The astonishing observation that the human heart beats at least 100,000 times a day and cycles through up to 30 kg of ATP daily (the energy required to climb a 100-story building) vividly illustrates the pertinence of energy metabolism to both cardiac health and disease. A key determinant of the efficient energy generation capacity of the heart is the pattern of cardiac substrate utilization. Although studies, such as the seminal coronary sinus sampling observations made by Richard Bing and colleagues that delineated the patterns of cardiac substrate metabolism, have informed our understanding of cardiac biology, their greatest limitation derives from the small number of “biased” candidate metabolites they have surveyed. Metabolomics, which seeks to comprehensively analyze and dynamically quantify many of the metabolites in biological samples, may thus be regarded as the logical sequitur to traditional substrate studies.

Metabolomic studies, ranging from the assessment of atrial sinus sampling in stress-induced cardiac ischemia and myocardial infarction, have accordingly already yielded insights into the metabolic sequelae of these disorders. This application of “systems biology” approaches to disentangle the complex biological variation underlying health and disease (eg, genome, transcriptome, proteome, “posttranslation-ome,” metabolome, and intestinal bacterial microbiome and environment) is one of the principal aims of contemporary biology. Metabolomics is exemplary in this regard, because the convergence of the different levels of biological organization onto a relatively small number of known and phylogenetically conserved metabolites (∼3000 in total) renders the metabolome more tractable and temporally/functionally closer to disease than analyses based on the other “-omics.”

Having emerged from the metabolic control theory of the 1960s, it is only with advances in nuclear magnetic resonance spectroscopy and mass spectrometry (MS) that metabolomics has recently prospered. However, although metabolomics has proved powerful in model organisms and refinements continue to facilitate high-throughput sampling, processing, and analysis, it has a number of limitations. These include: the lack of a systematized method for metabolite extraction; a bias to only the most abundant or processable chemical metabolites (MS and magnetic resonance spectroscopy require concentrations of at least 10⁻¹² mol and 10⁻⁷ mol, respectively); the lability of metabolites that require stringent extraction (eg, phosphocreatine and ATP); heterogeneity in human metabolic profiles; confounding variables (eg, age, gender, stress, comorbidity, pharmacotherapy, diet, and factors as diverse as the intestinal microbiome); the complexity of extrapolating from spectral “fingerprints” associated with a trait to identify specific molecules as mechanistic, diagnostic, or therapeutic targets; and the requirement for large studies to overcome the statistical limitations of multiple testing.

Accordingly, in this issue of Circulation, Turer et al, using an MS-based metabolomics approach (63 metabolites), provide a detailed metabolic account of the consequences of ischemia-reperfusion (I/R) in 37 consecutive patients who underwent coronary sinus blood sampling at serial time points during cardiac surgery. Importantly, by using patients as their own controls at different time points, Turer and colleagues reduced interpatient heterogeneity (increasing signal:noise ratio). The authors convincingly demonstrate that the preexisting baseline suppression of net substrate utilization in diseased hearts is exacerbated by surgical I/R when compared with control hearts. This effect is especially pronounced in those with left ventricular dysfunction and is associated with adverse hemodynamic sequelae. Finally, the authors propose that citric acid cycle (TCA) activity may have been compromised, as evidenced by the decreased uptake of anaplerotic glutamate and increased release of acetyl-carnitine/β-hydroxybutyryl-carnitine.

The broader applicability of these findings is qualified by the general challenges of metabolomics, the relatively small size of the cohort, the inevitable (but nevertheless confounding) nature of patient and procedural nonuniformity, and the necessity to use patients with valvular heart disease as “controls.” Furthermore, as the authors acknowledge, although the measurement of net arteriovenous differences in metabolites can be informative, drawing more incisive biological conclusions without a detailed account of metabolic fluxes can be challenging. An example of the limitations of inferring substrate metabolism from arteriovenous sampling relates to the assessment of myocardial glucose and lactate uptake. Because myocardial carbohydrate extraction and release occur concurrently, the measurement of net arteriovenous metabolite differences underestimates their flux. Thus, whereas myocardial glucose utilization, as added...
from arteriovenous differences, does not appear to increase (and may even decrease) during moderate exercise, radiolabeled substrate studies have revealed that lactate and glucose fluxes increase significantly.14

