Pharmacologic Stress Testing: Its Roots, Its Impact, and Its Future

Daniel S. Berman[1] and Alan Rozanski[2]

[1]Departments of Imaging and Medicine and Burns and Allen Research Institute, Cedars-Sinai Medical Center, and Department of Medicine, David Geffen School of Medicine, UCLA, Los Angeles, California; and [2]Department of Cardiology, Mount Sinai Morningside Hospital and Mount Sinai Heart, New York, New York

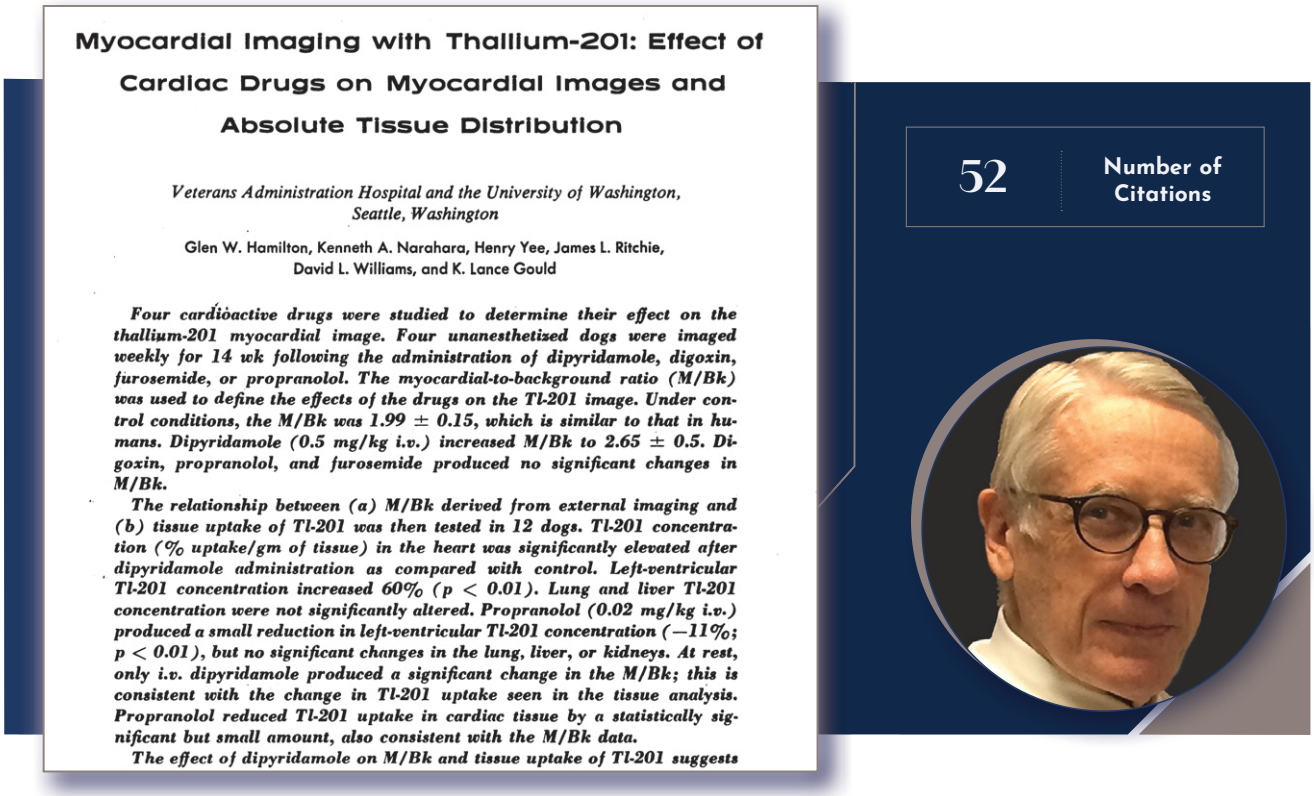
The 1970s was the inaugural decade of stress myocardial perfusion imaging (MPI). Initial imaging with ^{43}K in 1973 was followed by the potassium analogs ^{82}Rb in 1974 and ^{201}Tl in 1976. Because of its ease of imaging with the γ-camera, ^{201}Tl became the MPI agent of choice until the clinical availability of the ^{99m}Tc agents in 1990.

