Cardiac hypertrophy was initially defined by a directly observed increase in cardiac mass that was then assumed to be mainly linked to an increase in cardiomyocyte mass. When submitted to a physiological or pathological stress, the heart undergoes a process of remodeling that involves cardiomyocyte growth but also changes in other cell types: changes in intracellular and extracellular structure, protein expression, signaling pathways, energy metabolism, vascularization, and so forth. Although hypertrophy is only one manifestation of the multiparameter remodeling of the myocardium, progressively, this term has, by oversimplification, included all others aspects of the cardiac response to stress. Classically, hypertrophy induced by pressure overload was considered as adaptive via a decreased stress allowed by a thicker myocardium. The currently accepted concept is that of pathological hypertrophy with depressed ventricular function that leads to heart failure, as opposed to physiological hypertrophy induced by exercise, for example. In this view, hypertrophy development should be prevented during pressure overload. This was proposed 10 years ago in an editorial in Circulation.1 A large number of experimental studies have been published since then, and it appears that an evaluation of the results is necessary.

Many studies showed a beneficial effect of hypertrophy blockade. However, some studies showed the opposite. Before reviewing them in detail, we rapidly present the evolution over time of the concept of adaptive hypertrophy that varied during the last 30 years. This reminds us of some important elements of the previous facts and interpretations that were forgotten as new ones appeared. This also allows understanding of why inhibition of hypertrophy, per se, may not be the best therapeutic strategy in the management of pressure overload–induced hypertrophy.

Evolution of the Concept of Physiological Versus Pathological Hypertrophy

One of the first complete reports of the initiation and evolution of the hypertrophic process toward heart failure was that of Meerson2 in 1969. In this long-lasting view, a defect in the left ventricle (LV) is immediately followed by a phase he called hyperfunction, during which hypertrophy develops, that lasts from a few days to some weeks. A stable hypertrophy phase follows. It is designated as the compensatory phase, because no sign of hemodynamic failure is usually observed. This can be followed by a decompensation phase leading to heart failure. In line with this scheme, the adaptation of the whole ventricle to an increased afterload was described as a normalization of the pre-existing function.

Response by Schiattarella and Hill on p 1457
of wall stress through an increased wall thickness induced by hypertrophy\(^1\) (Figure 1). In parallel to this interpretation, biochemical modifications appearing in the hypertrophied LV were considered as beneficial through an economy of energy\(^4\) via a myosin isozyme shift leading to a decreased ATPase activity that had been described a few years before.\(^5\) This was the first description of the more general picture of ventricular adaptation to cardiac overload through a re-expression of the fetal phenotype (see a more recent review by Swynghedauw\(^6\)). The question that arose was: what is (are) the mechanism(s) that trigger(s) the transition to heart failure? The proteins involved in the excitation-contraction process seemed to be good candidates.\(^7,8\) Because ATP is absolutely required to fuel normal contractile function, an energy starvation has been suspected as the cause of heart failure.\(^9,7,8\) Other factors have been shown to play a role in the transition to heart failure, such as proteins of the cytoskeleton,\(^10\) but no definite answer has emerged.

A major turn in the interpretation of the concept of hypertrophy as an adaptive mechanism appeared with the publication of the article by Levy et al\(^11\) in 1990. Based on a population analysis of the Framingham Heart Study, it was demonstrated that an increase in LV mass predicted a higher incidence of clinical events, including death, attributable to cardiovascular disease. LV mass appeared as prognostic information beyond that provided by the evaluation of traditional cardiovascular risk factors.\(^11\) In line with this concept, pharmacological interventions or studies in transgenic animals\(^12,13\) challenged the concept of hypertrophy as an adaptive mechanism. It was put forward that not only was ventricular hypertrophy not necessary for adaptation to ventricular overload, but even more it was identified as a pathological process associated with an increased cardiovascular risk. However, it was also recognized that some ventricular hypertrophies, such as those observed during pregnancy or exercise training, were not pathological, because they did not lead to heart failure. These hypertrophies were called \textit{physiological hypertrophy}, as opposed to \textit{pathological hypertrophy}\(^14\) induced by pressure or volume overload of the LV.\(^14\) The opposition between pathological and physiological hypertrophy was also based on gross and microscopic anatomy. In concentric LV hypertrophy, mostly induced by pressure overloads, cardiomyocytes only grow in a transverse direction while keeping cell length constant (asymmetrical hypertrophy).\(^15\) In contrast, in response to exercise, for instance, cardiomyocytes grow proportionally in both longitudinal and transverse directions (symmetrical hypertrophy).

