

Comprehensive quantification of fuel use by the failing and nonfailing human heart

Danielle Murashige^{1 *}, Cholsoon Jang^{2 *†}, Michael Neinst^{1 ‡}, Jonathan J. Edwards³, Alexis Cowan², Matthew C. Hyman⁴, Joshua D. Rabinowitz², David S. Frankel⁴, Zolt Arany^{1 §}

¹ Perelman School of Medicine, Cardiovascular Institute, University of Pennsylvania, Philadelphia, PA 19104, USA. ² Department of Chemistry and Lewis-Sigler Institute for Integrative Genomics, Princeton University, Princeton, NJ 08544, USA. ³ Department of Pediatrics, Division of Pediatric Cardiology, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA. ⁴ Division of Cardiovascular Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA. *These authors contributed equally to this work. †Present address: Department of Biological Chemistry, University of California Irvine, Irvine, CA 92697, USA. ‡Present address: Department of Chemistry and Lewis-Sigler Institute for Integrative Genomics, Princeton University, Princeton, NJ 08544, USA

The heart consumes circulating nutrients to fuel lifelong contraction, but a comprehensive mapping of human cardiac fuel use is lacking. We used metabolomics on blood from artery, coronary sinus, and femoral vein in 110 patients with or without heart failure to quantify the uptake and release of 277 metabolites, including all major nutrients, by the human heart and leg. The heart primarily consumed fatty acids and, unexpectedly, little glucose; secreted glutamine and other nitrogen-rich amino acids, indicating active protein breakdown, at a rate ~10 times that of the leg; and released intermediates of the tricarboxylic acid cycle, balancing anaplerosis from amino acid breakdown. Both heart and leg consumed ketones, glutamate, and acetate in direct proportionality to circulating levels, indicating that availability is a key driver for consumption of these substrates. The failing heart consumed more ketones and lactate and had higher rates of proteolysis. These data provide a comprehensive and quantitative picture of human cardiac fuel use.