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The healthy heart demonstrates remarkable metabolic
plasticity. Although it utilizes predominantly fatty acids
for ATP generation, it also has the capacity to derive energy
from glucose, ketones, lactate, and particular amino acids.1
Such fuel flexibility helps to maintain adequate provision of
chemical energy to fuel the unrelenting mechanical work of
the heart, especially under conditions of increased physiologi-
cal or pathological stress. A predominant line of thinking has
been that, because of this large energy demand, myocardial
metabolic derangements are likely to be causative in heart
failure. This seems reasonable because the heart hydrolyzes
nearly 20x its mass in ATP each day.1 It is, therefore, reason-
able to assume that decrements in ATP production caused by
dysregulation of fat or glucose oxidation would promote del-
erious changes in cardiac function and structure.

Numerous studies seem to support the concept that metabo-

lism is altered in the failing heart, with a general consensus
that, during the course of myocardial remodeling, the heart
switches from fatty acid preference to glucose use.2–4 This
switch is associated with decreased levels of high energy
phosphate reserves,1 suggesting that the failing heart is a
fuel-deficient organ. Nevertheless, our understanding of how
these metabolic changes occur, when they happen, and to
what extent they change is unclear. Even the direction of the
changes is still being debated. For example, numerous stud-
ies have clearly shown that fat oxidation capacity is decreased
in rodent models of heart failure1; yet, the results of clinical
studies are variable, showing that fatty acid oxidation in the
failing heart is diminished,5 augmented,6–8 or unchanged.9
Although the failing or hypertrophied heart may rely more on

glucose metabolism,1 recent studies have shown that actual
rates of glycolysis and glucose oxidation may be decreased,10
due in part to myocardial insulin resistance10–13 or decrements
in mitochondrial oxidative capacity.14 Undoubtedly, a better
understanding of the metabolic changes occurring in the dis-
eased heart would be helpful in developing metabolic thera-
pies to improve pump sustenance and function.

In this issue of Circulation: Heart Failure, Lai et al used
molecular profiling strategies to derive broad mechanistic
understanding of the metabolic changes that occur in differ-
ent forms of cardiac hypertrophy in mice.15 The authors used
a broad systems biology approach, using both unbiased tran-
scriptomic profiling and targeted quantitative metabolic pro-

filing, to understand the metabolic changes associated with
compensated cardiac hypertrophy, exercise-induced physi-
ological hypertrophy, and heart failure. Compensated hyperto-
phy, induced by transverse aortic constriction, and heart failure,
induced by a combination of transverse aortic constriction and
a small apical myocardial infarction, resulted in a defined set
of >1000 differentially expressed genes. Interestingly, most of
these transcriptional changes were in directional concordance,
despite the marked differences in cardiac structure and func-
tion between the 2 models. Unlike the transcriptional profiles,
metabolite changes were sufficient to dichotomize the groups:
the compensated hypertrophic heart showed relatively few dif-
ferences in the abundance of metabolites, whereas the failing
heart showed elevated levels of numerous acylcarnitine esters,
higher lactate levels, and altered abundance of Krebs cycle
intermediates. The authors suggest that such elevations in lac-
tate and acylcarnitine species and lower abundance of many
Krebs cycle intermediates is suggestive of a bottleneck of car-
on flux into mitochondria, which could diminish the capacity
of the heart to produce ATP. The modest differences in amino
acid abundance in the compensated and decompensated heart
could be further suggestive of dysregulation in the balance of
myocardial anabolic and catabolic pathways. Taken together,
these data suggest a critical and rate-limiting role of mitochon-
drial oxidative metabolism in cardiac metabolism and provide
further evidence for profound dysregulation of mitochondrial
metabolism in the failing myocardium.