Pathological hypertrophy is considered to be associated with a depressed cardiac function and with an absence of reversal of cardiac remodeling when the overload is treated. The development of left ventricular assist devices that are used in the final phase of heart failure show that, even at that stage, a myocardial recovery may be observed when ventricular stress is decreased. It is called \textit{reverse remodeling}, supporting the notion that, in contrast with the present opinion, the regression of pathological hypertrophy is possible in humans.\(^16\)

The involvement of a number of receptors and pathways has been described. As reviewed recently,\(^17\) they include mechanical stretch, adrenergic receptors, growth factors, angiotensin receptors, cytokines, and all of the intracellular pathways among them, including protein kinase A, protein kinase C, calcineurin, phosphoinositide kinase 3-Akt, and transcription factors. Two of them have been described as differently activated in physiological and pathological hypertrophies: phosphoinositide kinase-3 and calcineurin. Studies of the phosphoinositide kinase-3 pathway are in favor of a protective role of phosphoinositide kinase-3 during the development of hypertrophy,\(^18,19\) whereas calcineurin is shown to have deleterious effects during the...
hypertrophy process and to be associated with its pathological form, particularly in response to pressure overload.\textsuperscript{14,20}

The concept of pathological hypertrophy triggered the hypothesis that hypertrophy blockade could be associated with a preservation of ventricular function and that blocking hypertrophy could be a good therapeutic strategy.\textsuperscript{1} A number of articles indeed showed a beneficial effect of hypertrophy development blockade, but some articles showed the opposite. The goal of the present review is to critically review these articles and to examine whether other approaches in the management of hypertrophy development would be more appropriate.

**Is the Prevention of Hypertrophy Induced by Pressure Overload Beneficial?**

The pioneer studies by Akhter et al\textsuperscript{12} and Sussman et al\textsuperscript{13} showed that hypertrophy blockade could prevent ventricular dilatation and histological signs of the diseases, but ventricular function and survival were not evaluated. Ventricular function was measured in all of the ensuing studies listed in Table 1. Calcineurin was the target in many studies,\textsuperscript{13,21–24} but inhibition of other receptors or pathways was shown to be able to block hypertrophy without affecting ventricular function or even improving it. This was the case for many pathways involved in the hypertrophy process, such as the inhibition of stress-activated-protein kinase,\textsuperscript{25} angiotensin receptor type 2,\textsuperscript{26} gp130 (a common receptor for the interleukin 6 family),\textsuperscript{20} Gq protein,\textsuperscript{12,27} and histone deacetylase,\textsuperscript{24} as well as overexpression of c-flip (a modulator of Fas),\textsuperscript{29} activation of p21-activated kinase 1 (a natural inhibitor of small GTPases),\textsuperscript{30} inhibition of mTORC1,\textsuperscript{31} and recently inhibition\textsuperscript{32,33} or activation\textsuperscript{34} of different microRNAs (Table 1). It was also proposed that nuclear-targeted Akt or Pim-1 overexpression can be antihypertrophic.

