Nature Reviews Cardiology | Published online 5 Oct 2017; doi:10.1038/nrcardio.2017.158

V. Summersby/Macmillan Publishers Limited

IMAGING

Mitochondria shine light on heart function

> “monitoring of mitochondria on the epicardial surface can predict the onset of cardiac arrest”

A novel technique that relies on continuous monitoring of mitochondria on the epicardial surface can predict the onset of cardiac arrest, according to a study in animal models of ischaemia and hypoxaemia. “We were able to visualize cellular energetics in real time, identifying the time when the myocardium is so energy deficient that it cannot function properly,” says co-lead investigator John Kheir.

Current assessment of adequacy of oxygen delivery to tissues involves monitoring of blood markers such as the oxygen extraction ratio, serum lactic acid, or markers of tissue injury; “these metrics provide only surrogate measures of tissue injury or ischaemia,” points out Kheir. “The purest determinant of how much oxygen a cell needs is the flux of electrons within the electron transport chain (ETC),” he says. The mitochondrial ETC contains multiple cytochrome complexes that can have different redox states in response to oxygen availability. “We realized that we could create a clinically relevant measure by looking at the entire mitochondrial ETC as a binary (reduced/oxidized) entity,” explains co-lead investigator Daryoosh Vakhshoori.

Previous studies used resonance Raman spectroscopy (RRS) — a technique in which differences in vibrational spectra are used to measure a redox-state spectral signature of a molecule — to measure the spectra of mitochondrial proteins or to estimate semiquantitatively the cytochrome redox state in isolated myocytes or in isolated, bloodless hearts. “We believed we could enhance the RRS platform to quantify the fraction of oxidized versus reduced mitochondrial cytochromes in living tissue,” explains Kheir. Vakhshoori’s group had previously developed a microvascular oximeter based on RRS with noninvasive probes for peripheral measurements. The research team built a new laser and a high-throughput, high-resolution spectrometer, developed a chemical RRS library, and created an algorithm to define a new metric, the resonance Raman reduced mitochondrial ratio (3RMR), which quantifies the reduced fraction of specific ETC cytochromes.

ETC cytochromes become more reduced under hypoxic conditions, which leads to higher 3RMR values. Indeed, myocardial 3RMR increased from $18.1 \pm 5.9\%$ at baseline to $44.0 \pm 16.9\%$ after inferior vena cava occlusion in rats. Of note, continuous 3RMR measurement predicted subsequent cardiac arrest in rat models of prolonged hypoxaemia: a 3RMR of >40% at 10 min predicted subsequent cardiac arrest with 95% sensitivity and 100% specificity (area under the curve (AUC) 0.98), outperforming currently used measures such as contractility (AUC 0.51) and ejection fraction (AUC 0.39). The 3RMR measurement also correlated with indices of intracellular redox state and energy production in a pig model of myocardial ischaemia–reperfusion. “This is the first demonstration that RRS can determine, in real time, whether the cells in live, blood-perfused tissues are receiving enough oxygen to meet their demand,” comments Kheir.

The research team plans to continue investigating the clinical applications of this technique, to monitor not only the heart, but also other organs, for example, during transplantation, or to monitor whole-body oxygen delivery.

Irene Fernández-Ruiz

ORIGINAL ARTICLE Perry, D. A. *et al.* Responsive monitoring of mitochondrial redox states in heart muscle predicts impending cardiac arrest. *Sci. Transl Med.* **9**, eaan0117 (2017)