

## Mihai Podgoreanu, M.D., Recipient of the 2009 Presidential Scholar Award

Mark F. Newman, M.D.\*

*"You see? That's why scientists persist in their investigations, why we struggle so desperately for every bit of knowledge, stay up nights seeking the answer to a problem, climb the steepest obstacles to the next fragment of understanding, to finally reach that joyous moment of the kick in the discovery, which is part of the pleasure of finding things out." —Richard Feynman*

MIHAI Podgoreanu, the 2009 recipient of the Presidential Scholar Award, is a wonderful testament to the passion for discovery that should drive anesthesiology to the highest levels of modern science. Mihai obtained his M.D. degree from Carol Davila University in Bucharest, Romania and trained as an anesthesiology resident at Yale University, New Haven, Connecticut. At Yale, he pursued the clinician-scientist track under the mentorship of David Silverman, M.D., focused on understanding the origin and control mechanisms of oscillations in microvascular flow in response to various physiologic perturbations. Expanding on investigations in healthy volunteers, Dr. Podgoreanu described for the first time in cardiac surgical patients the emergence and progressive synchronization of high-frequency microvascular oscillations under conditions of nonpulsatile perfusion (during cardiopulmonary bypass) in the absence of cardiac and respiratory activity, thus demonstrating their peripheral origin and providing insights into parasympathetic vasoregulatory mechanisms in response to systemic depul-<sup>1</sup>sation. This phenomenon is particularly important now with the advent of axial-flow ventricular assist devices. This work was recognized nationally in 2001, when he was named the winner of the resident research contest at the Postgraduate Assembly of the New York Society of Anesthesiologists. To expand his repertoire into animal models of disease, both *ex vivo* and *in vivo*, he participated during his residency in a project examining the effects of lidocaine on human lung fibroblasts and endothelium in a rat tracheal ring model system.<sup>2</sup>

These early investigations sparked his curiosity to understand the complex interplay between variability in physiologic parameters, molecular variability in the host responses to surgical insult, and the well-known variability in perioperative clinical trajectories of patients undergoing cardiothoracic surgery. The desire to develop as a perioperative physician-scientist and acquire the necessary knowledge to apply molecular medicine tools to



Mihai Podgoreanu, M.D., recipient of the American Society of Anesthesiologists 2009 Presidential Scholar Award.

cardiac surgical outcomes brought him to Duke University (Durham, North Carolina) in the summer of 2000, where he embarked on a 2-yr cardiothoracic anesthesia fellowship, followed by a critical care medicine fellowship. He combined this 3-yr continuum of subspecialty training with a postdoctoral fellowship in molecular genetics in the laboratory of Debra Schwinn, M.D., an internationally acclaimed expert in molecular pharmacology, cardiovascular autonomic control, and translational functional genomics. He received a postdoctoral fellowship award from the American Heart Association to study the effects of genetic variants in the  $\beta_2$  adrenergic receptor on adverse cardiac surgical outcomes.

Under Dr. Schwinn's mentorship, Mihai quickly became the central cog in the Perioperative Genomics and Safety Outcome Study (PEGASUS), a large Department of Anesthesiology genomics project focused on understanding the role of genetic variability in organ injury and dysfunction after cardiac surgery, and laid the foundations of a new field based on the use of genomic

\* Professor and Merel H. Harmel Chair, Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina. newma005@mc.duke.edu

Submitted for publication June 15, 2009. Accepted for publication June 16, 2009.

technologies in perioperative medicine (*i.e.*, perioperative genomics). The success of his leadership in this area is evidenced by a series of publications identifying key genetic variants associated with major adverse postoperative events after cardiac and major surgery,<sup>3-9</sup> as well as several review articles and book chapters introducing the concept of perioperative genomics to the broader cardiovascular and anesthesia communities,<sup>10-12</sup> including the first genomics chapter in a premier anesthesiology textbook.<sup>13</sup> He was a Vivien Thomas Young Investigator Award finalist at the American Heart Association 2005 Scientific Sessions for his study titled "Inflammatory gene polymorphisms and risk of postoperative myocardial infarction following cardiac surgery."<sup>3</sup>