<table>
<thead>
<tr>
<th>Model</th>
<th>Intervention</th>
<th>Hypertrophy</th>
<th>Cardiac Function</th>
<th>Survival</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal AS in mice (3 wk), GM</td>
<td>DN gp130</td>
<td>40% in WT 15% in TG</td>
<td>FS unchanged in WT and TG</td>
<td>ND</td>
<td>Uozumi et al\textsuperscript{20}</td>
</tr>
<tr>
<td>Abdominal AS in mice (10 wk), GM</td>
<td>AT2 deletion</td>
<td>≈60% in WT Blunted in GM</td>
<td>Small decrease (NS) in WT Unchanged in GM</td>
<td>ND</td>
<td>Senbonmatsu et al\textsuperscript{20}</td>
</tr>
<tr>
<td>TAC in mice (5 wk)</td>
<td>Csa</td>
<td>45% in NT Blunted in treated</td>
<td>Not significantly decreased in both groups</td>
<td>Similar mortality in both groups</td>
<td>Hill et al\textsuperscript{23}</td>
</tr>
<tr>
<td>TAC in TG mice (3 mo) GM</td>
<td>DN MCP1</td>
<td>70% in NT 40% in DN</td>
<td>FS maintained in GM and NT</td>
<td>Not different in both groups</td>
<td>Hill et al\textsuperscript{24}</td>
</tr>
<tr>
<td>TAC in mice (4 and 8 wk), GM</td>
<td>TgGq1 Dbh\textsuperscript{–/–}</td>
<td>Decreased hypertrophy in both GM mice strains</td>
<td>WT: 40% decreased FS and dilation TG: maintained function without dilation</td>
<td>Not different postoperatively No LT survival studied</td>
<td>Esposito et al\textsuperscript{27}</td>
</tr>
<tr>
<td>TAC in TG mice (2 wk) c-flip overexpress (modul of Fas)</td>
<td></td>
<td>35% in WT Blunted in TG</td>
<td>FS NS before and after TAC in both groups</td>
<td>Survival identical in both groups</td>
<td>Kong et al\textsuperscript{28}</td>
</tr>
<tr>
<td>TAC in mice (3 and 9 wk) Pharmacological HDAC inhibition</td>
<td>Hypertrophy partially inhibited in treated (values only in figures)</td>
<td>No statistical change in FS in both groups but decreased ESPVR in NT not in treated shift V1 V3 prevented</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAC in mice (5 wk), GM Pak 1 (p21-activated kinase1)</td>
<td>KO increases hypertrophy Activation inhibits hypertrophy</td>
<td>No change in FS in WT after 5-wk TAC and with Pak-1 activation Decreased function in KO with fibrosis</td>
<td></td>
<td>ND</td>
<td>Liuet al\textsuperscript{30}</td>
</tr>
<tr>
<td>TAC in mice with specific antagonir (3 and 6 wk) miRNA-199b</td>
<td>Inhibition and reversion of hypertrophy and fibrosis</td>
<td>FS decreased in NT FS restored with antagonir</td>
<td></td>
<td>ND</td>
<td>Martins et al\textsuperscript{32}</td>
</tr>
<tr>
<td>TAC in mice (3 wk), GM miRNA 212-132</td>
<td>Partial inhibition of hypertrophy</td>
<td>FS decreased in NT FS restored with antagonir</td>
<td></td>
<td>ND</td>
<td>Ucar et al\textsuperscript{33}</td>
</tr>
<tr>
<td>Gene delivery in ascendent AS mice (9 wk) miRNA-1 gene delivery</td>
<td>Decreased hypertrophy 7 wk after gene transfer</td>
<td>FS decreased in NT FS not different from sham in treated mice</td>
<td></td>
<td>ND</td>
<td>Karakikes et al\textsuperscript{34}</td>
</tr>
<tr>
<td>Gene transfer in TAC mice (4 wk) PRAS40 gene delivery</td>
<td>Partial inhibition of hypertrophy in treated mice</td>
<td>EF decreased in sham EF preserved in treated</td>
<td></td>
<td>ND</td>
<td>Völkers et al\textsuperscript{35}</td>
</tr>
</tbody>
</table>

The abbreviation of specific genes is given in the text. AS indicates aortic stenosis; Caa, cyclosporine; DN, dominant negative; EF, ejection fraction; ESPVR, end-systolic pressure-volume relation; FS, fractional shortening; GM, genetically modified; HF, heart failure; ND, not determined; TAC, transverse aortic constriction; TG, transgenic; and WT, wild-type.
and adaptive at the same time by promoting a hypercellular phenotype in mice.

