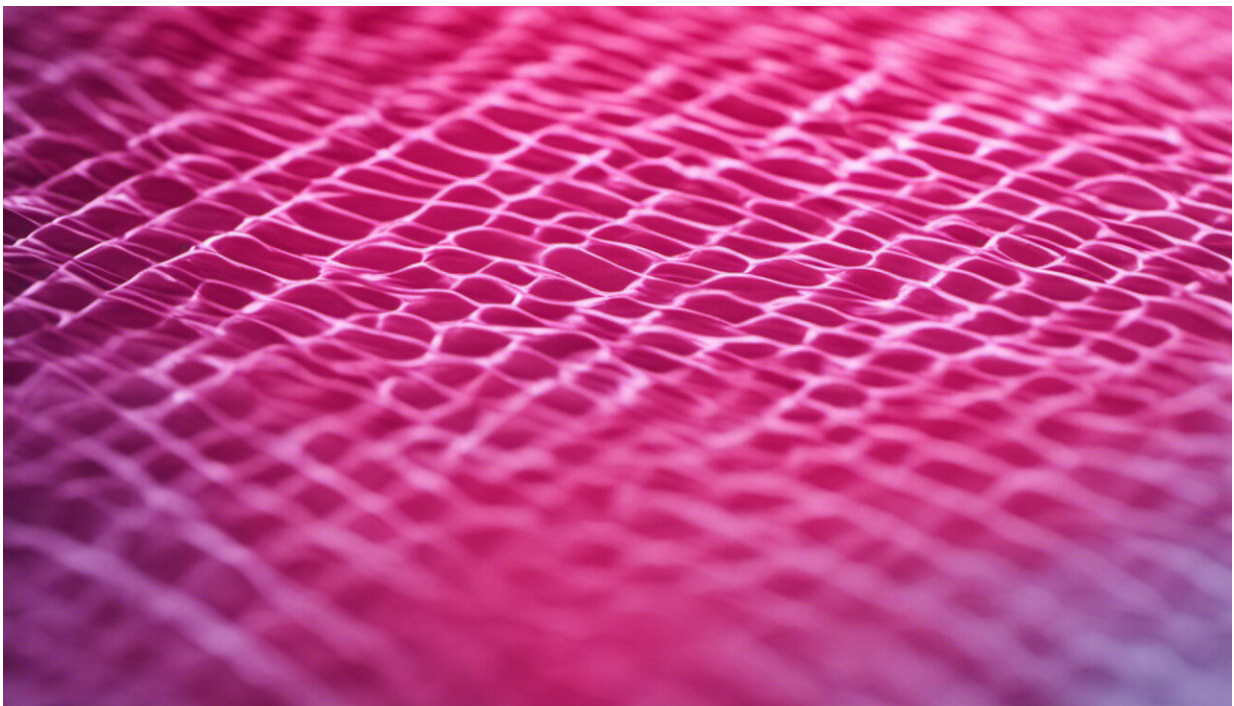# Laser device placed on the heart identifies insufficient oxygenation better than other measures

September 20 2017

Credit: AI-generated image (disclaimer)

A new device can assess in real time whether the body's tissues are receiving enough oxygen and, placed on the heart, can predict cardiac arrest in critically ill heart patients, report researchers at Boston Children's Hospital and scientists from Cambridge device maker Pendar

Technologies. Their study, conducted in animal models, is the cover article in today's issue of *Science Translational Medicine*.

"With current technologies, we cannot predict when a patient's heart will stop," says John Kheir, MD of Boston Children's Heart Center, who co-led the study. "We can examine heart function on the echocardiogram and measure blood pressure, but until the last second, the heart can compensate quite well for low oxygen conditions. Once cardiac arrest occurs, its consequences can be life-long, even when patients recover."

The device uses a technology called resonance Raman spectroscopy to measure whether enough oxygen is reaching the mitochondria, the organelles that provide cells with energy. In critically ill patients with compromised circulation or breathing, oxygen delivery is often impaired, making it hard for mitochondria to do their job. This is especially a problem for the heart, which has constant high energy needs.