Such considerations notwithstanding, The central observations of Turer et al are broadly in line with the existing cardiac metabolism literature.1,3,4 Although the healthy heart is a “metabolic omnivore,” capable of matching its substrate use to changing demand, the diseased heart appears to be less metabolically flexible.15 This dysmetabolic profile is exaggerated in heart failure. Thus, even though in early heart failure, free fatty acid (FFA) metabolism may be increased, the metabolic remodeling of advanced heart failure is characterized by panmetabolic downregulation.4 The shift to FFA metabolism in early heart failure is especially relevant to ischemic heart disease where oxygen is at a premium. Theoretically, FFAs require ~13% more oxygen than carbohydrates do to generate the same amount of ATP. Experimental studies suggest that FFA-using hearts may actually experience a 27% to 54% “oxygen-waste.”3,4 Thus, proposition of Turer et al that I/R superimposed on left ventricular dysfunction contributes to poorer surgical outcomes, because of the adverse metabolic profile, is plausible.

The mechanisms for the panmetabolic downregulation are increasingly well understood. In part, the reduction in FFA metabolism is explained by the downregulation of peroxisome proliferator-activated receptor α-regulated gene expression.3,15 Reduced carbohydrate metabolism is attributable to reduced pyruvate dehydrogenase complex activity. Pyruvate dehydrogenase facilitates the flow of carbohydrate carbon units from the cytoplasm (eg, from glycolysis) to the mitochondrial TCA cycle.3 In ischemia, the activation of the pyruvate dehydrogenase kinases inhibits pyruvate dehydrogenase via phosphorylation. As a corollary, restoring the mitochondrial TCA cycle. Nevertheless, irrespective of these methodological considerations, TCA cycle intermediates potentially have a fundamental role in modifying the myocardial metabolic response to hypoxia and deserve greater attention.19 For example, although changes in the concentrations of these intermediates in coronary sinus effluent are likely to be a marker of adaptive/maladaptive alterations in intermediary metabolism,7–9,12 these metabolites may have additional/alternative roles in myocardial signaling. G-protein–coupled receptors for both succinate and β-hydroxybutyrate have been identified (GPR9120 and GPR109a,21 respectively). Even though a role for succinate and GPR91 in myocardial ischemia remains to be established, this pathway has been shown to regulate the production of factors such as vascular endothelial growth factor in ischemic retinopathy.20

Systems biology strives to shift us away from traditional reductionist biological paradigms11 toward a more systematic approach to (1) identifying novel pathways for functional investigation, (2) delineating novel biomarkers, and (3) providing a rationale for targeted therapeutics.10,12 Although we should be cautious about the significance of the results of any single study purporting to achieve these goals pending replication in larger populations and functional biological validation, in light of their concordance with an existing body of literature, The observations of Turer et al provide a rationale to augment myocardial (particularly carbohydrate) metabolism, peri cardiac surgery. Established therapies such glucose-insulin-potassium (GIK), dichloroacetate, or partial fatty acid oxidation inhibitors represent obvious candidates for such trials.3 As a note of caution, however, it is possible (though relatively unlikely based on experimental data)10 that in I/R, acute metabolic downregulation (perhaps mediated by hypoxia-inducible factor [HIF] 1α) is actually beneficial. Driving substrate metabolism during ischemia might therefore adversely affect parameters such as cellular redox state (NADH/NAD+ ratio) and potentially result in harm.

It is likely that the “Human Metabolome Project” (the metabolic analogue of the “Human Genome Project”) will facilitate metabolome-wide association studies (relating “metabotypes” to disease) and will contribute to the development of personalized medicine.6,10 Such endeavors are expected to untangle some of the underlying complexities of 
biology and bring metabolomics closer to clinical practice. However, the success of systems biology will likely be founded on the systematic integration of the complementary, -omic technologies to provide a comprehensive account of how different biological levels interact in time and space.\textsuperscript{11} Such analyses should identify the networks that regulate cellular behavior and that insulate cells from the vagaries of environmental and genetic perturbations that result in disease.\textsuperscript{11} The ultimate potential of these techniques will only be realized if they are fully integrated into and informed by traditional hypothesis-driven investigative biology and by clinical translational studies. Such an integrated approach will maximize our capacity to capture, visualize, and act on the complex biology of systems and to significantly influence their pathological alterations.

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None.

**References**

Metabolomic Profiling of Cardiac Substrate Utilization: Fanning the Flames of Systems Biology?
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