Some articles conversely showed that hypertrophy blockade may be detrimental (Table 2). Some studies used calcineurin blockade. In contrast with the studies presented in Table 1, a detrimental effect of calcineurin inhibition during hypertrophy development was demonstrated. Other gene inhibitions or deletions have also been shown to be deleterious. Although their numbers are much smaller than those presented in Table 1, they open a number of questions that need to be answered before reaching the conclusion that hypertrophy blockade could be beneficial in patients. We examine first the possible limitations of these studies.

**Limitations of These Studies**

**Model**

The first remark applies to the experimental models. Most studies use abrupt transverse aortic stenosis (TAC) for a few weeks in mice. Whether TAC accurately reflects human pathology is open to doubt. Moreover, very tight TAC can induce subendocardial ischemia, which can lead to cell death and failure from that mechanism. This also occurs in the clinical setting during the transition to heart failure, but, at that phase, the myocardium is already hypertrophied so that studies of the effect of hypertrophy blockade in the initial phase of its development may not apply to clinical situations. The specific role of TAC is shown by the study of melusin-null mice. In this model, hypertrophy was blocked after TAC and this was detrimental. In contrast, the hypertrophic response was identical in wild-type and melusin-null mice after chronic administration of angiotensin II or phenylephrine.

There are other examples showing that a positive result in a model of hypertrophy may not be applicable to others. In a first series of articles, Senbonmatsu et al and Ichihara et al showed a beneficial role for angiotensin receptor type 2 receptor blockade that inhibited hypertrophy after pressure overload or chronic angiotensin infusion with a negligible amount of fibrosis and a preserved ventricular function (Table 1). However, in a further study, the same group presented data showing, in another model of overload (myocardial infarction), that targeted deletion of angiotensin receptor type 2 caused cardiac rupture. This indicates that, although fibrosis is a detrimental factor, some amount of fibrotic tissue may be necessary to protect a LV submitted to a large overload when myocardial ischemia is present.

The role of the intensity of the overload is illustrated in different studies. Fibroblast specific deletion of a transcription factor (Klf5) was shown to produce 2 opposite effects (beneficial or detrimental) depending on the intensity of the stimulus of hypertrophy. Similarly, hypertrophy development blockade by calcineurin inhibition was described as having a beneficial effect after TAC (Table 1), but 2 other studies in the same models showed that it was detrimental. It is likely that a higher degree of overload was responsible for the higher mortality rate during cyclosporin A treatment. It could be an explanation for the finding of a detrimental effect of calcineurin blockade during the development of hypertrophy published by Meguro et al in contrast with the beneficial effect presented by Hill et al.

Although this model does not reflect the clinical setting, no model can be proposed to completely mimic human pathology, which includes many types of etiologies with many associated disorders (hypertension, senescence, diabetes mellitus, etc). However, each model can answer a specific question. For instance, intermittent TAC, which induces a mild hypertrophy in contrast with permanent TAC, has been used to show

<table>
<thead>
<tr>
<th>Model</th>
<th>Inhibition</th>
<th>Hypertrophy</th>
<th>Function</th>
<th>Survival</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAC in TG mice, 7 d</td>
<td>RGS4 overexpression</td>
<td>Reduced</td>
<td>No fetal gene program induction in TG</td>
<td>Increased postoperative mortality in TG with tight TAC</td>
<td>Rogers et al</td>
</tr>
<tr>
<td>TAC in WT mice, 3 wk</td>
<td>Csa</td>
<td>Blunted</td>
<td>Decreased ventricular function and increased HF in treated mice</td>
<td>Increased mortality in treated mice</td>
<td>Meguro et al</td>
</tr>
<tr>
<td>TAC in WT mice, graded response 21 d</td>
<td>Csa or MCIP1</td>
<td>Reduced</td>
<td>ND</td>
<td>Increased mortality for severe stenosis with Csa</td>
<td>Rothermel et al</td>
</tr>
<tr>
<td>TAC in mice, 4 wk, GM</td>
<td>Melusin gene deletion</td>
<td>Hypertrophy post TAC in WT Reduced in KO</td>
<td>Normal FS in WT Decreased FS and dilatation and HF in KO</td>
<td>Increased mortality</td>
<td>Brancaccio et al</td>
</tr>
<tr>
<td>TAC in rats, 20 wk</td>
<td>Sex difference</td>
<td>More hypertrophy in females</td>
<td>Decreased function in male</td>
<td>ND</td>
<td>Douglas et al</td>
</tr>
<tr>
<td>TAC in rats, 20 wk</td>
<td>Sex difference</td>
<td>More hypertrophy in females</td>
<td>Decreased function in male</td>
<td>ND</td>
<td>Loyer et al</td>
</tr>
<tr>
<td>TAC</td>
<td>Calcineurin</td>
<td>Blunted</td>
<td>Diastolic abnormalities</td>
<td>ND</td>
<td>Gelpi et al</td>
</tr>
</tbody>
</table>