Within its first decade, MPI was extensively validated for a wide range of clinical applications including its use for diagnosing coronary artery disease, sizing the magnitude of inducible myocardial ischemia, assessing angiographic stenoses of borderline significance, and evaluating myocardial viability. Initial studies of quantitation were also introduced, providing objective measurements of perfusion defects and, given the washout characteristics of ^{201}Tl, even allowing for the detection of balanced reduction of flow. One particular development in the 1970s was unique and ultimately far-reaching: development of the ability to assess regional myocardial perfusion with pharmacologic agents, thus extending the application of MPI to patients who could not exercise.

In this context, an article in *JNM* published by the late Glenn Hamilton, one of Lance Gould's key collaborators, with Lance Gould as the senior author, has been selected as one of the most important papers in the *JNM* from the 1970s (*1*). This work was one of a series of papers in which Gould and a team of investigators at the University of Washington systematically studied dipyridamole and ^{201}Tl planar imaging in a combination of animal and human studies, after their initial assessments of early coronary blood flow based on contrastinduced coronary vasodilation (*1–3*). Their work with vasodilator stress had a profound effect on MPI. It not only opened the possibility of imaging patients who could not exercise,

Received Jun. 9, 2020; revision accepted Jun. 12, 2020.
For correspondence or reprints contact: Daniel Berman, Cedars-Sinai Medical Center, 8700 Beverly Blvd. Los Angeles, CA 90048.
E-mail: daniel.berman@cshs.org

DOI: 10.2967/jnumed.120.251298



but also defined the strengths and limitations of imaging with available perfusion tracers, and laid the groundwork for assessing absolute myocardial blood flow and flow reserve. Herein, we highlight their key achievements from that period.

In 1978, they published a series of 6 articles describing MPI with dipyridamole as the vasodilator in dogs and patients. In the initial study using microsphere-measured myocardial blood flow in dogs, they established that the optimal dose of dipyridamole, 0.142 mg/kg/min administered over 4 min, produced an increase in myocardial blood flow 4 min after injection that achieved 95% of maximal flow determined by intracoronary papaverine (*2*). They further showed that the increase in flow was greater with dipyridamole than with maximal exercise. They simultaneously reported a comparison of ^{201}Tl imaging with both dipyridamole and exercise stress in patients (*3*), finding improved image quality with dipyridamole stress and that the myocardial-to-background ratio was higher with the patient walking in place after dipyridamole administration—the forerunner of the standard combination of low-level exercise with vasodilator stress that is used today (*3*). Importantly, in their series of articles, they demonstrated that ^{201}Tl uptake consistently tracked with flow measured by microspheres at flow rates above baseline, but in a nonlinear pattern, confirming an initial observation by Strauss et al. in 1975; that is, as flow increased, the degree of increase in uptake was progressively reduced. In the specific article that was chosen as a highlight for *JNM* in the 1970s, Hamilton and Gould studied ^{201}Tl distribution in normal dogs with several imaging sessions using dipyridamole and other cardiac drugs (*1*). Their work included tissue sampling during the final session, with correlation to imaging. They observed that dipyridamole increased the tissue concentration of ^{201}Tl by 60%, further supporting the observation of the roll-off of ^{201}Tl uptake at high flow rates.

The pioneering work of this group continues to reverberate throughout cardiac imaging today. Specifically, since its introduction, the use of pharmacologic testing has grown steadily and now constitutes more than half of cardiac stress tests in most clinical laboratories.

Importantly, the mere need to perform pharmacologic testing in lieu of exercise testing has become one of the principal indicators of adverse prognosis, signaling a 2- to 3-fold increase in cardiac and overall mortality risk compared with patients who can exercise at the time of cardiac stress testing (*4*). The clinical implications of this observation will be investigated for years to come.

