

**Simplified Quantification of Myocardial Flow Reserve with <sup>18</sup>F-Flurpiridaz: Validation with Microspheres in a Pig Model**

**TO THE EDITOR:** Sherif et al., in the discussion section of their recent article examining the <sup>18</sup>F tracer flurpiridaz, propose that "...[standardized uptake values (SUVs)] could be used as a substitute for absolute [myocardial blood flow (MBF)] values in assessing [myocardial flow reserve (MFR)] quantitatively. . . . SUV is a particularly attractive measure, because it does not require determination of tracer input function and, thus, could be measured even when the tracer is injected outside the scanner" (1).

These conclusions are not correct based on fundamental indicator dilution methodology. Both radionuclide uptake and SUV are directly proportional to coronary blood flow but inversely proportional to the cardiac output regardless of myocardial extraction (2,3). Because the increased cardiac output with exercise dilutes the intravenous dose of the radionuclide—thereby reducing the arterial input function, compared with rest—the arterial input function must be measured during rest and exercise to quantify absolute MBF. For example, myocardial uptake of <sup>201</sup>Tl decreases after exercise but increases after dipyridamole stress (Figs. 2 and 3 of Gould et al. (2), the "Implications for Thallium Imaging" of Sorensen et al. (3), and Fig. 15.9 of Gould (4)), because cardiac output increases greatly with exercise (5) but increases only slightly after dipyridamole infusion, compared with rest (2,3,6). However, coronary blood flow increases in both cases. The increase in cardiac output with a fall in the extraction of <sup>201</sup>Tl at higher flows reduces myocardial tracer uptake after exercise, compared with resting uptake. By contrast, for the same fall in extraction at high flows, myocardial uptake of <sup>201</sup>Tl after dipyridamole increases, compared with rest, because cardiac output does not substantially increase.

A tracer with constant extraction (or near-constant extraction, such as flurpiridaz) will, for identical changes in coronary blood flow, show no or minimal change in SUV with exercise, compared with rest, but will show an increase in SUV with vasodilator stress (as seen in the work by Sherif et al. (1)). Therefore, SUV alone cannot be used as a substitute for MBF or MFR. An arterial input function must be measured to quantify MBF or MFR regardless of the tracer. The highly linear relationship between SUV and MBF or MFR described by Sherif et al. (1) arises from their use of mainly vasodilator stress produced by adenosine, mixed with a pressor effect from dobutamine to avoid hypotension, producing a relatively larger increase in coronary blood flow, compared with a smaller increase in cardiac output under idealized, controlled, uniform experimental conditions (research animals, anesthesia, regular ventilation, controlled hemodynamics). Results in humans during exercise would not reproduce these findings or the same slope of the SUV-to-flow regression because of the increased cardiac output with exercise that is highly variable in patients relative to coronary flow.

In conclusion, to quantify myocardial perfusion in cm<sup>3</sup>/min/g or myocardial or coronary flow reserve, the arterial input would have to be imaged quantitatively while <sup>18</sup>F-flurpiridaz was being administered intravenously during stress perfusion imaging.

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**REPLY:** We appreciate the thoughtful letter from Drs. Johnson and Gould expressing their concerns with an extrapolation from our study that the ratio of standardized uptake values from stress and rest studies could serve as an index of myocardial flow reserve when a physical stress test is used (1). Consistent with remarks by Drs. Johnson and Gould, in human studies at 30 min after flurpiridaz injection, myocardial standardized uptake value was found to be 5.2, 10.8, and 5.5 at rest, pharmacologic stress, and exercise stress, respectively (2). Consequently, we fully agree that a noninvasive assessment of the arterial input function to estimate myocardial blood flow is the appropriate strategy for this stress condition. Furthermore, studies in humans under different stress conditions are necessary to evaluate whether simplified acquisition and analysis schemes are applicable.

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