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Review article

Using metabolomics to assess myocardial metabolism and energetics in heart failure☆

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ABSTRACT

There is a long history of investigation into the metabolism of the failing heart. Congestive heart failure is marked both by severe disruptions in myocardial energy supply and an inability of the heart to efficiently uptake and oxidize fuels. Despite the many advancements in our understanding, there are still even more outstanding questions in the field. Metabolomics has the power to assist our understanding of the metabolic derangements which accompany myocardial dysfunction. Metabolomic investigations in animal models of heart failure have already highlighted several novel, potentially important pathways of substrate selection and toxicity. Metabolomic biomarker studies in humans, already successfully applied to other forms of cardiovascular disease, have the potential to improve diagnosis and patient care. This article is part of a Special Issue entitled 'Focus on Cardiac Metabolism'.

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Contents

1. Introduction

Heart failure (HF) is estimated to affect approximately 6.6 million patients in the U.S. alone, underscoring its significant public health and economic impact. Unfortunately, with HF risk factors (e.g. obesity, diabetes) on the rise globally, an increasing incidence can safely be predicted (25% by 2030 in the U.S.) [1].

While advances in medical therapy (e.g. ACE-inhibitors, β-blockers) have significantly improved the quality of life and survival of patients with HF, morbidity and mortality from this condition are still high. Hospitalizations for HF have remained stable over the past decade [2], and once the diagnosis of HF has been made, future hospitalizations are common (>80%) [3]. Ultimately, half of patients with HF will die within 5 years of the diagnosis [2,4]. These statistics support the need to find

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complementary treatments for HF and to identify patients at high risk for disease progression.

As will be discussed below, the metabolism of the failing heart is profoundly perturbed from its baseline state. For this reason, it has been an attractive target not only for pharmacologic intervention, but biomarker and pathway discovery, as well. This review will focus on what we know about cardiac metabolism in HF and what additional insights the exciting field of *metabolomics* has given us into this condition.

2. The failing heart is energy-depleted

The normal heart must generate impressive amounts of adenosine triphosphate (ATP) daily to supply the needs of its contractile elements and ion pumps. However, in the failing heart total myocardial ATP levels are significantly reduced by ~40% through a variety of mechanisms [5,6. Indeed, the entire intramyocellular pool of adenosine nucleotides is depleted in HF [6].

Although the ultimate source of ATP generation is derived from glycolyic and oxidative metabolism, the creatine kinase (CK) system provides an important system of buffering to maintain cellular ATP levels by rapidly transferring high-energy phosphates from phosphocreatine (PCr) to ADP [7,8]. In the context of HF, human studies have shown that there is a drop in total CK activity ~20–45% and a shift in CK-isoform distribution [9–11]. The CK enzymes are important components of a spatially-localized metabolic relay which link high-energy phosphate production (i.e. mitochondria) and use (i.e. sarcomeric proteins) to ensure efficient and rapid energy transfer without the need to equilibrate the ATP supply with the bulk of sarcoplasmic pools [12]. Defects in this system lead to ultrastructural [13] and molecular remodeling [14] which may have more substantial consequences to efficient energy exchange in HF than gross measures of total ATP levels alone might indicate.

In parallel with CK, levels of its substrate, creatine, are reduced by as much as half in the failing heart [10], likely secondary to the downregulation of the creatine transporter responsible for myocardial uptake of this metabolite from the circulation [15]. Levels of the plasma membrane isoform of this transporter appear to regulate intracellular creatine concentrations [16]. What, in turn, regulates the creatine transporter is unclear, but in the setting of renal epithelium, at least, AMP-kinase is involved [17]. If also the case in the heart, this would conceivably link intracellular energy-sensing and creatine levels.

Paradoxically, however, transgenic overexpression of the creatine transporter leads to a *decrease* in ATP levels and impairment in LV function despite a significant increase in myocardial creatine concentrations and the PCr/ATP ratio [18]. This unexpected finding, taken together with the fact that mice lacking both the myofibrillar- and mitochondrial-CK isoforms do not develop overt HF [19], emphasizes the difficulty in assigning a causal role of impaired energy reserve and transfer in the development of HF. However, a recently-described myofibrillar CK conditional overexpressing mouse was shown to have improved contractile function and survival following afterload-induced LV dysfunction, again bringing the potential causal importance of the CK-system back to the fore [20].