In 2005, Dr. Podgoreanu assumed leadership of the multidisciplinary Duke Perioperative Genomics Program and expanded it beyond pure genetic epidemiology studies to include relevant small and large animal models of disease,<sup>14,15</sup> cell model systems and integrative computational biology support in a comprehensive programmatic translational approach to study host responses to surgical injury and the robust stressors characteristic of the perioperative period. Capitalizing on his premed experience in mathematics, he established the Systems Modeling of Perioperative Cardiovascular Injury Laboratory, which applies systems biology approaches to address three main goals: 1) understand mechanisms underlying acute myocardial responses to surgical ischemia-reperfusion injury, with a primary focus on inflammation and metabolic deregulation; 2) discover organ-specific biomarkers that differentiate clinically relevant subtypes of perioperative myocardial injury; and 3) identify and test new molecular targets for cardioprotection. Most recently, Dr. Podgoreanu was senior investigator on the first comprehensive study of myocardial metabolic responses to cardioplegic arrest in humans using novel quantitative targeted metabolomic approaches.<sup>16</sup> Such systems-level approaches are extremely relevant to the perioperative clinician, as they will enable us to anticipate the consequences of surgical perturbations and design personalized preventive strategies for organ protection.

In parallel with this pioneering work, Dr. Podgoreanu successfully transitioned to independent investigator status by receiving an R01 grant from the National Heart Lung and Blood Institute to study the role of genetic variants in progression and severity of saphenous vein graft disease and 5-yr incidence of major adverse cardiac events after coronary artery bypass surgery ("Genetics of myocardial adverse outcomes and graft failure after CABG"—GeneMAGIC). In the fall of 2007 he was awarded a second R01 grant from the National Institutes of Health titled "Cross-species analysis of myocardial

susceptibility to perioperative stress," which incorporates novel comparative and evolutionary biology approaches to delineate the mechanisms by which robust "planned" environmental perturbations associated with cardiac surgery interact with genetic susceptibility to result in perioperative myocardial injury. In this regard, cardiac and major surgery can be considered a suitable experimental system that recapitulates several adverse environmental effects and gene-environment interactions. Receipt of funding in the first peer-review cycle was an attestation to the quality of this proposal.

Mihai's teaching contributions are multiple and reflect his dedication to research and use of that research to influence clinical care. He is involved in the Cardiothoracic Anesthesia Fellow Seminar Series by providing basic science reviews on mechanisms of perioperative organ injury and advanced cardiovascular physiology. In the 5 yr since his faculty appointment at Duke, Dr. Podgoreanu has formally mentored 12 trainees at different levels on various projects related to applications of functional genomics to perioperative medicine, resulting in several awards, presentations at national and international meetings, and peer-reviewed publications. Evaluations from anesthesiology residents have consistently ranked Dr. Podgoreanu's teaching dedication and skills in the top 5th percentile among his peers. To improve understanding of the scientific principles, epidemiological study design, and computational issues associated with perioperative genomics research as well as being able to quickly update the existing level of knowledge in the field, Dr. Podgoreanu has designed an educational Web site for Duke's Perioperative Genomics Program.<sup>†</sup> As evidence of his rapidly rising stature, Mihai has given 30 lectures, visiting professorships, and grand rounds over the past 5 yr, both at the national and international level. When he is not doing the work described above, he plays a major role in the department in provision of clinical care for cardiac surgical and critically ill patients.

Dr. Podgoreanu is the type of individual who provides hope and inspiration for our specialty. By effectively interfacing cutting-edge genomic and molecular investigative tools with clinical practice, his work expands not only our specialty, but all of medicine. This is a physician-scientist to watch. Despite the difficult times we are facing in many ways, science offers greater opportunity to triumph over disease than ever before, and Dr. Podgoreanu has seized the moment. That he has succeeded in this effort so early in his career is a testament to his skills and his "passion to discover." We are honored to be his partners in anesthesiology and critical care medicine.

## References

1. Podgoreanu MV, Stout RG, El-Moalem HE, Silverman DG: Synchronous rhythmical vasomotion in the human cutaneous microvasculature during non-pulsatile cardiopulmonary bypass. *ANESTHESIOLOGY* 2002; 97:1110-7

<sup>†</sup> <http://pegasus.duke.edu>. Accessed June 15, 2009.

