

# Featured research

## Abstracts and commentaries

### Metabolic profiling reveals distinct patterns of myocardial substrate use in humans with coronary artery disease or left ventricular dysfunction during surgical ischemia-reperfusion

Turer AT, Stevens RD, Bain JR, et al. *Circulation*. 2009;119:1736–1746.

Human myocardial metabolism has been incompletely characterized in the setting of surgical cardioplegic arrest and ischemia-reperfusion. Furthermore, the effect of the pre-existing ventricular state on ischemia-induced metabolic derangements has not been established. We used a technique based on mass spectrometry to profile 63 intermediary metabolites in serial paired peripheral arterial and coronary sinus blood effluents obtained from 37 patients undergoing cardiac surgery, stratified by presence of coronary artery disease and left ventricular dysfunction. The myocardium was a net user of a number of fuel substrates before ischemia, with significant differences between patients with and without coronary artery disease. After reperfusion, significantly lower extraction ratios were found for most substrates, in addition to significant release of two specific acylcarnitine species, acetyl carnitine and 3-hydroxybutyryl carnitine. These changes were especially evident in patients with impaired ventricular function, who exhibited profound limitations in the extraction of all forms of metabolic fuel. Principal component analysis highlighted several metabolic groupings as potentially important in the postoperative clinical course. We conclude that the pre-existing ventricular state is associated with significant differences in myocardial fuel uptake both at baseline and after ischemia-reperfusion. The dysfunctional ventricle is characterized by global suppression of the uptake of metabolic fuel and limited myocardial metabolic reserve and flexibility after global ischemia-reperfusion stress in the setting of cardiac surgery. Altered metabolic profiles after ischemia-reperfusion are associated with the postoperative hemodynamic course and suggest a role for perioperative metabolic monitoring and targeted optimization in cardiac surgical patients.

### Commentary

This study by Turer et al determined which energy substrates are used in patients undergoing elective cardiac surgical procedures that included planned placement of a coronary sinus catheter for the delivery of retrograde cardioplegia. This was achieved utilizing a technique of metabolomic profiling that was based on mass spectrometry, to analyze the transmyocardial extraction of a number of important energy substrates both before aortic cross-clamping (ischemia) and during reperfusion. The study population was divided into three cohorts: control patients (valvular lesions with normal systolic function/normal coronary arteries;  $n=17$ ), patients with coronary artery disease (CAD) (luminal stenosis  $>50\%$ ;  $n=12$ ), and patients with left ventricular dysfunction (LVD) (left ventricular ejection fraction  $<45\%$ ;  $n=10$ ).

Before ischemia there was no difference in the absolute extraction ( $\mu\text{mol/L}$ ) of glucose, lactate, or fatty acids between control patients, those with CAD, and those with LVD. However, during reperfusion after ischemia, glucose, lactate, and fatty acid extraction persisted only in control patients. The values for glucose and fatty acid extraction were clearly suppressed during reperfusion in the control patients; however, the relative proportion of fatty acid/glucose extraction nearly doubled. During reperfusion, defects in glucose uptake (ie, net glucose elution) coupled to net lactate release were observed in patients with CAD and LVD, with continued extraction of fatty acid. Thus, although depressed compared with pre-ischemic values, fatty acid extraction did persist during reperfusion, and probably represented the major substrate contributing to myocardial ATP requirements. Importantly, during this time period, the increased reliance on fatty acids as a metabolic fuel probably uncoupled glycolysis and glucose oxidation at the level of pyruvate dehydrogenase, as indicated by transmyocardial lactate release. Furthermore, during reperfusion, the apparent relative reliance on fatty acids as a metabolic fuel was accompanied by net myocardial release of  $\beta$ -hydroxybutyryl carnitine, which has been implicated as a marker of incomplete fatty acid oxidation,

particularly when the supply of fatty-acid-derived acetyl coenzyme A exceeds the capacity of the tricarboxylic acid cycle to utilize it. An important clinical correlate of these findings was that the need for post-operative inotropic support, both immediately after cardiopulmonary bypass and during the stay in the intensive care unit, was greater in patients manifesting net lactate release compared with those who exhibited continued lactate extraction and, hence, continued myocardial carbohydrate oxidation.

This study has important implications for the utilization of metabolic modulation as a therapeutic strategy in the treatment of ischemic heart disease. It implies that incomplete fatty acid oxidation can decrease ventricular performance, and thus can necessitate the requirement for inotropic support

during reperfusion in the clinical setting. Furthermore, this study supports the concepts, (1) that there is an increased relative reliance on fatty acids as a metabolic fuel during reperfusion after ischemia and (2) that shifting energy substrate preference from the use of fatty acids to the use of carbohydrates as an oxidative fuel can limit cardiac dysfunction in the setting of ischemic heart disease. These findings warrant future studies assessing the ability of partial fatty acid  $\beta$ -oxidation inhibitors to reduce incomplete fatty acid oxidation as a potential mechanism contributing to cardioprotection in both experimental and clinical settings.

*Jagdip S. Jaswal and Gary D. Lopaschuk*

---