The abbreviation of specific genes is given in the text. Csa indicates cyclosporine; FS, fractional shortening; GM, genetically modified; HF, heart failure; MI, myocardial infarction; ND, not determined; TAC, transverse aortic constriction; TG, transgenic; and WT, wild-type.
the importance of the growth signaling and not hypertrophy development as the trigger of cardiac dysfunction. Problems may appear when the conclusions obtained with a specific model are generalized.

**Long-Term Survival**

Another important limitation of the studies presented in the tables is the absence of systematic evaluation of survival that must be addressed in clinical trials. Survival was evaluated in only 4 of the studies presented in Table 1. In general, the duration of the study was short except in one lasting 9 weeks that the authors considered to be equivalent to 10 years in humans. In all of the studies, however, the number of animals was small and the survival rate was high in the control group (>70%), with most deaths appearing in the early postoperative period without progressive mortality during the evolution of the disease. Survival was not evaluated in cohorts with a high mortality rate in the control arm to determine whether hypertrophy blockade is beneficial or detrimental in this condition, which is closer to heart failure observed clinically. In contrast, some studies (Table 2) showed an increased mortality when the hypertrophy process was inhibited. A possible mechanism for this increased mortality is the role of inotropic stimulation necessary to maintain cardiac function when the myocardium is submitted to an increase in afterload and is not allowed to hypertrophy.

**Inotropic State**

Basic principles of cardiac mechanics indicate that an increased inotropic state is necessary to maintain ventricular function when wall stress is increased without compensatory hypertrophy (Figure 1). This was shown in the study by Esposito et al in which, 7 days after TAC, a clear increase in inotropic state was demonstrated by a precise measurement of the stress-strain relations when hypertrophy development was blocked. This response is similar to the transient (24 hours after stenosis) increase in inotropic state we showed in dogs with pressure overload (Figure 1). In the study by Esposito et al, LV function was shown to be maintained 8 weeks after TAC in mice without hypertrophy, in contrast with wild-type mice that exhibited ventricular dilatation and decreased function. An increase in inotropic state may have protected mice with a very severe TAC that otherwise would have presented a vicious cycle of decreased ventricular function, in turn decreasing ventricular perfusion. However, a generalized beneficial effect of increased inotropic state can be questioned. As noted previously, this study was performed in the model of TAC in which a severe stenosis induces subendocardial ischemia. Long-term survival studies have not been performed in less abrupt overloads. It is well known that randomized clinical trials in patients with heart failure demonstrated that, although positive inotropic agents had beneficial effects on the hemodynamic status of patients with acute heart failure, a detrimental effect of chronic inotropic stimulation on survival appeared using positive β-adrenergic agents or inhibitors of phosphodiesterases. This is the reason why these agents are no longer used for treating chronic heart failure. LV function preservation during the blockade of hypertrophy is associated with a natural increase in inotropic state that resembles treatments with inotropic agents. It remains to be established whether, in other models with a less abrupt initiation of pressure overload, longer durations of surveys, such as those performed in large clinical trials, would demonstrate a beneficial effect of hypertrophy blockade.

