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Coronary Flow Reserve and Pharmacologic Stress Perfusion Imaging: Beginnings and Evolution

K. Lance Gould

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iSTORY

HISTORICAL PERSPECTIVE

Coronary Flow Reserve and Pharmacologic Stress Perfusion Imaging

Beginnings and Evolution

K. Lance Gould, MD

Houston, Texas

Coronary Flow Reserve

Pharmacologic stress for myocardial perfusion imaging fell out of my first experiment measuring coronary flow during progressive stenosis in 1972, published in 1974 (1). The arteriogram and flowmeter dramatically showed the 3 fundamental physiological concepts underlying all stress myocardial perfusion imaging. The first was the concept of coronary flow reserve as a physiological measure of stenosis severity separately from anatomical or dimensional severity and shown in Figure 1. The second was the correlation of this physiological coronary function with arteriographic stenosis dimensions and demonstration of critical stenosis that lowers resting flow. The third was pharmacologic arteriolar vasodilation as the stressor for stimulating maximal coronary flow that, in these early studies, was contrast media.

Human Coronary Physiology

The relevance of the initial animal studies to humans was an open question then. Human coronary physiology and stenosis fluid dynamics were not well known. To test the concept of coronary flow reserve and pharmacologic stress imaging in humans, we injected intracoronary macroaggregated albumin labeled with technetium 99 (Tc-

MAA) during the hyperemia immediately after intracoronary contrast media for coronary arteriography. Planar images of hyperemic Tc-MAA in patients with coronary artery stenosis showed corresponding regional perfusion defects, confirming the concepts of coronary flow reserve and pharmacologic stress imaging in coronary artery disease (CAD) (2).

Pharmacologic Stress: Dipyridamole

With the basic concepts established, an alternative to intracoronary contrast media was needed, with some literature suggesting intravenous dipyridamole as a possibility (3,4). It was the basis for a series of integrated experimental and human studies entitled "Noninvasive Assessment of Coronary Stenoses by Myocardial Imaging During Coronary Vasodilation: Part I Through Part VIII," published in the *American Journal of Cardiology* (5–12) under the creative editorship of Simon Dack.

The first 3 parts of this series addressed dipyridamole perfusion imaging, including the first human dipyridamole perfusion study, done on myself, using thallium-201 at the start of the clinical cases. However, these initial studies also revealed the limitations of planar imaging compared to direct flow measurements for assessing stenosis severity. The fourth study showed the power of experimental post-mortem imaging of short-axis sections of the heart after dipyridamole hyperemia and intravenous thallium-201, leading to positron emis-

From the Department of Medicine, The Weatherhead PET Center for Preventing and Reversing Atherosclerosis, University of Texas Medical School at Houston and Memorial Hermann Hospital, Houston, Texas.

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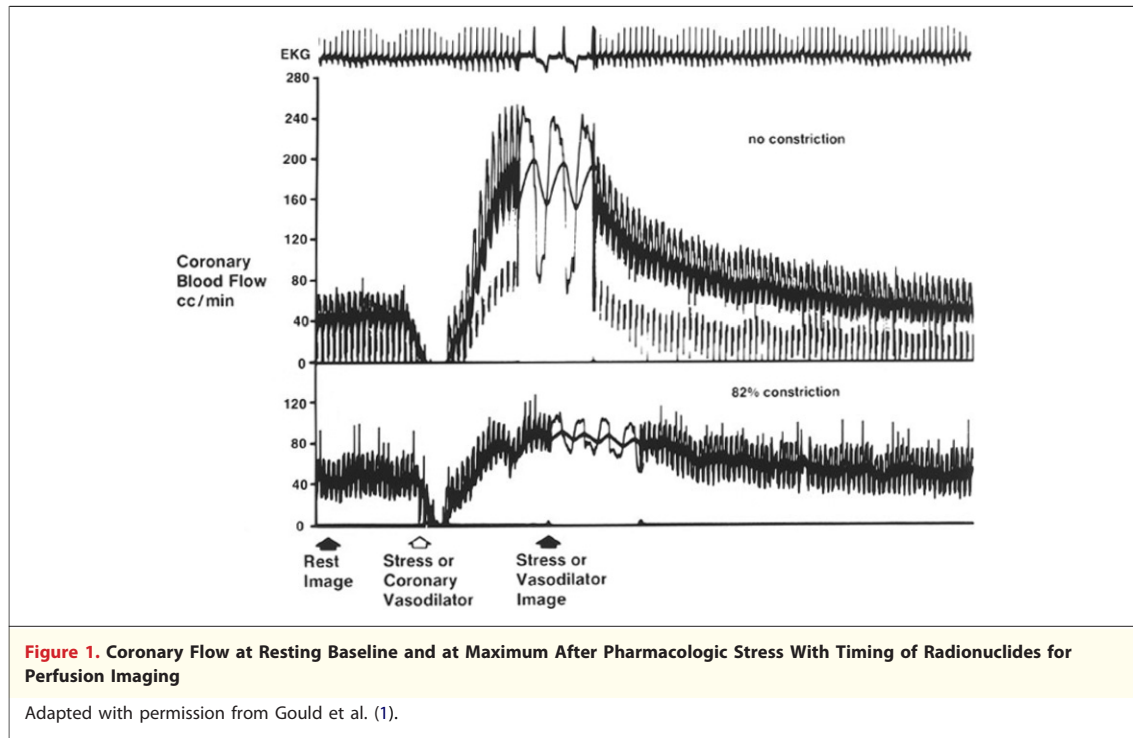


