JACC: CARDIOVASCULAR IMAGING
VOL. 7, NO. 11, 2014

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcmg.2014.07.013

EDITORIAL COMMENT

Is Cardiac Hypertrophy Good or Bad?

The Answer, Of Course, Is Yes*

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In this issue of *iJACC*, Petrov et al. (1) examined patterns of hypertrophy in patients with aortic stenosis. They found that women had "adaptive" hypertrophy more often than men, but when women had "maladaptive" hypertrophy, their mortality was increased, adding more proof of the sex differences that exist in response to pressure overload (2). Obviously, the subject matter itself raises the issue of what exactly is adaptive hypertrophy?

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The heart is a muscle, and all muscles have as their basic purpose the ability to generate force. However, unlike most other muscles in the body, the heart must use the force it generates to propel its contents (volume) forward. In ejecting adequate blood from its chamber, it must have adequate chamber size to fulfill the cardiac output needs of the body, and it should also model itself in such a way as to normalize systolic wall stress, the afterload opposing ejection, because excess afterload impairs ejection thereby reducing cardiac output. To be truly adaptive, the process should allow for normal cardiac output, normal systolic and diastolic function, and normal life span.

PHYSIOLOGIC HYPERTROPHY

Although modest myocyte division may occur throughout life (3), it is generally held that most myocytes are terminally differentiated shortly after birth. Thus, most of the 10-fold increase in heart size that must occur as the body grows from infancy to adulthood occurs through hypertrophy, a process whereby individual myocytes enlarge instead of dividing. Not only is this physiologic hypertrophy not pathologic, but it is necessary for life. In addition, the heart appears to truly adapt to the cardiac output needs of trained athletes or to occupations that require increased cardiac output (4,5). For instance, in isotonic aerobic exercise such as seen in long distance running, eccentric hypertrophy allows for increased cardiac output with concomitantly normal systolic and diastolic function (5,6). Isometric exercise such as weight lifting generates concentric hypertrophy also associated with normal function (6). Thus, the mere presence of hypertrophy by itself is not necessarily deleterious.

HYPERTROPHY IN RESPONSE TO HEMODYNAMIC OVERLOAD

Hemodynamic overload on the myocardium also induces hypertrophy that is usually considered compensatory at least in its early stages. However, persistent severe overload eventually causes myocardial damage, leading to systolic and diastolic dysfunction, heart failure, and death. A presumed key difference between physiologic and pathologic hypertrophy is that conditions causing physiologic hypertrophy are intermittent (the runner rests between training sessions), whereas conditions causing pathologic hypertrophy persistently load the heart on every beat.

Four decades ago, Grossman et al. (7) hypothesized that hypertrophy was driven by wall stress where stress (σ) = (P × r)/(2 × th), where P = pressure, r = radius, and th = thickness. They hypothesized that pressure overload increased systolic stress, causing additional sarcomeres to be laid down in parallel, increasing myocyte thickness, and leading to concentric hypertrophy. In this way,

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

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JACC: CARDIOVASCULAR IMAGING, VOL. 7, NO. 11, 2014
NOVEMBER 2014:1081–3

increased wall thickness in the denominator of the Laplace equation offsets increased pressure in the numerator, normalizing wall stress (afterload) and maintaining normal ejection performance. Alternately, volume overload increased diastolic stress, leading to additional sarcomeres laid down in series, thus elongating myocytes, and thereby increasing chamber volume and stroke volume.

SO, IS HYPERTROPHY OCCURRING FROM PRESSURE OVERLOAD GOOD OR BAD?

A reasonable way to address this question would be to examine the outcomes in subjects where hypertrophy does or does not occur in response to pressure overload and outcomes where hypertrophy is or is not compensatory. Although this approach seems logical, the results of such an examination are incredibly confusing.

Esposito et al. (8) examined the results of pressure overload in mice in which genetic alterations prevented hypertrophy from occurring and compared them to wild-type mice in which hypertrophy occurred. Wall stress increased acutely (at 7 days) in the altered mice, and ejection performance fell modestly. However, at 8 weeks, mortality was similar in both groups and LV function was reduced more in the wild-type mice with LVH than in the genetically-altered mice. Hill et al. (9) found similar results, suggesting that LVH was not necessary for compensation to occur. However, in 2 other mouse models, the prevention of LVH led to cardiac decompensation and increased mortality (10,11). In humans with aortic stenosis, Kupari et al. (12) found a greater reduction in ejection fraction in patients with LVH than in patients with concentric remodeling without LVH. In the latter group, a small LV radius together with increased relative wall thickness allowed for stress normalization in the absence of increased LV mass.

In the dog, as in man, the hypertrophic response to a given pressure overload is variable. In a model where the contractility of individual myocytes could be studied, abundant hypertrophy that normalized stress preserved myocyte contractile function (13). However, when only modest hypertrophy developed, increased stress led to depressed contractility of myocytes isolated from the left ventricles.

Although it is hard to compare the adaptive definition in the current study to the data from previous works, it appears that adaptive LVH here is consistent with smaller ventricular radius and increased relative wall thickness that would normalize stress. Yet, this is usually the geometry seen in patients with paradoxic low flow, low gradient AS, where mortality seems higher than for typical aortic stenosis (14). Further, in a study of propensity-matched pairs of AS patients, those with concentric LVH had double the mortality and morbidity than those without concentric LVH (15).

HOW CAN THESE APPARENT CONTRADICTIONS BE RESOLVED?

First, some fundamental principles of ventricular function are immutable. Ejection is regulated by pre-load, afterload, and contractility. If afterload increases, either pre-load, contractility, or both must increase to maintain stroke volume and ejection performance. These mechanisms would be expected to lead to increased filling pressure and oxygen consumption, respectively, both potentially deleterious effects. Conversely, the presence of enough LVH to normalize stress is almost inexorably linked to diastolic dysfunction and impaired coronary blood flow reserve, also deleterious occurrences. Thus, there are negative consequences both when afterload is or is not normalized, potentiating adverse outcomes. And, finally, some patients appear to do well despite LVH (or maybe because of it).

The problem is that, on a patient-by-patient comparison, we are only examining gross morphology and not the inner workings of the myocardium. It is highly unlikely that a given relative wall thickness or mass index imparts the same pathological myocardial changes (or beneficial ones) identically in all patients. But, clinically, we are in effect judging each book by its cover. Only when we begin to understand both the histologic and physiologic changes that pressure overload imparts on the specific patient of interest will we begin to answer the question: is LVH good or bad for that patient.

The work by Petrov et al. (1) emphasizes the wide variation in left ventricular adaptation to the pressure overload of aortic stenosis. Our challenge now is to understand the relationships between these morphologic changes and the biology underpinning them, and then translating that knowledge into prognosticating and improving patient outcomes.

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KEY WORDS aortic valve replacement, cardiac fibrosis, hypertrophy regression, survival, sex