Fueling the Hypertrophied Heart

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Substrate utilization by heart muscle provides the fuel for both maintenance of structure and function of the myocardium and for ample reserve capacity to meet sudden surges in cardiac energy requirements. Many factors influence the balance of substrate uptake by the myocardium, but in general, utilization of lipids versus carbohydrates correlates to their concentration in the arterial blood.

There is evidence in humans that severe cardiomyopathy and heart failure are accompanied by alterations in the balance of substrates used and of energy reserves, and these may limit myocardial function. However, myocardial metabolic changes have not been well described in human hearts with compensated hypertrophy.

Compensated cardiac hypertrophy due to systolic overload in experimental animals is associated with a recapitulation of a fetal genetic pattern. This is most dramatically demonstrated in the hearts of rodents in which their contractile proteins switch from a predominance of α-myosin to a more energy conserving β-myosin pattern, but also involves enzymes in metabolic pathways of energy transfer. Many of these genetic alterations affect reactions that influence the balance between carbohydrate and lipid use by the heart. GLUT-4 protein, the main insulin sensitive glucose transporter may be normal or its mRNA reduced. GLUT-4 deletion leads to hypertrophy and upregulation of GLUT-1, a glucose independent transporter, and to enhanced insulin independent glucose transport. However, selective GLUT-1 upregulation protects heart function, but may also promote cardiac hypertrophy. On the lipid side, transcription of PPAR-α and other genes related to fatty acid oxidation is also reduced. If an imbalance between glucose and lipid use occurs, particularly a deviation away from metabolism of carbohydrate and toward greater dependence on lipids, this might decrease the efficiency of energy production and thereby the ability of the heart to respond to stress. This is observed in conditions including diabetes, myocardial ischemia, the failing heart, and even the nonfailing hypertrophied myocardium. In some of these conditions, pharmacological manipulation of substrate use restoring a more normal pattern can be associated with improvements in heart function.

As noted above, hypertrophy induced by systolic overload in experimental animals is generally associated with upregulation of glucose transport by noninsulin dependent mechanisms, and this is associated with increased aerobic glycolysis. Greater glucose transport has enabled the heart response to increased load. The increase in glucose transport is reversed when hypertrophy is reversed. The article by Nascimben et al in the current issue of Hypertension provides persuasive evidence that the mechanism for increased glucose transport in hypertrophic myocardium is via diminished energy stores, resulting in accumulation of ATP breakdown metabolites and activation of AMP-activated protein kinase. ADP and AMP are known to allosterically increase the activity of a key enzyme in the glycolytic pathway, phosphofructokinase, and to enhance glucose transport. This raises questions about whether this is a necessary or useful adaptation, or one which might in the long run be deleterious, and whether the reversal of this change in metabolism would be helpful or harmful to the hypertrophied myocardium.

In addition to altered energy generation, some evidence suggests that changes in lipid and carbohydrate availability, independent of hypertrophy, may effect genetic control of important myocardial proteins. These include myosin isoenzymes. It is possible that other important structural and control proteins might also be altered by changes in substrate balance, but this has not been examined in depth. There are significant data that demonstrate that the availability and the type of substrate metabolized by the heart may affect the growth of the heart. For instance, GLUT-4-deficient mice develop cardiac hypertrophy in the absence of hemodynamic overload and mice with upregulated GLUT-1 genes and enhanced glucose transport develop hypertrophy. Thus, systolic overload and increased noninsulin dependent glucose uptake might work in concert to exaggerate the hypertrophy.

As noted previously, several genes related to lipid metabolism are downregulated in cardiac hypertrophy. Deficiency of the fatty acid transfer protein CD36 in rodent models may facilitate cardiac hypertrophy, and although mutations of this protein have been observed in certain persons with hypertrophic cardiomyopathy, a direct cause and effect relationship has been difficult to document.

It will be important to understand if the substrate relationships found in carefully controlled animal studies have relevance to hypertrophy in human hearts. Metabolic experiments conducted in isolated hearts from rodents perfused with aqueous media are useful in answering very specific metabolic questions such as the one addressed in the article by Nascimben et al. However, these are quite remote from studies in humans in which cardiac mechanics are difficult to control, in which blood contains a variety of substrates that compete for uptake by the heart, and in which neurohumoral influences are usually not controlled and frequently not
known. A few investigations have been reported in human hearts, but these are often in patients with end stage failure, and therefore may not be relevant to the compensated hypertrophic state.

Contrary to the animal data, there have been reports of increased fatty acid and decreased carbohydrate metabolism in failing human hearts and correction of glucose uptake by β-adrenergic blockade therapy. In one study in which glucose uptake was measured carefully in subjects with compensated hypertrophy, glucose uptake was similar in hearts from normal subjects, and in hearts from patients with hypertension either with or without hypertrophy. In patients with hypertension without cardiac hypertrophy, myocardial glucose uptake was increased, but only in proportion to the increase in cardiac work, suggesting an appropriate, but not disproportional rise in cardiac glucose metabolism. Currently, investigations in humans have been fragmentary, and few studies have explored substrate use in compensated hypertrophied hearts in humans using precise and convincing methods.

Because the current article implicates an alteration in energy balance initiating the increased glucose transport, it is useful to consider the state of energy balance in hypertrophied human hearts. There is evidence that defects in energy metabolism in the human heart can lead to hypertrophy, and this would be consistent with the findings in the current report. This comes mainly from hearts with genetic abnormalities in mitochondrial function, which are associated with cardiomyopathy in humans. It is of interest that one mutation site is AMP kinase, the same locus of activity as the current report.

Cardiomyopathies in humans are also associated with evidence of defects in energy stores, yet these abnormalities appear to occur in the more severe forms of hypertrophic cardiomyopathy. There are almost no investigations in patients with compensated hypertensive hypertrophy. Such studies would need to be coupled to careful measures of substrate utilization, and probably should explore the heart’s metabolic response to stress.

Finally, assuming that differences are found between hypertrophied human hearts and those of experimental animals, these might be due in some cases to hearts entering a stage of maladaption by the time of study, to species differences, and/or the likely probability that all types of hypertrophies, even in humans, do not respond in the same manner. Therefore, clarification of this confused area by rigorous investigations is essential.

It has been well substantiated that in the presence of hypertension in humans, cardiac hypertrophy is associated with increased arrhythmogenesis and decreased survival as compared with hypertensive individuals without myocardial hypertrophy. There is also evidence that reversal of hypertrophy is associated with improved outcomes in patients treated for hypertension. The mechanisms are unclear. Therefore, extending the exploration of metabolism to human hearts with compensated hypertrophy might lead to the development of preventive and therapeutic strategies.

References

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