrophy and how it might
be harnessed as a therapeutic application, it is important to
define those targetable biochemical events that determine
whether hypertrophy is beneficial or detrimental. Studies of
various candidate signaling factors and pathways have generally
used pharmacological inhibition or genetic gain and/or
loss of function. Because the genetic approach can be targeted
to the heart and may be more specific than pharmacological
inhibition, this has become the preferred approach.

As noted above, pathological hypertrophy is caused by any
of a number of partially redundant neurohumoral path-
ways that produce activation of parallel hypertrophy signaling
effectors.5,38,60 In brief, multiple agonist–receptor pairs,
such as those for angiotensin II, endothelin, catecholamines,
and others, produce pathological hypertrophy through activa-
tion of Gq-coupled signaling pathways (Figure 4). Down-
stream of Gq, which appears to be a common transducer of
most pathological hypertrophy signals,34,61,62 is phospho-
lipase C

\[
\text{PLC}_\beta \rightarrow \text{IP}_3 + \text{DAG}
\]

Inositol trisphosphate causes the release of calcium from intracellular
stores, which can activate the phosphatase calcineurin, which
regulates pathological hypertrophy gene expression by de-
phosphorylating and causing nuclear translocation of the
nuclear factor of activated T cells family transcription factors.
Diacylglycerol, with or without calcium, activates the protein
kinase C family members, some of which also contribute to
hypertrophic gene expression.58

In contrast, exercise-induced hypertrophy appears to be
mediated by peptide growth factors and signaling through the
PI3K/Akt pathway (Figure 4). IGF and growth hormone,
which increases IGF production, are the major stimuli for
both physiological hypertrophy and normal developmental
growth.63,64 Briefly, these and other peptide growth factors

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**Figure 4.** Schematic depiction of shared and distinct signaling events for physiological (left) and pathological (right) hypertrophy. GF indicates growth factor; GFR, growth factor receptor; GSK-3, glycogen synthase kinase-3β; mTOR, mammalian target of rapamycin; NH, neurohor-
mone; GPCR, G-protein coupled receptor; PLCβ, phospholipase Cβ; DAG, diacylglycerol; IP3, 1,4,5-
inositol trisphosphate; NFAT, nuclear factor of activated T-cells. Arrows indicate activation; blocked
lines indicate inhibition.
bind to their membrane receptor tyrosine kinases causing receptor dimerization, autophosphorylation, and activation of p110α PI3K, which phosphorylates phosphatidylinositol bisphosphate to create phosphatidylinositol triphasate. Phosphatidylinositol triphasate causes recruitment of the kinase Akt to the plasma membrane and its activation by phosphorylation. Akt then stimulates cell protein synthetic machinery by activation of the mammalian target of rapamycin and by inhibition of glycogen synthase kinase (GSK).

There is substantial evidence that the PI3K/Akt signaling axis is critical for transducing physiological or adaptive hypertrophy but also that overstimulation of the pathway can result in hypertrophy with pathological features. Constitutive PI3K signaling achieved by cardiac-specific transgenic expression of an active mutant resulted in hypertrophy that did not transition into failure, whereas inhibition of PI3K signaling through transgenic expression of a dominant inhibitory mutant inhibited both exercise-induced hypertrophy and normal postnatal cardiac growth. Importantly, inhibition of PI3K did not prevent pathological hypertrophy induced by pressure overloading. Thus, PI3K is both necessary and sufficient for physiological hypertrophy but not pathological hypertrophy. Analogous studies of the PI3K effector Akt provide similar results but also suggest that, as with exercise-induced hypertrophy, too much of a stimulus for physiological hypertrophy can be maladaptive. Cardiac-specific overexpression of activated Akt produced physiological hypertrophy (ie, did not transition to failure) in studies with lower expression but hypertrophy with pathological features at higher levels. In contrast, the gene knockout for Akt reduced heart size (and the size of other organs) by \( \approx 20\% \).

Figure 4 illustrates not only the separate putative signaling pathways for physiological and pathological hypertrophy but also several nodes where the paths cross-regulate each other. Of note, membrane phosphatidylinositol bisphosphate is a substrate for both physiological hypertrophy, through phosphorylation by PI3K, and for pathological hypertrophy, through hydrolysis by phospholipase C. Thus, events that qualitatively or quantitatively modulate membrane phospholipid content may be expected to impact one or both of the cellular growth responses. Furthermore, an alternate isoform of PI3K from that activated by growth factor receptors is activated through Gq pathways, possibly explaining how protein synthesis is increased by Gq signaling. However, the most striking point of signaling cross-talk between physiological and pathological hypertrophy is at the level of GSK. GSK-3β is a negative regulator of hypertrophy that is regulated by, and that has modulatory effects on, both growth factor and neurohormone signaling pathways. Accordingly, GSK inhibits both normal growth of the heart and isoproterenol- or pressure-overload-induced hypertrophy. As indicated in Figure 4 and reviewed in detail elsewhere, GSK exhibits tonic activity in the normal cell, helping to maintain basal protein synthesis for normal turnover, but is inhibited by hypertrophic stimuli. Thus, GSK effects on downstream effectors, including the calcineurin substrate nuclear factor of activated T cells and the protein translation initiation factor eIF2B, are achieved after disinhibition by either physiological stimuli (via Akt) or pathological stimuli (via protein kinase C).

