

KEITH REIMER, M.D.

1946-2002

Keith Arnold Reimer, M.D., Ph.D., Professor of Pathology at Duke University Medical School, internationally recognized cardiovascular scientist, pathologist, and teacher, died on March 15, 2002 of metastatic renal cell carcinoma at the age of 56. Keith began his career in experimental pathology studying ischemic injury of the kidney, however he quickly shifted his focus to myocardial ischemic injury, the field in which he went on to make his major scientific contributions. After completing the MD/PhD program at Northwestern University in Chicago, Keith joined the faculty at Duke University in 1975 as Assistant Professor of Pathology. Early in his career, working in collaboration with Dr. Robert B. Jennings, he published landmark studies describing and characterizing the "wavefront phenomenon" of myocardial ischemic cell death. These studies, published in two papers (*Circulation* 56: 786-794, 1977; and *Laboratory Investigation* 40: 633-644, 1979), have been cited more than 1000 times. During the early 1980s, Keith developed methods to measure baseline predictors of infarct size, such as area at risk and collateral flow, that have become the standard for generating reliable and reproducible data to test cardioprotective interventions. The effort to discover cardioprotective interventions led to one of Keith's most notable achievements – the description of one of the strongest and most reproducible interventions for reducing infarct size: ischemic preconditioning. Numerous investigators and laboratories have worked to better understand this remarkably effective intervention, and the ever-expanding number of studies on ischemic preconditioning, in a wide variety of tissues, have consistently confirmed the original observation that brief periods of ischemia and reperfusion are not detrimental, but are actually markedly protective. The original article describing the phenomenon of ischemic preconditioning, "Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium" (*Circulation* 74: 1124-1136, 1986) has been cited more than 3700 times (the most cited paper in *Circulation*).

Keith was an active member of the ISHR since 1976, and was elected a Councilor of the American Section in 1979, serving until 1985. He was a finalist for the Richard Bing Young Investigator Award of the ISHR in 1980. Keith served as Secretary of the American Section from 1985-1994, and as a member of the Council of the International Society from 1989-1995. In 1997, he became President-Elect of the American Section and was the sitting President of the American Section, as well as a member of the International ISHR Council, when he died.

About the Award...

Each year, the International Council selects a speaker to deliver the Keith Reimer Distinguished Lecture at the World Congress or at the annual section meeting of one of the three largest ISHR Sections. The purpose of this lecture is to honor the memory of Dr. Reimer and to recognize his contributions to cardiovascular research. The topic of the lecture must be in the field of ischemia, coronary hemodynamics, cardiac metabolism, or contractile mechanisms. The speaker receives a plaque and \$1,000 honorarium in addition to travel expenses.

*This award is funded by a generous contribution from
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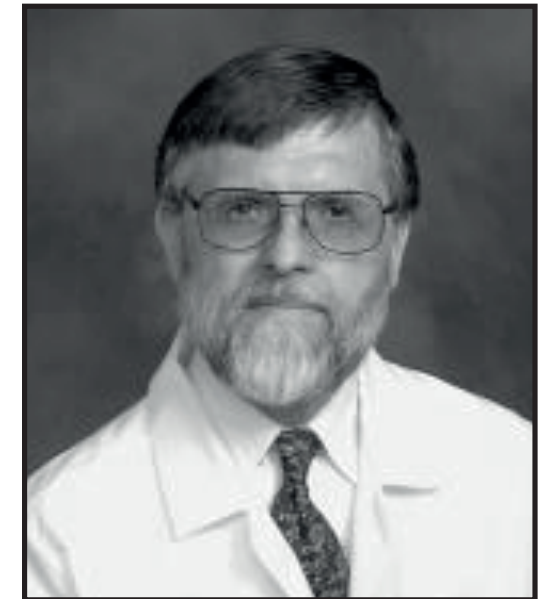
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THE KEITH REIMER DISTINGUISHED LECTURE 2017



Keith Reimer, M.D. 1946-2002

Honored Speaker

Dr. Brian O'Rourke

**"Life on the Edge:
Mitochondria, Emergence,
and Heart Disease"**

Brian O'Rourke, PhD

2017 Honored Speaker Hamburg, Germany



Brian O'Rourke is a Professor in the Division of Cardiology and Vice Chair of Basic and Translational Research for the Department of Medicine. He also directs the Bernard Laboratory of Fundamental Research in Preventive Cardiology. He has been involved in cardiovascular research for more than 30 years,

and his research focuses on the biophysics and physiology of cardiac cells in normal and diseased states, with particular expertise in the areas of mitochondria, excitation-contraction coupling, redox/free radical balance, and the coupling of bioenergetics to the integrated function of the cell. In particular, his lab is interested in characterizing novel therapeutic targets to prevent ischemia-reperfusion injury, sudden cardiac death, and heart failure.

