Clinical relevance aims to uncover novel regulators of human coronary artery function

The microcirculation is made up of a network of blood vessels, including small arteries, arterioles, and capillaries. Its primary function is to supply oxygen and nutrients to tissues and remove metabolic waste. The microcirculation is responsible for orchestrating adjustments of blood vessels to match local blood supply with oxygen demand of tissues – both in normal resting conditions and in response to external stimuli (e.g., increased heart rate) that require increased amounts of oxygen and nutrients.

The microcirculation is well-known for its role in the regulation of vascular tone and function. Understanding the regulation of microvascular function is critical to understanding and treatment of a variety of cardiovascular disorders.

A NOVEL APPROACH

The human microcirculation not only plays a role in regulating tissue perfusion but has been recognised as a modulator of the local tissue environment. The team believes that this provides an explanation for the multitude of dilator and constrictor factors released from the endothelium (the cells lining the blood vessel walls) that influence vessels further downstream and the function of surrounding tissues. The team has a wealth of expertise in studying microcirculatory function in intact tissue samples, an approach that provides obvious clinical relevance.

ASSESSING MICROVASCULAR FUNCTION

The team has a wealth of expertise in studying microcirculatory function in intact human tissue samples, an approach that provides obvious clinical relevance. Their specialised method employs direct video-microscopy of cannulated, pressurized vessels to study microcirculatory function in intact human subjects. This allows for the investigation of pathological changes observed in vitro, which are often not seen in vivo. The team has developed a non-invasive method for treatment and prevention of human heart conditions.

The researchers are investigating adaptive mechanisms that allow vessels to maintain function in response to inflammation and other stimuli. They have discovered that the production of nitric oxide (NO, which causes vessel dilation) preserves normal tissue function but is necessary for the endothelial shear-stress-mediated release of hydrogen peroxide (H₂O₂) from mitochondria in the endothelial cells lining the blood vessel walls. This release promotes latency, whereas H₂O₂ promotes inflammation and atherosclerosis. The team’s findings offer new insights into the role of NO and H₂O₂ in vascular function.

Cardiovascular stress and disease expose the dynamic nature of the mediators of microvascular dilation, which can be changed either acutely (e.g., by changes in pressure within the vessel or pharmacological interventions) or by chronic diseases such as CAD. The HVRG team and collaborators explore changes in the dilator pathways, hoping to shed light on ways that microcirculation-provided dysfunction leads to clinical implications (e.g., atherosclerosis).

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A PIVOTAL ROLE OF ENDOTHELIAL MITOCHONDRIAL FUNCTION

Two pathways involving the production of ceramide and a reduction in telomerase activity are critical in the shift from NO to mitochondrial NO synthase (mNOS) ceramide and reduced telomerase activity are known to suppress mitochondrial function and promote mitochondrial dysfunction.

The researchers are investigating adaptive pathways that provide obvious clinical relevance. They have discovered that the production of nitric oxide (NO, which causes vessel dilation) preserves normal tissue function but is necessary for the endothelial shear-stress-mediated release of hydrogen peroxide (H₂O₂) from mitochondria in the endothelial cells lining the blood vessel walls. This release promotes latency, whereas H₂O₂ promotes inflammation and atherosclerosis. The team’s findings offer new insights into the role of NO and H₂O₂ in vascular function.

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At the same time, NO has a well-known role in vascular complications. The underlying causes that lead to an increased intraluminal pressure, flow through the microvasculature releases hydrogen peroxide, creating a proinflammatory environment throughout the organ, potentially leading to hypertrophy, fibrosis, and atherosclerosis.

IN THE HUMAN MICROCIRCULATION
REGULATION OF THE MECHANISM OF FLOW INDUCED DILATION

Their theory neatly explains why microvascular dysfunction is such a powerful predictor of cardiovascular injury. The peripheral microcirculation (leg) is significantly impaired after a stroke and that improvements in microvascular function contribute to the improvement of motor function in this population. Further, the Durand lab is exploring simple non-invasive means to improve microvascular function. Application of a technique called ischemic conditioning (short, intermittent bouts of limb ischemia using a blood pressure cuff) is sufficient to improve parietal leg strength and hyperemic blood flow by approximately 15%. This improvement in strength is also accompanied by an acute improvement in arterial flow-mediated dilation. Currently, Drs. Durand and Freed from the HVRG are jointly conducting a clinical trial which will examine the effects of ischemic conditioning on peripheral vascular function and frailty in pre-surgical, elderly colon cancer patients who traditionally have poor surgical outcomes. Together these findings underline the growing recognition that dysfunction of the microcirculation contributes to the development of cardiovascular and other chronic diseases in humans. Ongoing research from the HVRG connects known functions of the microvasculature that neatly explains its intimate link to disease development in humans. Applying clinically relevant data from human tissues, the HVRG team hopes to provide a detailed mechanistic understanding of disease with the goal to develop novel therapeutics that can translate into the clinic.