**Stimulus Specificity of Cardiac Hypertrophy**

A traditional phenomenological means of characterizing various forms of hypertrophy within the physiological/pathological spectrum has been on the basis of the inciting stimulus, that is, pressure overload, volume overload, genetics, athleticism, and so forth (see Figure 2). Recently, the elucidation of distinct molecular and biochemical signatures for exercise-induced and pressure-overload hypertrophy has provided further support for the idea that hypertrophies are stress-specific responses. A direct examination of this critical hypothesis was lacking until recently, with publication of the findings of Perrino et al. In this important study, functional, histological, biochemical, and molecular characteristics of 3 forms of intermittent stress, running, swimming, and intermittent aortic coarctation, were compared. Expressed in fuzzy logic terms, the study objective was to determine where on the physiological/pathological hypertrophy continuum comparable degrees of hypertrophy caused by voluntary exercise, forced exercise, or intermittent pressure overload would fall. In this experiment, sedentary mice represented normal hearts, and chronic pressure overload from continuous aortic banding represented pathological hypertrophy, that is, the two ends of the hypertrophic spectrum depicted in Figure 2.

Intermittent pressure overload produced functionally compensated concentric hypertrophy with little fibrosis, and that was not associated with the typically striking increases in β-myosin heavy chain isoform, ANF, or brain natriuretic factor gene expression. These are functional, histological, and molecular characteristics of a more physiological hypertrophy. However, myocardial capillary density was decreased to similar degrees in intermittent and chronic pressure overload, whereas it remained unchanged in swimming- and running-induced hypertrophy. Furthermore, unloaded cardiomyocyte contractile function was modestly reduced with intermittent pressure overload, and both intermittent and chronic pressure-overload cardiac myocytes exhibited diminished contractile responsiveness to a β-adrenergic agonist and decreased levels of the sarcoplasmic reticular calcium pump. Although a more complete and nonbiased transcriptome analysis will be required to determine whether the molecular signature of intermittent pressure overload is truly nonpathological, and additional studies will further determine the possible role of calcium cycling abnormalities in cardiomyocyte contractile dysfunction in this model, these studies lend further credence to the notion that there is little meaning to the concept of pure physiological and pathological hypertrophy and that individual aspects of different forms of hypertrophy can be dissociated based on physiological milieu.

**Therapeutic Applications for Physiological Hypertrophy**

There is little doubt that exercise conditioning is beneficial in cardiac disease, not only because of its cardiac effects but because of generally favorable changes in metabolic function and vascularization. Physiological changes caused by exercise and peptide growth hormone treatment have favorable effects on pathological hypertrophy. However, human patients are not always physically able to perform levels of exercise necessary to achieve the benefits associated with conditioning, and so it might be preferable to
have a “magic bullet” to confer physiological hypertrophy, or at least its most beneficial aspects, to heart failure patients. This is a different approach than simply inhibiting the hypertrophic response, which has been proposed based on accumulating data that hypertrophic growth, per se, may not be essential to successful cardiac short-term adaptation to pressure overload. Nevertheless, it seems evident that increased muscle mass could help the heart adapt to increased load if that muscle were qualitatively normal. So, what is the best target for a magic bullet?

Based on available data as reviewed herein, it seems that the primary objective should be to increase cardiomyocyte synthesis of normal contractile proteins, metabolic enzymes, and mitochondria. This needs to occur without inducing those features of reactive hypertrophy that seem to be most deleterious, that is, fetal isomorph changes in contractile proteins, fibrosis/collagen production, and a shift toward glucose use. Oxygen delivery through neovascularization must also be increased in proportion to the growth of cardiomyocytes to fibrosis/collagen production, and a shift toward glucose use.

**Conclusions**

Physiological hypertrophy can be defined as a harmless, completely reversible increase in cardiac muscle mass that occurs in response to workload. It does not occur in humans as the response to hemodynamic stress, for which hypertrophy provides early functional compensation, but is characterized by maladaptive changes in the molecular, biochemical, and metabolic makeup of heart muscle that ultimately lead to heart failure. Even apparently qualitatively normal exercise-induced hypertrophy is associated with adverse outcomes in a small number of highly trained athletes. Likewise, the physiological hypertrophy of pregnancy can sometimes, and for unknown reasons, progress to peripartum cardiomyopathy. Thus, most human reactive hypertrophies exhibit both pathological and physiological properties. Pathological hypertrophy can be adaptive if the primary cause is reversed before the development of intrinsic myocardial disease, and physiological hypertrophy can be maladaptive if it is quantitatively excessive and sustained. By identifying those genetic and metabolic aspects of reactive hypertrophy that are most deleterious, it should be possible, through targeted modifications, to shift hypertrophy of many etiologies toward the physiological end of the spectrum.

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