Dr. O'Rourke earned his undergraduate degree in Biochemistry from Pennsylvania State University in 1983 and obtained his Ph.D. in Physiology from Thomas Jefferson University in 1990, which was also the year he first arrived at Johns Hopkins as a postdoctoral fellow in the laboratory of Eduardo Marbán, M.D., Ph.D. He joined the faculty in 1993 and has led an active research program, funded by the American Heart Association and the NHLBI. He was the recipient of an NIH MERIT award and has extensive experience leading multidisciplinary teams of investigators on thematically-focused research programs, including serving as PI on a Program Project on the role of mitochondrial function in ischemic cardiac disease, and on multi-PI, multi-institutional, grants on mitochondrial dysfunction in cardiac hypertrophy and failure. Dr. O'Rourke has also been successful in establishing and directing imaging and bioenergetics core facilities at Johns Hopkins, and with expert collaborators, he has also been a key contributor to expanding proteomics and metabolomics capabilities at

JHU. Dr. O'Rourke served as Associate Editor of *Circulation Research*, currently serves as Associate Editor of *Cardiovascular Research*, and is on the editorial boards of *Circulation*, the *Journal of Molecular and Cellular Physiology*, *Basic Research in Cardiology*, and the *Journal of General Physiology*. He spent many years contributing to the peer review process as a permanent member and chair of the NIH Electrical Signaling, Transport and Arrhythmias study section and as well as on numerous AHA committees.

The multidisciplinary flavor of the work from Dr. O'Rourke's lab, described in over 200 publications, stems from his vision of cardiovascular disease as a *cascade of failures* that disrupts the integration between the major subsystems of the cardiac cell, i.e., the electrophysiological, Ca^{2+} cycling, contractile, and energetic machinery. His approach has been to understand the physiology and pathophysiology at multiple scales. Experimentally, his lab not only probes how individual proteins, enzymes, or ion channels behave at the molecular level, but also tries to understand their function at different levels of integration, for example, at the level of isolated mitochondria, intact cells and the intact organ. Data obtained with diverse technologies such as patch-clamp, microfluorimetry, conventional and two-photon fluorescence imaging, proteomics, metabolomics, and molecular biology are utilized to build state-of-the-art models to analyze the impact of a particular target on the systems biology of the cell and whole heart. This is crucial for understanding complex phenomena such as cardiac arrhythmogenesis, heart failure, and ischemia-reperfusion injury.

Dr. O'Rourke's group has made important discoveries in several areas of cardiovascular research, including: 1) the role of energy metabolism in dynamically regulating cardiac excitability and excitation-contraction coupling, 2) elucidating mechanisms of contractile and electrical dysfunction in heart failure, 3) discovering novel *mitochondrial ion channels* on the inner membrane and establishing the paradigm that they have specific effects on bioenergetics and cell life and death, 4) developing the concept that *mitochondrial criticality* underlies self-organized emergent behavior in the mitochondrial network that scales to produce cardiac arrhythmias, in part, through the formation of *metabolic current sinks*

and repolarization heterogeneity in the tissue, and 5) elucidating how the interplay between *mitochondrial Ca^{2+} flux and energy demand* impacts mitochondrial redox/ROS balance, leading to the articulation of the *Redox-optimized ROS Balance hypothesis*. In addition to the experimental and conceptual advances described above, Dr. O'Rourke's group has pioneered the development of computational models of the cardiac cell that incorporated energy metabolism, mitochondrial ROS production and scavenging, mitochondrial Ca^{2+} handling, and mitochondrial network properties, ultimately scaling the models to the level of the myocardial syncytium in order to simulate arrhythmia mechanisms. Most recently, work in Dr. O'Rourke's lab has extended this systems biology approach to include multi-omics strategies to understand the *casual networks* underlying the pathobiology of cardiovascular disease, particularly the ROS-dependent signal transduction pathways contributing to *heart failure gene/protein remodeling and sudden cardiac death*.

This strategy has helped to move the field forward, generating new mechanistic insights as to how loss of mitochondrial function precipitates ventricular fibrillation after a heart attack, how altered Ca^{2+} dynamics in the cytoplasm and mitochondria contribute to pump failure and sudden cardiac death in congestive heart failure, and how K^+ channels in the mitochondria contribute to protecting the heart cell from death. Most importantly, understanding the cascade of failures involved in the disease process has led to novel therapeutic strategies aimed at interrupting the vicious cycle at key controlling steps that can be translated into clinical interventions in the near future.

Previous Award Winners...

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Richard Moss, PhD: 2010
Elizabeth Murphy, PhD: 2009
David Eisner, PhD: 2008
Eduardo Marbán, MD: 2007
Garrett Gross, PhD: 2006
Masao Endoh, MD, PhD: 2005
R. John Solaro, PhD: 2004
Gerd Heusch, MD, PhD: 2003
Roberto Bolli, MD: 2002