**Sex**

As shown in Table 2, in response to TAC the degree of hypertrophy is larger in females than in males, with a smaller decrease in ventricular function in females. Thus, in female rats submitted to TAC, hypertrophy development is associated with a better ventricular function. However, it is impossible to date to determine whether hypertrophy is beneficial or not in female patients. In, human heart failure the role of sex differences is complex because the risk factors and the etiologies of heart failure are different (more hypertension and diabetes mellitus in women and more coronary artery disease in men). Although there are conflicting results, it is generally considered that ventricular function is less decreased in women because they develop heart failure with preserved ejection fraction. In that respect, it is interesting to note that no study was directed toward heart failure with preserved ejection fraction, which is a more recently identified entity. No experimental model exists thus far. It is possible that, in the future, more cases of evolution of pure aortic stenosis toward heart failure with preserved systolic function will be recognized, and the conclusions about the possible advantages of treating hypertrophy versus not treating hypertrophy might change.

Thus, although many studies underline a beneficial effect of hypertrophy blockade on ventricular function in pressure overload hypertrophy, a number of issues need to be examined before it can be concluded that it is a good therapeutic strategy, particularly the major end point, survival, remains to be evaluated in large trials as in a clinical situation with different etiologies and different associated pathologies. In that respect, it can be noted that all of the experimental studies were performed in permanently resting animals. The adaptation to a normal life with exercise of animals for which hypertrophy has been blocked is completely unknown.

In spite of these limitations, it remains established that hypertrophy is a cardiovascular risk factor. Blocking its development may thus appear as an obvious strategy by the search for deleterious intracellular signal transduction pathways. However, ventricles are not constituted only of cardiomyocytes. The next section examines other possible factors that could be involved in the deleterious effects of hypertrophy. This could open new therapeutic options in the management of hypertrophy development.
Hypertrophy as a Cardiovascular Risk Factor: Possibly Involved Factors

Malignant ventricular arrhythmias are considered responsible for the high incidence of sudden death in patients with aortic stenosis and thus contribute to make ventricular hypertrophy a cardiovascular risk factor. It is beyond the scope of this review to discuss in detail the mechanisms of ventricular arrhythmias in pressure overload. The review will evaluate the possible roles of 3 factors.

Myocardial Perfusion

When myocardial energetic demand of dogs with LV hypertrophy is increased by pacing, a subendocardial coronary perfusion deficit appears. The same abnormality was described during exercise in a pressure overload model produced by aortic banding in puppies. This was attributed to a reduced subendocardial coronary reserve related in part to the larger compressive forces in the subendocardium where stress is larger. A vicious cycle can thus be initiated, in which an increased subendocardial stress present in severe hypertrophies produces a subendocardial exhaustion of blood flow reserve leading to subendocardial ischemia and increased fibrosis, aggravating heart failure.

Other than these effects of compressive forces on the intramyocardial coronary vessels, vascular growth may be abnormal during myocardial growth. As reviewed long ago by Anversa et al., structural factors that are modified during cardiac hypertrophy include capillary luminal volume density, capillary luminal surface density, and the average diffusion distance for oxygen. During maturation, a well-balanced growth was observed, because capillary microvasculature and myocytes grow in proportion to the increase in cardiac mass. In contrast, when pressure- or volume-overloaded hearts were examined, all 3 of the aforementioned parameters were altered, showing an inadequate growth adaptation of the component structures responsible for tissue oxygenation. It was thus concluded that this myocardial enlargement might increase its vulnerability to ischemia.

In patients, the presence of signs suggestive of myocardial ischemia despite normal coronary angiograms is a relatively frequent finding that has been called coronary microvascular dysfunction. It may be explained by the same abnormalities as those described in experimental animals: inadequate vascular growth during hypertrophy and compressive forces.