Figure 1. Coronary Flow at Resting Baseline and at Maximum After Pharmacologic Stress With Timing of Radionuclides for Perfusion Imaging

Adapted with permission from Gould et al. (1).

sion tomography (PET) and the remaining reports of the series (9,10,12,13).

PET

In an intense 3-week collaboration with Heinrich Schelbert, I flew a group of chronically instrumented animals to the University of California at Los Angeles for the first study of dipyridamole PET perfusion imaging. It showed dipyridamole-induced myocardial perfusion defects for 47% diameter coronary stenosis, with the severity of the defects proportional to quantitative arteriographic severity. As the last experiment finished, the scanner went down with a blown power supply. An all-night data analysis and writing session made the deadline and won the von Hevesy Prize for research in 1978 (9).

Stenosis Pressure-Flow Characteristics

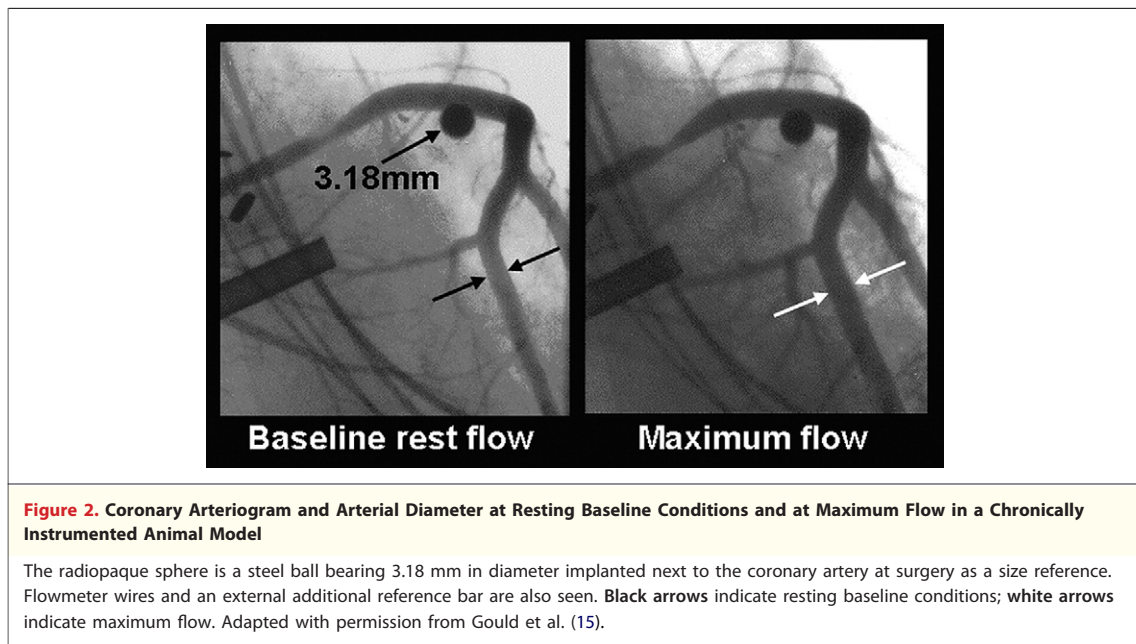
In retrospect, at this point a very important issue slipped by me because of my intense focus on stenosis. My pressure-flow data with quantitative arteriographic dimension of stenosis fit classic quadratic equations described in the fluid dynamic literature (14) at resting conditions. At maximum flow, the data failed to fit the same equations that worked at rest. This discrepancy was deeply disturbing for 1 year because it called into question everything done before—data quality, the physio-

logical and fluid dynamic concepts—nightmares of failure. Finally, I realized that the data at maximum hyperemic flow fit the classic fluid dynamic equations only if the stenosis dimensions were worse than at baseline resting flow conditions.

