Metabolic Staging in Human Heart Failure
Circulating Acylcarnitines and the Failing Heart’s Energetic Signature*

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In this issue of the Journal, Ahmad et al. (1) report on an important novel metabolic phenotype assayed in peripheral blood that is associated with human heart failure (HF). Their study identified circulating metabolites that hold prognostic and potentially mechanistic insights toward a more complete understanding of HF disease progression. These metabolites, measured with high precision in plasma using tandem mass spectroscopy with the addition of internal standards, not only provided prognostic information, but did so in a HF stage-dependent manner.

The authors should be congratulated on the study design: first identifying the metabolite groups that were associated with peak oxygen consumption obtained during baseline testing for the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial, then subsequently finding the circulating metabolites associated with the outcome of all-cause mortality and hospitalization adjudicated within the trial. Finally, in an independent cohort of advanced HF patients who required mechanical assist device support, the investigators found increased plasma metabolite levels in those subjects with American College of Cardiology/American Heart Association stage D HF compared with those with chronic, less advanced HF. These levels returned to those associated with a less severe phenotype with the reversal and restaging of HF that has been reported with left ventricular assist device therapy (2,3).

What are these metabolites of interest and how significant are they in elucidating the metabolic adaptations taking place in human HF? The metabolites—long-chain acylcarnitines—represent an important subgroup of lipids for fatty acid oxidation in muscle and liver. Thus, altered circulating levels of an acylcarnitine species may reflect a specific metabolic deficit, which, if corrected, would allow for the metabolic flux to be restored within a certain pathway. The essential questions to ask here: what metabolic alteration in human HF produces the increased circulating long-chain acylcarnitines, and where are these metabolite species identified by Ahmad et al. (1) originating from?

Recent work from several groups has contributed to the characterization of a “metabolic signature” in human HF. The components described thus far include: 1) systemic and myocardial insulin resistance; 2) weight loss resulting in cachexia; 3) a metabolic switch from the predominant fatty acid oxidation for substrate utilization to generate acetyl-coenzyme A (CoA) to glucose oxidation in the failing myocardium; and 4) mitochondrial dysfunction in the process of downstream substrate oxidation (Krebs cycle and oxidative phosphorylation). This new paper by Ahmad et al. (1) overlines another facet of the failing metabolic phenotype: increased circulating acylcarnitines, especially those derived from the most
abundant dietary fatty acids (C16, C18) common with worsening stages of HF.

Whereas the authors provided strong evidence for this novel metabolic phenotype associated with HF progression, they proposed a mechanism that ultimately may not prove to be true. To wit, the authors suggested that the increased signal for peripheral long-chain acylcarnitines is derived from a failing heart that is not capable of utilizing this energetic lipid pool due to deficiency in the carnitine palmitoyl transferase system (CPT1/CPT2) and carnitine acylcarnitine translocase systems of acyl-CoA transport. However, it is not fully established that these systems of fatty acid oxidation are necessarily decreased in nondiabetic, lean HF patients, especially in the more advanced stage associated with worse outcomes and requiring mechanical assist device support. It may be the case that the rate of fatty acid oxidation exceeds the flux of the tricarboxylic acid (Krebs) cycle, and the feedback from this leads to decreased processing of acylcarnitines, in turn leading to effective efflux of acylcarnitines into the plasma pool (5–7). Some studies have found that the intramyocardial acylcarnitine pool is decreased in HF (7,8), thus refuting this as a possible mechanism and the heart as a possible source of effluxed long-chain acylcarnitines into the peripheral blood. As suggested by the authors, not only is the source of the circulating long-chain acylcarnitines of interest in determining the active sites of lipid turnover in HF, but the peripheral acylcarnitine excess may affect the state of systemic insulin resistance via mechanisms yet to be determined, but that most likely involve chronic neurohormonal activation (9).

Because our group and others have identified increased circulating nonesterified fatty acids and ketones (7,10) to be characteristic of the peripheral milieu in advanced nondiabetic human HF, an
alternative mechanism could explain the key finding by Ahmad et al. (1) of increased long-chain acylcarnitines in the plasma (Figure 1). Here, the sustained lipolysis due to chronic activation of both the sympathetic and natriuretic peptide systems in HF (11,12) results in overload of peripheral free fatty acids, while the peripheral adipocyte mass is depleted in a cachectic phenotype. The free fatty acid overload is handled primarily by the liver, where increased fatty acid oxidation may exceed downstream pathways to further oxidize acetyl-CoA, resulting in a state of active hepatic ketogenesis and acylcarnitine efflux to the plasma compartment to prevent CoA trapping and hepatic lipotoxicity (13). As our recent data suggest that the failing myocardium in end-stage HF utilizes ketones that are readily available from the periphery (14), a more complete and consistent signature of metabolic adaptations in chronic human HF may finally be emerging (Figure 1).

The strong evidence provided in this new paper that the long-chain acylcarnitine pool may be an important intermediate phenotype is central to this understanding of the metabolic stages in human HF and may allow for the development of therapeutic interventions that heretofore have not been considered for restaging this chronic syndrome in humans.

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REFERENCES


KEY WORDS left ventricular assist device, phenotyping