The current standard for measuring tissue oxygenation, known as mixed venous saturation (SvO2), requires repeated blood draws, adding extra risk in critically ill patients. More importantly, SvO2 cannot tell whether oxygen supply is sufficient to meet the dynamic demands of heart muscle.
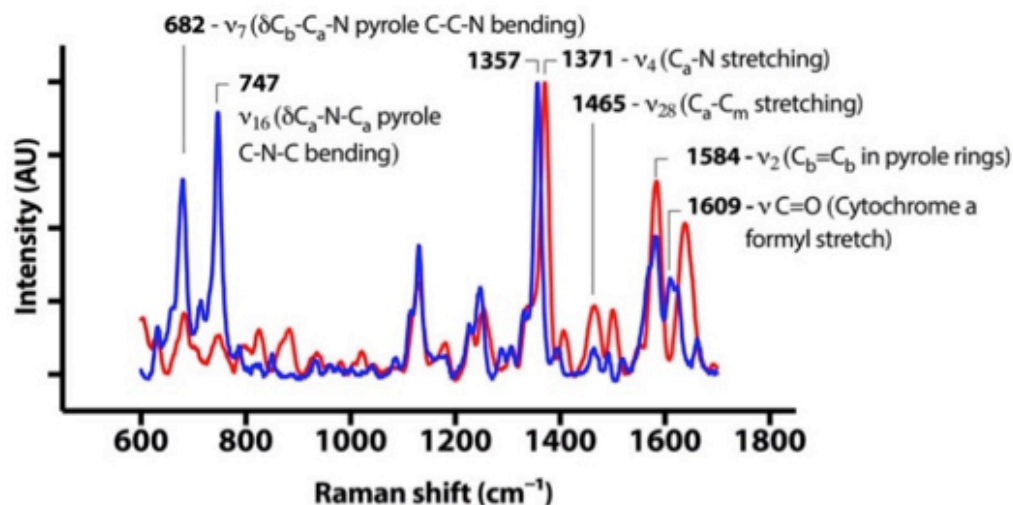
"We wanted to create an organ-specific, continuous, reliable readout of how adequately mitochondria are being fed oxygen," says Kheir. "This is the first demonstration of a device that can monitor mitochondria in living tissues to predict impending organ failure."
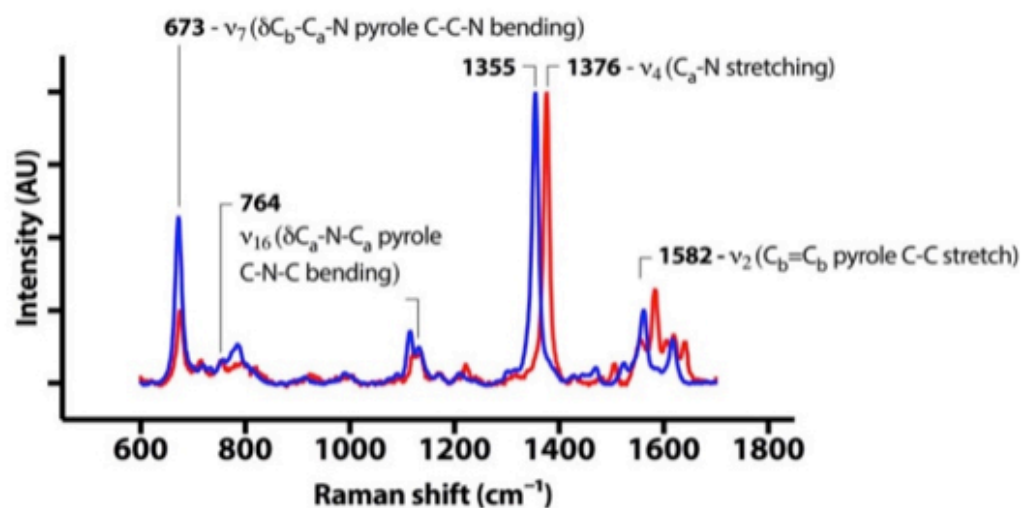
Using light to monitor mitochondria

This technology is the product of a collaboration between the Translational Research Lab in Boston Children's Heart Center, co-led by Kheir and Brian Polizzotti, PhD, and Pendar Technologies (Cambridge,

Mass.). "At the bedside, we saw patients who had a limitation to coronary blood flow, and wanted a device that could provide an early warning sign," Kheir says.
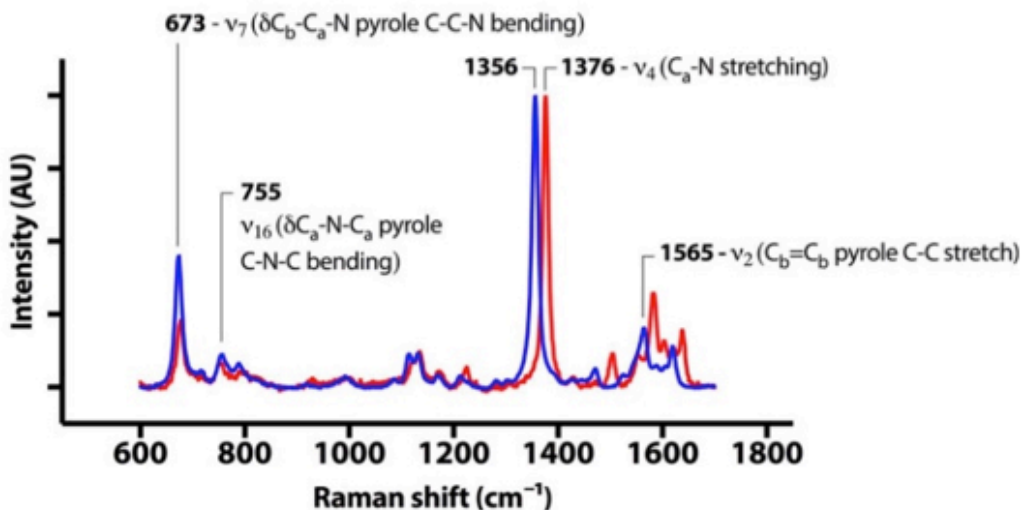
Mitochondrial spectrum