Flow-Mediated Vasodilation

How could the stenosis at maximum hyperemic flow be worse with a fixed rigid mechanical constriction on the coronary artery? The answer was on the arteriograms done with pressure flow data, shown in Figure 2. At maximum hyperemic flow, the normal coronary artery on each side of the stenosis dilated substantially so that the percent stenosis was worse, thereby explaining more severe pressure flow characteristics during hyperemia compared to resting baseline conditions, as published in 1978 (15).

This first demonstration of flow-mediated epicardial coronary vasodilation was interesting because the mechanism was unknown. However, having tied together the concepts of coronary flow reserve, pharmacologic stress, and the pressure-flow-anatomy relations of coronary artery stenosis, I headed for the University of Texas at Houston as Chief of Cardiology to establish the first dedicated clinical cardiac PET center, and failed to pursue those mechanisms. In 1980, Furchgott (16) re-



ported the mechanism of flow-mediated coronary vasodilation as endothelial acetylcholine.

Clinical Cardiac PET

In Texas, my PET technical team, under the direction of Nizar Mullani, Ross Hartz, and David Bristow, designed and built the first multiring PET scanner for imaging the entire heart in 1 acquisition without indexed repositioning for each tomographic slice. As this scanner was completed, before the cyclotron building was finished, we did the first large clinical trial of generator-produced rubidium-82 compared with quantitative coronary arteriography (12,13).

Dipyridamole PET perfusion imaging was also identifying early asymptomatic CAD, raising the difficult issue of management not found in traditional paradigms of cardiovascular medicine at the time. However, cardiac PET perfusion imaging was incorporated into a trial of extremely low-fat, complete intravenous alimentation in patients with inoperable CAD. Dipyridamole PET showed smaller stress-induced perfusion defects immediately after 90 days of low-fat intravenous alimentation compared with baseline PET before treatment or with PET at 60 days after treatment was ended (17). We hypothesized that this short-term improvement in myocardial perfusion was caused by improved endothelial function, later confirmed by others.

The Lifestyle Heart Trial (18) confirmed improved myocardial perfusion by PET imaging in

CAD patients after 1 year on a low-fat diet; PET imaging further confirmed improved myocardial perfusion in association with and predictive of reduced coronary events after 5 years of combined vigorous lifestyle and lipid-lowering drugs (19,20). Additional experimental studies defined relative and absolute coronary flow reserve as the physiological basis for quantitative PET perfusion imaging (21).

The Weatherhead PET Center for Preventing and Reversing Atherosclerosis

The technology has evolved to PET-computed tomography (CT) that has strengths but also significant complexities and potential errors not widely recognized or resolved (22). Having developed solutions to these problems, the Weatherhead PET Center for Preventing and Reversing Atherosclerosis now routinely uses PET for identifying early or advanced CAD, for assessing its physiological severity as the basis for invasive procedures or not, for following up changes in severity, and for improving patient adherence. Quantitative PET perfusion images show the entire range of absolute flows and coronary flow reserves of each artery down to small branches with single or multiple stenosis, diffuse disease, and/or myocardial steal indicating collateralization, illustrated in Figure 3. Here, PET imaging has become integral to and inseparable from management of CAD—integrated diagnosis, treatment, and procedural guide (23–25).

