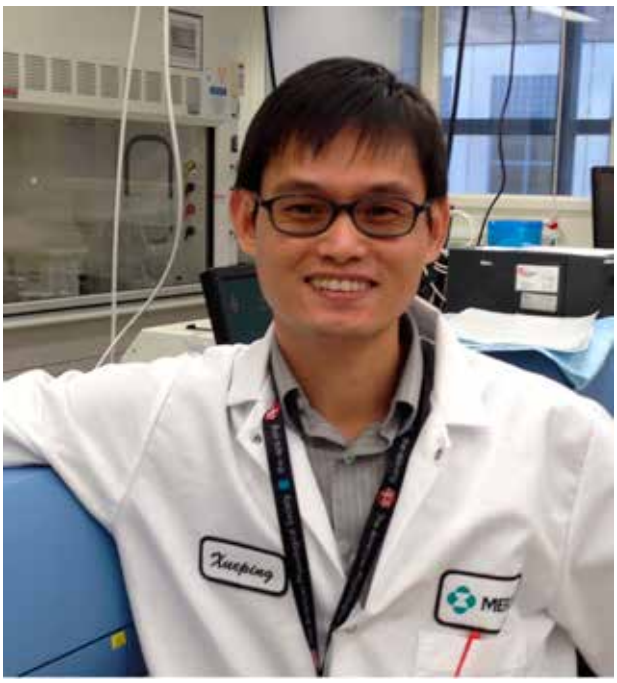
Featured Young Investigators: Recent Studies in *Microcirculation* *

from Volume 22 Issue 7 (pages 518-527)

Sex Difference in Coronary Endothelial Dysfunction in Apolipoprotein E Knockout Mouse: Role of NO and A2A Adenosine Receptor

Featuring: ***Xueping Zhou****, Bunyen Teng and S. J. Mustafa,* ***West Virginia University***



Sex plays an important role in the pathophysiology of cardiovascular diseases. While women are believed to be protected against cardiovascular diseases, partially due to the effect of estrogen, increasing clinical data reveal a higher mortality and cardiovascular event in female vs. male patients with ischemic heart disease. The mechanisms involved in the sex-related difference in cardiovascular events, particularly in those with coronary artery diseases (CAD) remains poorly understood. Our recent study (Microcirculation, 22: 518-527), using murine ApoE KO model of atherosclerosis, demonstrated an interesting finding that female ApoE KO mice presented a more severely impaired NO-dependent coronary vasodilation compared with male. Additionally, a functional up-regulation of A2A AR serves as an important mechanism to compensate the coronary endothelial dysfunction, resulting in a less comprised cardiac perfusion during ischemia in both sexes. However, while this compensatory mechanism is sufficient to maintain normal coronary ischemic vasodilation in males, the same mechanism fails to rescue the more severely impaired cardiac perfusion in females. This difference may explain the clinical evidence that female patients with ischemic heart disease, though found with less atherosclerosis in coronary vasculature, tend to have a higher mortality rate and cardiovascular events. Therefore, an improvement of cardiac perfusion by rescuing the impaired NO-dependent coronary vasodilation, predominantly in the microvasculature, should be an important therapeutic strategy in female patients with CAD. More importantly, the findings of this study highlight considerations that should be taken in experimental design and data interpretation regarding sex-related difference in the pathophysiology cardiovascular diseases.

**Note: Featured Articles by Young Investigators will appear in each MCS Newsletter and will be chosen from recent publications in* Microcirculation *our Official Journal. If you have a recent publication in* Microcirculation, *that includes young investigators as authors, and would like your study to be considered for this Featured Article, then send your study and reference to MCS Secretary, W. Lee Murfee, at secretary@microcirc.org*

Journal News

From the Laboratories of MCS Members: Recent Studies in *Microcirculation*

Cerebral Cortical Microvascular Rarefaction in Metabolic Syndrome is Dependent on Insulin Resistance and Loss of Nitric Oxide Bioavailability

from Volume 22 Issue 7 (pages 435-445)

Featuring: Paul D. Chantler, Carl D. Shrader, Lawrence E. Tabone, Alexandre C. d'Audiffret, Khumara Huseynova, Steven D. Brooks, Kayla W. Branyan, Kristin A. Grogg and Jefferson C. Frisbee - West Virginia University

Not only is metabolic syndrome associated with increased cardiovascular disease events and mortality, but it is an established risk factor for cognitive decline, dementia, and stroke. In our study, we proposed that the damaging effects of metabolic syndrome on cerebral vascular integrity are, in part, dependent on the progressive decline in cortical microvessel density, thereby limiting cerebrovascular reserve capacity and compromising mass transport and exchange both prior to and following ischemic events.

In the obese Zucker rat model of the metabolic syndrome, mechanistically divergent treatments against the constituent pathologies (e.g., hypertension, impaired glycemic control, etc.) were able to not only lower risk the appropriate risk factors, but were also able to blunt the severity of rarefaction if they had the additional pleiotropic effect of improving oxidant stress/inflammatory status and chronic nitric oxide bioavailability. Interestingly, while anti-hypertensive treatments improved outcomes, treatments targeted at chronically improving glycemic control and pro-oxidant status (metformin and rosiglitazone) were superior at blunting the loss in cerebral cortical microvessel density. Speculatively, chronic maintenance of glycemic control may be an effective strategy to confer vascular protection, and aggressively pursued in individuals presenting with early warning signs of metabolic syndrome.

Modeling Perfusion Dynamics in the Skin During Iontophoresis of Vasoactive Drugs Using Single-Pulse and Multiple-Pulse Protocols

from Volume 22 Issue 7 (pages 446-453)

Featuring: Fredrik Iredahl, Veeranjaneyulu Sadda, Liam J. Ward, Johannes Hackethal, Simon Farnebo, Erik Tesselaar and Folke Sjöberg - Linköping University

Transdermal iontophoresis of vasoactive drugs has become a common experimental technique to study microvascular function in vivo. The technique somewhat resembles in vitro dose-response experiments, since drugs can be delivered into the skin in increasing doses. There are, however, a number of factors that complicate the interpretation of microvascular drug responses during iontophoresis. These are related to the complexity of the living tissue, in particular the presence of intact vasculature, blood flow, and circulating vasoactive substances.

In our current work, we are trying to unravel some of this complexity. Specifically, we intend to understand how local drug kinetics affect blood flow responses when drugs are delivered either by a single delivery, or by multiple pulses separated by current-free intervals.

Our ultimate goal is to use this knowledge to get more insight in the underlying mechanisms governing the microvascular responses to vasoactive drugs in the skin and to develop a model that more closely can examine drug effects on the microvasculature in humans *in vivo*.