The fusion of –omics strategies, such as that used by Lai et
al, has a remarkable potential for increasing our understand-
ing of how metabolic changes integrate and contribute to car-
diovascular disease. Illustrative of this power is the finding
that many metabolic changes in the hypertrophic heart are not
reflected in the transcriptional profile. With the exception of
fatty acid oxidation, which was inhibited in mitochondria iso-
lated from the failing heart and showed harmonious changes
in both the myocardial transcriptome and metabolome, there
were few changes in the expression of genes related with
mitochondrial function. This is a surprising finding given the

Editorial
Insights Into Metabolic Remodeling of the Hypertrophic
and Failing Myocardium

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The opinions expressed in this article are not necessarily those of the
editors or of the American Heart Association.

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numerous published studies showing reduced expression of electron transport chain proteins in the hypertrophied or failing heart. Such a result also raises many questions: (1) How can so many changes in metabolism occur without remarkable differences in the metabolic transcriptome? (2) Are different forms of hypertrophy caused, at some level, by metabolic changes or are metabolic changes simply reflective of altered cardiac structure and function? and (3) What do changes in each metabolic pathway tell us about cardiac growth and remodeling?

Post-translational regulation could be one explanation for some of the changes in metabolism that occur in the hypertrophied heart. This idea is most robustly supported by data showing remarkable differences in acylcarnitine and organic acid abundance in the hearts of mice subjected to voluntary wheel running, despite differential expression of only six genes compared with hearts of sedentary mice. Although this form of metabolic remodeling does not seem to require changes in gene expression, in the failing heart, both the transcriptomic and metabolomic data were congruent with the measured decrease in mitochondrial fat oxidation. Hence, these findings not only demonstrate converse changes in metabolism between physiological and pathological forms of hypertrophy, but they also suggest different mechanisms for regulating the same metabolic pathway. It seems that, in the failing heart, a bottleneck phenomenon occurs where mitochondrial carbon influx from fat and glucose catabolism is deficient, which is at least partially caused by downregulation of the fatty acid oxidation machinery. In the physiologically hypertrophied heart, however, these metabolic pathways are enhanced—the carbon valves for fat and glucose catabolism are effectively open—yet this does not require transcriptional changes. Thus, pathological hypertrophy seems to be associated more with transcriptional metabolic changes, whereas the exercised heart maintains fuel flexibility by regulating metabolism at the post-translational level. It would be of high interest and importance to identify the metabolic proteins and specific post-translational modifications involved in the regulation of myocardial metabolism, which may promote beneficial forms of cardiac hypertrophy. Potential candidates include acetylated, nitro(l)ated, or succinylated metabolic proteins, which could elicit changes in myocardial metabolism and educe structural and functional changes.

The current study provides evidence for dysregulation of other critical metabolic pathways as well. Modest changes in several amino acids in hypertrophied and failing hearts were associated with changes in the expression of genes involved in the degradation of proline, alanine, tryptophan, and branched-chain amino acids. Because amino acids are critical for anabolic processes underlying myocyte growth, it is possible that changes in amino acid uptake or intracellular catabolism could regulate nodal cell signaling pathways involved in the hypertrophic response (eg, mammalian target of rapamycin). Further work is required to shed light on the role of amino acid metabolism in heart failure.

Overall, the findings by Lai et al pave the way for future mechanistic studies on the role of specific metabolic transcriptional programs and post-translational modifications in heart disease. The work also underscores high discordance in the literature pertaining to metabolic changes in the hypertrophied and failing heart. Are disagreements in glucose and fatty acid metabolic changes in the failing heart caused by species- or model-specific differences? Lai et al used female mice, whereas most other studies have predominantly used male mice. Are discrepant findings in lipid metabolism, for example, caused by such sex differences or are they caused by dissimilar procedural protocols? These are important questions that must be addressed to further clarify the role of metabolism in heart failure. Without doubt, the work by Lai et al is a first step toward opening productive dialogue on these issues, while at the same time illustrating the potential of multisystems approaches for unveiling new insights on the role of metabolism in cardiac remodeling.

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References


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