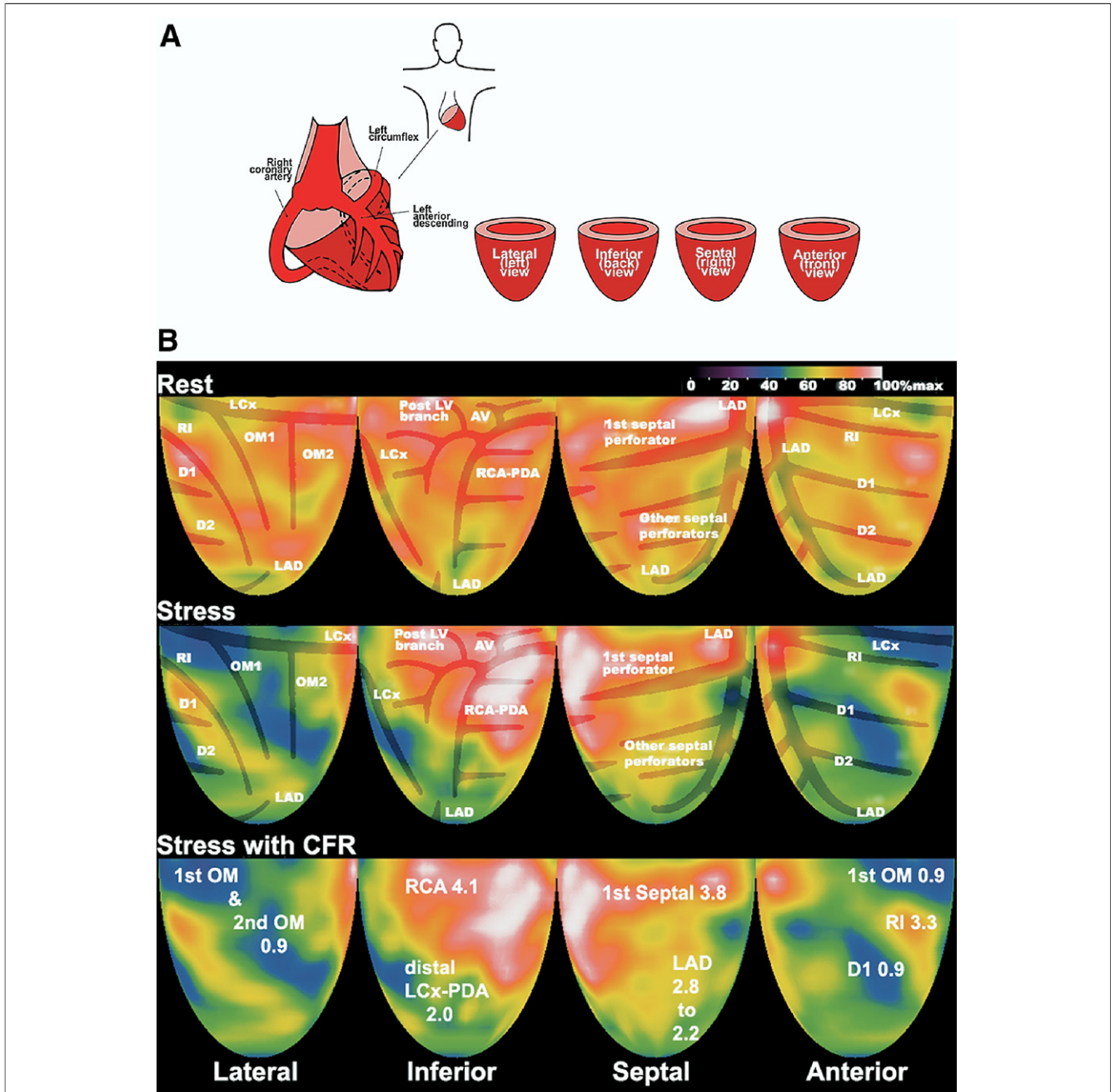


Figure 3. PET of Myocardial Perfusion

(A) Orientation of views. Adapted with permission from Sdringola et al. (20). (B) Myocardial uptake of rubidium-82 at rest and during dipyridamole stress showing relative myocardial perfusion reserve according to the color bar scale, ranging from maximum (white) in steps down to next highest (red), intermediate normal (yellow), intermediate low (green), low (blue), and lowest (black). The superimposed generic arterial map based on 1,000 PET-arteriogram correlations shows the precision of coronary arterial distributions by PET. In the lowest panel, values for absolute coronary flow reserve based on absolute myocardial perfusion in ml/min/g range from normal of 4.1 to intermediate low of 2.2 to 0.9, indicating myocardial steal characterizing collateralized occluded coronary arteries. In this example, the PET scans indicate severe diffuse disease of the left anterior descending, the left circumflex, and the distal posterior descending coronary arteries with collateralized occluded diagonal and obtuse marginal branches without myocardial scar on resting images, confirmed by coronary arteriogram. PET = positron emission tomography.

Assessing myocardial perfusion has evolved from initial concepts shown by flowmeter in experimental models to integration with detailed stenosis geometry to complex endothelial function to routine measurements of absolute myocardial flow and flow reserve of every artery and branch of the coronary tree as a guide to management of CAD.

The Future

Cardiovascular medicine and procedures are largely involved with coronary blood flow directly

or indirectly. However, few people measure or understand it in humans. Artifact-free, quantitative perfusion images, absolute myocardial flow in milliliters per minute per gram, and coronary flow reserve open profound new windows into the heart with awaiting discoveries and clinical applications.

Reprint requests and correspondence: Dr. K. Lance Gould, The Weatherhead PET Center, University of Texas Medical School, 6431 Fannin Street, Room 4.256MSB, Houston, Texas 77030. *E-mail:* k.lance.gould@uth.tmc.edu.

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Key Words: coronary flow reserve ■ myocardial perfusion ■ pharmacologic stress ■ stenosis fluid dynamics.

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