Their subsequent work with pharmacologic stress using PET led to the ability to assess absolute myocardial blood flow and myocardial flow reserve (*5*), which has fueled the marked increase in the use of PET MPI over the last decade. Multiple studies have demonstrated that these measurements add significantly to perfusion defects for prognostic assessment (*5*) and, more recently, that they can predict survival benefit from coronary revascularization (*6*). Of note, these measurements solve a central limitation of static imaging with SPECT or PET MPI: that of a balanced reduction of blood flow that does not result in regional perfusion defects, potentially underestimating flow abnormality in patients with extensive coronary artery disease. Interesting, it was through the work of Gould's group in the early 1970s that this phenomenon was first noted. The ability to assess myocardial flow reserve with vasodilator stress has also enhanced the study of coronary microvascular dysfunction, which is the primary cause of ischemia with no obstructive coronary artery disease *(7)*. This syndrome is an increasingly recognized potential source of chest pain and adverse prognosis, particularly in women. Thus, the work of Hamilton and Gould has contributed greatly to the past, present, and future of nuclear cardiology. On a personal note, Glenn was brilliant, was so caring about patients and friends, and had a great sense of humor. Lance is a true and continued inspiring giant in the field.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Hamilton GW, Narahara KA, Yee H, Ritchie JL, Williams D, Gould KL. Myocardial imaging with 201-thallium: effect of cardiac drugs on myocardial images and absolute tissue distribution. *J Nucl Med*. 1978;19:10–16.
2. Gould KL. Noninvasive assessment of coronary stenoses by myocardial imaging during coronary vasodilation. I. Physiologic principles and experimental validation. *Am J Cardiol*. 1978;41:267–278.
3. Gould KL, Westcott JR, Hamilton GW. Noninvasive assessment of coronary stenoses by myocardial imaging during coronary vasodilation. II. Clinical methodology and feasibility. *Am J Cardiol*. 1978;41:279–287.
4. Rozanski A, Gransar H, Hayes SW, Friedman JD, Hachamovitch R, Berman DS. Comparison of long-term mortality risk following normal exercise vs adenosine myocardial perfusion SPECT. *J Nucl Cardiol*. 2010;17:999–1008.
5. Murthy VL, Bateman TM, Beanlands RS, et al. Clinical quantification of myocardial blood flow using PET: joint position paper of the SNMMI Cardiovascular Council and the ASNC. *J Nucl Med*. 2018;59:273–293.
6. Patel KK, Spertus JA, Chan PS, et al. Myocardial blood flow reserve assessed by positron emission tomography myocardial perfusion imaging identifies patients with a survival benefit from early revascularization. *Eur Heart J*. 2020;41:759–768.
7. Bairey Merz CN, Pepine CJ, Walsh MN, Fleg JL. Ischemia and No Obstructive Coronary Artery Disease (INOCA): developing evidence-based therapies and research agenda for the next decade. *Circulation*. 2017;135:1075–1092.

exercise. Comparative Sensitivity to Electrocardiography in Coronary Artery Disease. *Circulation* 55: 79–87, 1977
3. Ritchie JL, Trobauch GB, Hamilton GW, et al: Myocardial imaging with ^{201}Thallium at rest and during exercise: comparison with coronary arteriography and resting and stress electrocardiography. *Circulation* 56: 66–71, 1977
4. Lebowitz E, Greene MW, Fairchild R, et al: Thallium-201 for medical use. I. *J Nucl Med* 16: 151–155, 1975
5. Bradley-Moore PR, Lebowitz E, Greene MW, et al: Thallium-201 for medical use. II. Biologic behavior. *J Nucl Med* 16: 156–160, 1975
6. Coleman A, Robertson M, Williams DL, et al: Development of a reliable and reproducible method for determining myocardial/background ratios from Tl-201 myocardial images. *J Nucl Med Tech* 4: 99, 1976 (abst)
7. Gregg DE: The George E. Brown Memorial Lecture. Physiology of the coronary circulation. *Circulation* 27: 1128–1137, 1963
8. Strauss HW, Harrison K, Langan JK, et al: Thailium-201 for myocardial imaging. Relation of Thallium-201 to regional perfusion. *Circulation* 51: 641–645, 1975
9. Yipintsoi T, Dobbs WA, Scanlon PD, et al: Regional distribution of diffusible tracers and carbonized microspheres in the left ventricle of isolated dog hearts. *Circ Res* 33: 573–587, 1973
10. Costin JC, Zaret BL: Effect of propranolol and digitalis upon radioactive thallium and potassium uptake in myocardial and skeletal muscle. *J Nucl Med* 17: 535, 1976 (abst)
11. Goldstein RE, Epstein SE: Medical management of patients with angina pectoris. *Prog Cardiovasc Dis* 14: 360–398, 1972
12. Becker LC, Fortuin NJ, Pitt B: Effect of ischemia and antianginal drugs on the distribution of radioactive microspheres in the canine left ventricle. *Circ Res* 28: 263–269, 1971