The role of a nonparallel growth of myocytes and vasculature has been shown in a model of conditional transgenic mice with a sequential development of hypertrophy. Both heart size and cardiac function were shown to be angiogenesis dependent, and disruption of coordinated cardiac hypertrophy and angiogenesis appeared as contributing to the transition to heart failure. This finding is a major example of possible therapeutic strategies that could be directed toward a re-ordination of tissue growth and angiogenesis during some sequences of the development of hypertrophy rather than trying to block hypertrophy, per se. Any other approach aimed at improving cardiomyocyte homeostasis will improve function and decrease hypertrophy (see, eg, dietary copper supplementation or genetic conditional ablation of fibronectin).

Fibrosis

Other than cardiomyocytes, the myocardium is composed of arteries, fibroblasts, and extracellular matrix. Fibrosis increases with hypertrophy. It is no longer proportional to ventricular mass when hypertrophy is large, reaching ≈30% of the ventricular weight.

The development of fibrosis may be a cause of ventricular dysadaptation. Collagen deposition increases during the development of pressure overload and correlates with diastolic and systolic abnormalities in mice with pressure overload. The absence of a complete recovery of ventricular function after aortic valve replacement in patients correlates with the degree of fibrosis in aortic stenosis. However, the presence of fibrosis was not found only in pathological hypertrophy but also in strenuous prolonged exercise training, particularly in older athletes. Fibrosis is thus a detrimental factor both in pathological and physiological hypertrophies, with inadequate coronary perfusion playing a role in its development and suggesting that the intensity and the duration of the overload more than its type are responsible for the appearance of fibrosis.

Nevertheless, fibrosis is not purely detrimental. As discussed above, fibrosis is sometimes necessary for survival after acute myocardial infarction, and a cross-talk between fibroblasts and cardiomyocytes can modulate cardiac remodeling. This suggests a possible therapeutic approach directed toward modulation of fibroblast function and interaction with cardiomyocytes.

Cellular Architecture and Energetics

Adult cardiomyocytes exhibit a sophisticated subcellular architecture in which large mitochondria are strictly ordered between rows of contractile proteins and are specifically arranged with the sarcoplasmic reticulum and myofilaments into intracellular energetic units. The close proximity among sites of calcium sequestration (sarcoplasmic reticulum), energy production (mitochondria), and energy utilization (myofilaments, etc) create energetic and calcium microdomains that ensure optimal contractile efficiency. When a myofiber disarray appears, it affects energy exchange and contractile function.

Ventricular hypertrophy mainly results, but not only from the enlargement of cardiomyocytes. As depicted in Figure 2, in mild hypertrophy, there is an increase in mitochondrial volume with a strict respect of the cell organization and maintained ratio and interactions between the different organelles. Although this arrangement is perturbed during the transient phases of the hypertrophic growth, the overall cell architecture is preserved in compensated hypertrophy without dysfunction. However, cell enlargement increases the intracellular diffusion distances of oxygen and metabolites, possibly compromising energy supply during increased workload.

Under severe overload or heart failure, the general feature of the cardiomyocyte progressively evolves toward
increased cytosolic space, disorganization and misalignment of myofibrils, heterogeneity of mitochondrial shape, defective mitochondrial biogenesis, and mitochondrial degradation (Figure 2). The mitochondrial network is fragmented and disorganized, and numerous small mitochondria appear in clusters. The misalignment of mitochondria and myofibrils affects the interaction between organelles and alters calcium and energetic microdomains, resulting in decreased contractile homogeneity and energetic inefficiency. It has been shown that mitochondrial injury positively correlates with indexes of heart failure severity, like plasma norepinephrine, LV end-diastolic pressure, and ejection fraction. This disorganization of the cell structure, which probably appears progressively during the transition from hypertrophy to heart failure, likely results from excessive mechanical constraints and hormonal overdrive of heart failure. A metabolic therapy of heart failure...
is increasingly proposed as a new option, and cellular architecture should also be considered as an innovative therapeutic target.

**Other Factors**

Many other factors may play a role in making hypertrophy pathological. Inflammation, for instance, plays an important role in the development of fibrosis in pressure overload hypertrophy. Strategies intended to inhibit the inflammation process, such as the use of the bacillus of Calmette and Guérin, proved to be able to reduce hypertrophy and fibrosis induced by abdominal aortic stenosis. Similarly, heat shock protein 70 is able to inhibit hypertrophy by blocking the inflammatory response without adverse effect. It is possible that the procedures intended to inhibit hypertrophy are beneficial in part by blocking upstream the inflammatory response, particularly when the induction of the overload is brutal.