The failing heart is characterized by low intracellular concentrations of high-energy phosphates — both in the form of adenosine nucleotides, as well as shuttles, such as phosphocreatine. But what causes this low-energy state?

3. Substrate selection and oxidation

The heart is normally a promiscuous user of metabolic substrates. Although the heart extracts glucose, lactate, ketone bodies, and amino acids, fatty acid oxidation accounts for the majority of ATP production (70–90%). Whereas, glucose levels are kept fairly constant under normal conditions, levels of non-esterified fatty acids (NEFAs) can vary dramatically over the course of the day. The myocardium is, nonetheless, able to constantly extract circulating NEFAs via both passive and active transport mechanisms, e.g. CD36. Once intracellular, fatty acids are esterified to their cognate acyl-CoAs in the cytoplasm and transported via the carnitine shuttle across the mitochondrial matrix. Successive rounds of β-oxidation result in two-carbon units which enter the TCA cycle (along with the acetyl-CoA from pyruvate decarboxylation).

Although NEFAs provide the bulk of the heart's fuel, the flexibility to utilize an array of substrates appears important to normal cardiac function. Murine models of either excessive myocardial glucose [21,22] or fatty acid [23–26] delivery lead to cardiac dysfunction. In humans, the situation is similar although certainly more complex. There have been no GLUT4 (SLC2A4) null humans described to date, and patients with GLUT1-deficiency have prominent neurological but no described cardiac phenotypes. The closest clinical correlate is probably the so-called "diabetic cardiomyopathy" — a state of myocardial insulin-resistance and disproportionate reliance on fatty acid oxidation — which results in a range of reported diastolic and systolic abnormalities [27]. At the other end of the spectrum, inborn errors of fatty acid metabolism, such as carnitine uptake deficiency, very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency and L-3-OH acyl-CoA dehydrogenase (LCHAD) deficiency, are very clearly associated with cardiomyopathies (either hypertrophic or dilated), and which may improve with dietary therapy [28–30]. These facts demonstrate that HF may develop under conditions in which the high energy demands of the heart cannot be satisfied by adequate fatty acid utilization.

To this point, abnormalities in several sites of fatty acid metabolism have been noted to accompany HF, including fatty acid transport [31], oxidation [31–34], and respiratory chain [35–37]. Such observations have been noted in both animal models and human patients with LV dysfunction. Thus, it is a widely held belief that HF is associated with a shift towards (presumably non-oxidative) glycolytic metabolism, i.e. recapitulating a "fetal phenotype" [38,39]. It should be stressed, however, that the timing and directionality of 'substrate-switching' in human patients with HF is still a contentious notion [40], particularly the relatively small number of patients studied to date relative to variety of clinical stages (i.e. New York Heart Association class) and etiologies of LV dysfunction. Some studies have shown increased glucose/lower fatty acid uptake with patients with HF [41,42], while others have not [43–48].

While a considerable amount about myocardial metabolism and energetics during cardiac failure may be known, there is clearly much yet to learn. What are the roles of alternative substrates in HF? Are any other biochemical pathways relevant in the progression of HF? Do metabolic 'signatures' change as HF progresses or during episodes of clinical decompensation? These types of discovery questions are ideally suited to a relatively new branch of metabolic investigation — *metabolomics*.

4. What can metabolomics tell us about metabolism in HF?

4.1. What is metabolomics?

The classic paradigm regarding the flow of cellular information recognizes the progression of DNA → RNA → protein, but small-molecule metabolites may, in many cases, be the ultimate product of this sequence (Fig. 1). The goal of metabolomics is to interrogate the *metabolome* using traditional spectroscopic techniques borrowed from analytic chemistry, most notably mass spectrometry (MS)- and nuclear magnetic resonance (NMR)-based methods [49]. These techniques allow for simultaneous interrogation of multiple (several-to-hundreds, depending on the method employed) metabolites in the same biological sample. Correspondingly, the exact identity of the analytes under investigation may be known (targeted) or unknown (unbiased). To assist the investigator with interpretation of data, the Human Metabolome Database has annotated information on ~8000 human metabolites [50].

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