682 - ν_7 (δC_b-C_a-N pyrole C-C-N bending)

747
ν_{16} (δC_a-N-C_a pyrole C-N-C bending)

1357 ┐┌ **1371** - ν_4 (C_a-N stretching)

1465 - ν_{28} (C_a-C_m stretching)

1584 - ν_2 (C_b=C_b in pyrole rings)

1609 - ν C=O (Cytochrome a formyl stretch)

Intensity (AU)

Raman shift (cm⁻¹)

Myoglobin spectrum

673 - ν_7 (δC_b-C_a-N pyrole C-C-N bending)

1355 ┐┌ **1376** - ν_4 (C_a-N stretching)

764
ν_{16} (δC_a-N-C_a pyrole C-N-C bending)

1582 - ν_2 (C_b=C_b pyrole C-C stretch)

Intensity (AU)

Raman shift (cm⁻¹)

Hemoglobin spectrum

673 - ν_7 (δC_b-C_a-N pyrole C-C-N bending)

1356 ┐┌ **1376** - ν_4 (C_a-N stretching)

755
ν_{16} (δC_a-N-C_a pyrole C-N-C bending)

1565 - ν_2 (C_b=C_b pyrole C-C stretch)

Intensity (AU)

Raman shift (cm⁻¹)

These Raman spectroscopy images show the intensity and wavelengths of reflected light from each of three cellular proteins -- mitochondrial cytochrome, myoglobin and hemoglobin -- when a laser is shined on the cell. The light spectra produced when the proteins are oxygenated are shown in red, de-oxygenated in blue. The different oxygen conditions cause differences in the bending and stretching of chemical bonds in the proteins' porphyrin rings, scattering the light differently. Raman spectroscopy thus provides an index of how much oxygen the mitochondria are receiving relative to the cell's energy needs. Credit: Dr. John Kheir, Boston Children's Hospital

The team created a metric they call 3RMR that uses light readings generated by resonance Raman spectroscopy to quantify oxygenation and mitochondrial function in real time.

When a cell's oxygen levels are too low, its energy balance changes. Electrons start to build up in certain cellular proteins—hemoglobin, myoglobin and mitochondrial cytochromes. This energy shift reduces or shuts down mitochondrial energy production and can also trigger cell death. All of this sets the stage for organ injury or dysfunction and, in the worst case, cardiac arrest, says Kheir.

Resonance Raman spectroscopy quantifies the fraction of mitochondrial proteins with electrons on them based on how light is scattered when a laser is shined on them. Under low-oxygen conditions, the gain in electrons causes these molecules to distort and, as a result, their spectrum changes.

"This system tells us how satisfied the mitochondria are with their oxygen supply," Kheir explains.

The team used a precise laser and a complex algorithm to distill the information in real time.

"Distinguishing mitochondrial signals from other biological signals with accuracy and speed was the most significant scientific advance here," says Pendar CEO Daryoosh Vakhshoori, PhD, who oversaw the engineering aspect of the project.

Predicting cardiac arrest

Joshua Salvin, MD, MPH and Dorothy Perry, MBChB of the Heart Center, the study's co-first authors, tested the device in rat models. They found that reduced oxygenation of the heart corresponded with elevations in 3RMR, regardless of the cause of reduced oxygen delivery. Elevations of more than 40 percent, measured after 10 minutes of low-oxygen conditions, predicted reduced heart contractility and subsequent cardiac arrest with 97 percent specificity and 100 percent sensitivity, outperforming all other measurement techniques.

The team further tested the device during simulated congenital heart surgery in a pig model. They were able to measure how satisfied the heart muscle was with its oxygen supply, something that cannot currently be done.

"Our likely first application of this device will be to monitor oxygen delivery during and after heart surgery," says Kheir. The current probe is the size of a pen, but eventually, the team would like to develop a smaller probe that could be left inside the chest, so patients could be monitored in the ICU during highest-risk times.

Future applications

Kheir and colleagues also believe the technology could be used to monitor tissue viability in other operations in which tissues and organs are exposed. Potential applications might include monitoring organs intended for transplantation and detection of dangerously reduced blood flow in limbs.

"I think there would be many surgical uses," says Vakhshoori, co-corresponding author on the study. "There really is no technology currently that can assess, in real time, whether oxygen delivery to a tissue is adequate at the level of the mitochondrion."

Kheir also thinks the tool could be helpful in cancer research, since mitochondrial function is central to cancer biology.

The team's goal is to seek FDA approval and commercialize a bedside monitor of mitochondrial oxygenation. In the meantime, Kheir and colleagues plan to seek approval to test the device to monitor heart patients.

More information: D.A. Perry el al., "Responsive monitoring of mitochondrial redox states in heart muscle predicts impending cardiac arrest," *Science Translational Medicine* (2017). stm.sciencemag.org/lookup/doi/ … scitranslmed.aan0117

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