2. Akhtar S, Podgoreanu M, Harrison BA, Brull SJ: Effect of lidocaine on endothelin-1-mediated airway smooth muscle contraction in the rat trachea. *Minerva Anesthesiol* 2008; 74:643-50
3. Podgoreanu MV, White WD, Morris RW, Mathew JP, Stafford-Smith M, Welsby IJ, Grocott HP, Milano CA, Newman MF, Schwinn DA: Inflammatory gene polymorphisms and risk of postoperative myocardial infarction after cardiac surgery. *Circulation* 2006; 114:1275-81
4. Grocott HP, White WD, Morris RW, Podgoreanu MV, Mathew JP, Nielsen DM, Schwinn DA, Newman MF: Perioperative Genetics and Safety Outcomes Study (PEGASUS) Investigative Team Genetic polymorphisms and the risk of stroke after cardiac surgery. *Stroke* 2005; 36:1854-8
5. Mathew JP, Podgoreanu MV, Grocott HP, White WD, Morris RW, Stafford-Smith M, Mackensen GB, Rinder CS, Blumenthal JA, Schwinn DA, Newman MF: Genetic variants in P-selectin and C-reactive protein influence susceptibility to cognitive decline after cardiac surgery. *J Am Coll Cardiol* 2007; 49:1934-42
6. Moretti EW, Morris RW, Podgoreanu M, Schwinn DA, Newman MF, Bennett E, Moulin VG, Mba UU, Laskowitz DT: APOE polymorphism is associated with risk of severe sepsis in surgical patients. *Crit Care Med* 2005; 33:2521-6
7. Phillips-Bute B, Mathew JP, Blumenthal JA, Morris RW, Podgoreanu MV, Smith M, Stafford-Smith M, Grocott HP, Schwinn DA, Newman MF: Relationship of genetic variability and depressive symptoms to adverse events after coronary artery bypass graft surgery. *Psychosom Med* 2008; 70:953-9
8. Stafford-Smith M, Podgoreanu M, Swaminathan M, Phillips-Bute B, Mathew JP, Hauser EH, Winn MP, Milano C, Nielsen DM, Smith M, Morris R, Newman MF, Schwinn DA: Association of genetic polymorphisms with risk of renal injury after coronary bypass graft surgery. *Am J Kidney Dis* 2005; 45:519-30
9. Welsby IJ, Podgoreanu MV, Phillips-Bute B, Mathew JP, Smith PK, Newman MF, Schwinn DA, Stafford-Smith M: Genetic factors contribute to bleeding after cardiac surgery. *J Thromb Haemost* 2005; 3:1206-12
10. Podgoreanu MV, Schwinn DA: New paradigms in cardiovascular medicine: Emerging technologies and practices: Perioperative genomics. *J Am Coll Cardiol* 2005; 46:1965-77
11. Podgoreanu MV, Schwinn DA: Genomics and the circulation. *Br J Anaesth* 2004; 93:140-8
12. Schwinn DA, Podgoreanu M: Pharmacogenomics and end-organ susceptibility to injury in the perioperative period. *Best Pract Res Clin Anaesthesiol* 2008; 22:23-37
13. Podgoreanu MV, Mathew JP: Genomic basis of perioperative medicine. In: Barash P, Cullen B, Stoelting RK, eds. *Clinical anesthesia*, 5th ed. Philadelphia, Lippincott Williams & Wilkins, 2005; pp 133-48
14. Podgoreanu MV, Michelotti GA, Sato Y, Smith MP, Lin S, Morris RW, Grocott HP, Mathew JP, Schwinn DA: Differential cardiac gene expression during cardiopulmonary bypass: Ischemia-independent upregulation of proinflammatory genes. *J Thorac Cardiovasc Surg* 2005; 130:330-9
15. de Lange F, Yoshitani K, Podgoreanu MV, Grocott HP, Mackensen GB: A novel survival model of cardioplegic arrest and cardiopulmonary bypass in rats: A methodology paper. *J Cardiothorac Surg* 2008; 3:51
16. Turer AT, Stevens RD, Bain JR, Muehlbauer MJ, van der Westhuizen J, Mathew JP, Schwinn DA, Glower DD, Newgard CB, Podgoreanu MV: Metabolomic profiling reveals distinct patterns of myocardial substrate use in humans with coronary artery disease or left ventricular dysfunction during surgical ischemia/reperfusion. *Circulation* 2009; 119:1736-46