Another potentially promising approach could be to stimulate survival and proliferation of stem cell populations. Instead of a simple increase in ventricular mass because of triggering by hypertrophy development are purely beneficial or detrimental, and all may have both aspects depending on the characteristics of the stimulation (intensity of the overload, the brutality of its onset, and its duration). As discussed, fibroblast stimulation, for instance, is detrimental in many circumstances by the fibrosis it induces, but some degree of fibrosis may be necessary, and fibroblast stimulation allows cross-talk with cardiomyocytes. Similarly, cardiomyocyte hypertrophy may be harmful by the inadequate intracellular architecture that it may produce, but it also allows LV wall stress adaptation. Thus, although hypertrophy is an independent CV risk factor, inhibition of its development may be harmful in some instances. Instead, new therapeutic strategies as summarized in Figure 3 could be developed to try to coordinate the growth of the different elements that constitute the ventricles.

**Conclusion**

Rather than a simple increase in ventricular mass because of larger cardiomyocytes, LV hypertrophy is produced by the growth of different constitutive elements (principally neovesels, fibrosis, and cardiomyocytes with their intracellular organelles) that may be uncoordinated. None of the processes triggered by hypertrophy development are purely beneficial or detrimental, but all may have both aspects depending on the characteristics of the stimulation (intensity of the overload, the brutality of its onset, and its duration). As discussed, fibroblast stimulation, for instance, is detrimental in many circumstances by the fibrosis it induces, but some degree of fibrosis may be necessary, and fibroblast stimulation allows cross-talk with cardiomyocytes. Similarly, cardiomyocyte hypertrophy may be harmful by the inadequate intracellular architecture that it may produce, but it also allows LV wall stress adaptation. Thus, although hypertrophy is an independent CV risk factor, inhibition of its development may be harmful in some instances. Instead, new therapeutic strategies as summarized in Figure 3 could be developed to try to coordinate the growth of the different elements that constitute the ventricles.

**Disclosures**

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**References**


Response to Crozatier and Ventura-Clapier

Gabriele G. Schiattarella, MD; Joseph A. Hill, MD, PhD

We see much agreement between our perspective and that of Crozatier and Ventura-Clapier. We both point to a robust epidemiological literature, coupled with a large body of preclinical evidence, indicating that load-induced ventricular hypertrophy is maladaptive. We agree that several signaling cascades that trigger ventricular hypertrophy can be interrupted effectively, without harm, and with hints of benefit. We also agree that there are cascades, albeit relatively few, where inhibition is not well tolerated.

These authors emphasize 2 important points. Transverse aortic constriction entails an abrupt increase in afterload, which does not faithfully mimic all aspects of afterload stress in patients. Rather, afterload stress in humans is typically long term and progressive (e.g., hypertension or aortic stenosis). These investigators also emphasize that 3 to 4 weeks in mice cannot be titrated for therapeutic gain. We agree. For all of these reasons, we submit that the time has come to test this biology in humans. Carefully conceived clinical trials are warranted to determine whether this ventricular response to stress, the only one untouched by therapeutic manipulation, can be titrated for therapeutic gain.

We continue to favor a model in which load-induced ventricular hypertrophy is similar to other evolutionarily conserved prosurvival mechanisms. Just as the β-adrenergic cascade and renin-angiotensin-aldosterone axis are activated by life-threatening stress, leading to enhanced cardiac performance and improved survival, it is well established that chronic suppression of these responses is beneficial. We suggest that ventricular hypertrophy is the same. In light of this, suppression of ventricular hypertrophy warrants careful consideration as a therapeutic intervention.
Inhibition of Hypertrophy, Per Se, May Not Be a Good Therapeutic Strategy in Ventricular Pressure Overload: Other Approaches Could Be More Beneficial
Bertrand Crozatier and Renée Ventura-Clapier

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