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Is Load-Induced Ventricular Hypertrophy Ever Compensatory?

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Introduction

When muscle is subjected to increased workload, it grows by means of a cellular process termed hypertrophy. When one lifts weights, skeletal muscle hypertrophies in a manner that increases muscle strength and work capacity. When cardiac muscle is exposed to increased workload demand, it, too, hypertrophies. When the increase in workload stems from physiological stress, such as exercise, the now hypertrophied myocardium is strengthened. Similarly, when the heart “lifts weight” due to increased afterload (e.g. hypertension, aortic stenosis), it hypertrophies. However, considerable evidence suggests that this hypertrophied heart is weaker, not stronger. Further, a large body of preclinical evidence points to the fact that this afterload-triggered heart growth is not required to maintain ventricular size and contractile performance even in the face of persistently increased load. This fact, which has yet to be tested in large animals, begs the question of the concept of “compensatory hypertrophy”, an issue we explore here. [It is important to emphasize that we are referring exclusively to disease stress-triggered heart growth, not the unequivocally beneficial myocardial hypertrophy that occurs with exercise.]

Where did the concept of compensatory hypertrophy emerge?

In the 1890's, Woods and colleagues proposed that the left ventricle (LV) could be modelled according to the Law of Laplace[1]. Whereas it was apparent from the outset that the LV violates the law's first principle assumptions, including spherical shape and homogeneous wall characteristics, a simplified model emerged in which wall stress is directly proportional to left ventricular pressure and radius and inversely proportional to wall thickness. Today, this represents the simplest model proposed to analyze ventricular wall mechanics and pervades our thinking (and textbooks) in terms of the relationships among cavity size, intraventricular pressure, and wall stress.

Studies in the 1960's by Meerson and coworkers divided load-induced hypertrophic growth into distinct stages[2]. They posited that “short term” hypertrophy is beneficial by means of

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normalization of wall stress; conversely, prolonged hypertrophy is detrimental due to increased oxygen consumption and cardiomyocyte death.

In the mid 1970's, the pioneering work of Grossman and colleagues related patterns of left ventricular hypertrophy (LVH) to the different components of LV wall stress during the cardiac cycle[3]. Using an integrated, multimodality approach with simultaneous measurements of LV dimension, wall thickness and LV pressure, these investigators demonstrated that concentric hypertrophy effectively normalized both systolic and diastolic LV wall stress in patients with aortic stenosis. Concentric hypertrophy was deduced to be a compensatory mechanism serving to counter the untoward effects of elevated pressures on wall stress and oxygen demand. Conversely, eccentric hypertrophy, as occurs in in patients with mitral or aortic regurgitation, fails to normalize diastolic wall stress despite the correction of systolic wall stress. This observation in eccentric hypertrophy raised the prospect that the extent of LV hypertrophy may not always be “adequate” to the level of wall stress; persistently “uncompensated” wall stress in the setting of modest hypertrophy was posited to promote contractile dysfunction.

Thus, important work in preclinical and clinical models correlated the presence of LVH with a variety of physiological variables, including wall stress and oxygen consumption. Nowadays, we call these variables “surrogate markers”, and we all are acutely aware that such markers can, at times, mislead. In any event, the concept of compensatory hypertrophy has persisted as a *hypothesis* which has never been tested.

What evidence suggests that load-induced hypertrophy is not compensatory?

A large body of preclinical evidence demonstrates that it is possible to blunt load-induced hypertrophy, even in the presence of persistent afterload stress, without adversely affecting contractile function[4]. These studies have gone on to delineate a strategy in which it is possible to target maladaptive hypertrophy directly and thus prevent the detrimental consequences of long-term activation of this response. In so doing, these studies raise the prospect that targeting the hypertrophic response *per se* is not harmful but rather beneficial.

Whereas causal inferences cannot be derived from epidemiological studies, a number of such reports are consistent with the notion that LVH is not benign but rather represents a risk factor more powerful than other conventional risk factors. For example, studies from the Framingham Heart Study revealed marked increases in coronary heart disease, heart failure and sudden cardiac death associated with LVH detected by either electrocardiographic and echocardiographic means.

In addition to the robust preclinical literature pointing to the dispensability of afterload-induced LVH, clinical evidence suggests that interventions to limit and possibly even reverse LVH are desirable, even in the absence of contractile dysfunction. For one, regression of LVH is associated with improved outcomes. It goes without saying that targeting hypertension, one of the most effects means of hypertrophy regression, would be expected to have favorable effects on many organs, not just the heart. However, the fact that

myocardium-specific endpoints are improved, such as contractile dysfunction, heart failure, and sudden death, suggest that at least some of the benefits of blood pressure reduction derive from effects directly on the heart. Thus, in many instances, load-induced LVH is both dispensable (animal models) and associated with untoward events (epidemiological observations).

Although all antihypertensive drugs are efficacious in LVH regression, some evidence suggests that neurohormone-targeting drugs are the most effective pharmacological agents for LVH reduction. For example, the LIFE study (Losartan Intervention for Endpoint Reduction in a Hypertension) demonstrated greater reduction in LV mass index in the losartan-treated cohort compared with an atenolol-based regimen. Similarly, several other trials reached the same conclusion suggesting a class-effect on LVH regression of neurohormonal antagonism. Collectively these data point to strong associations with LVH reduction and improved clinical outcomes, although we emphasize that causal inferences cannot be drawn from these data.

Whereas blood pressure lowering affords a wide range of benefits, including some occurring directly at the myocardium, a robust preclinical literature indicates that interruption of intracellular molecular events that govern myocyte growth, with no changes in blood pressure, can also be beneficial. In many instances, blocking the afterload-induced cellular growth response directly in cardiomyocytes by interrupting signaling cascades that lead to hypertrophy does not provoke circulatory compromise. Rather, ventricular size and performance are maintained. These data, which presently derive exclusively from rodent models, suggest that the hypertrophic response itself may emerge as a *bona fide* target of therapeutic intervention.

What needs to be done to resolve these questions?

Time is overdue to test the hypothesis that afterload-induced LVH is a compensatory response. It is now clear that this is a pathologic and not compensatory response in animals. Following the initial report in 2000[5], we estimate that >100 studies have confirmed this observation. Importantly this question has never been posed in a nonrodent model. Such is sorely needed. Pending the results of such studies, studies in humans may ensue.

Conclusions

The notion of compensatory hypertrophic growth of the LV in response to elevated afterload is a hypothesis yearning to be tested. Whereas it makes intuitive sense, especially in light of the well established benefits of hypertrophic growth of skeletal muscle, a large body of evidence suggests that this view is incorrect. The field awaits rigorous mechanistic studies in large animals, and ultimately in humans, to test this hypothesis. If, perchance, the hypertrophic growth triggered by elevated afterload proves not to be compensatory, and possibly even detrimental, then an entirely new therapeutic target emerges immediately. We may find that targeting specific growth pathways, even in the presence of persistent afterload stress, is beneficial, indicating that the hypertrophic response is detrimental from the start. In the end, it will be patients who benefit from these efforts. In the meantime, we discourage

use of the term “compensatory ventricular hypertrophy” as established dogma, because it is not.

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