Quantification of Myocardial Flow Reserve Using Positron Emission Imaging

The Journey to Clinical Use*

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*A journey of a thousand miles begins with a single step*
—Lao-tzu, The Way of Lao-tzu

Chinese philosopher (604 BC to 531 BC) (1)

Of the many advantages of positron emission tomography (PET) imaging, its ability to quantify biological parameters is often identified as the most important. Yet, data linking PET-derived parameters to outcomes are often lacking. In this issue of the Journal, Herzog et al. (2) present one of the first studies to evaluate the prognostic value of PET-derived quantification of coronary flow reserve (CFR) using $^{13}$N-ammonia ($^{13}$NH$_3$) in patients with suspected ischemia and the first to evaluate its added prognostic value compared with relative myocardial perfusion imaging (MPI). Such evaluation is a key step on the journey to establish the clinical role of this approach.

The coronary circulation is a dynamic vascular bed that matches blood flow with oxygen requirements governed by autoregulatory mechanisms. In myocardium supplied by an obstructive coronary artery stenosis, blood flow is maintained through such mechanisms until there is a more critical stenosis or there is an increase in demand, which results in a supply-demand imbalance leading to ischemia. As such, myocardial blood flow (MBF) has long been recognized as a key physiological parameter in cardiovascular health and disease (3). Accordingly, MPI has evolved as a diagnostic method to evaluate the hemodynamic significance of obstructive coronary artery disease (CAD). The role of MPI in diagnosis and prognostication is well established for single-photon emission computed tomography (SPECT) (4) and more recently, PET (5–7). PET is also capable of flow quantification in absolute terms (ml/min/g) during stress and rest, the ratio of which is the CFR (8,9). Measurement of CFR may have a role in early detection of coronary atherosclerotic disease (microvascular dysfunction) (9) or reveal the presence of diffuse obstructive CAD (9,10). Although this approach has been firmly established in research settings for almost 3 decades (11), its widespread role in the clinical arena has not been realized. Even so, there is growing interest in its potential added value due to the current limitations of relative MPI in these settings.

In the journey to translate PET quantitative flow analysis into a useful routinely applied clinical tool, several steps need to be accomplished. First, the parameter must have pathophysiological relevance in relation to disease. Subsequently, methods to measure the parameter must be validated and reproducible, available, easy to apply, and must demonstrate added value for diagnostic or prognostic applications that affect therapy decisions leading to improved outcomes.

Gould et al. (3) described the value of CFR as an index of the functional severity of coronary stenosis, supporting its pathophysiological relevance (12). Resting MBF remains normal until there is an 80% to 85% diameter stenosis; CFR decreases progressively if the stenosis is >40% (12). Flow quantification with PET has been well validated and shown to be reproducible (13–15). With expanding application in cancer, PET is becoming more widely available. List mode acquisition now enables simultaneous gating with dynamic acquisitions for kinetic modeling, making routine flow quantification possible. However, whether flow quantification with PET provides added value to current MPI has not been widely evaluated to date. The study by Herzog et al. (2) is a timely step in this regard.

Herzog et al. (2) included 229 patients, of whom: 69% were males, 66% had known CAD, 62% had angina, and 82% were on anti-ischemic medications. This is a relevant cohort for evaluation, though slightly different than other studies, which included more women (5,6) but fewer patients with known CAD (40% to 53%). The authors used $^{13}$NH$_3$, a well-validated tracer for flow quantification.

Patients with abnormal CFR had significantly worse outcomes than those with normal CFR: 45.1% versus 23.6% major adverse cardiac events and 20.6% versus 6.3% cardiac death, respectively, over a mean follow-up of 5.5 years. This adds to the growing literature supporting the prognostic value of PET-derived flow and CFR in patients with nonatherosclerotic cardiomyopathies (16,17) and in patients with severe CAD not amenable to revascularization with...
left ventricular dysfunction (18). To date, such CFR data have not been shown to alter management decisions that affect symptoms, quality of life, or outcomes.

The study by Herzog et al. (2) suggests that CFR yields added value for patients with abnormal perfusion and enables risk stratification with normal perfusion. In patients with abnormal perfusion, an impaired CFR was associated with higher rates of major adverse cardiac events and cardiac death. So, it seems that a reduction of CFR in this subgroup of patients affords incremental prognostic information. However, the study was too small to determine if the incremental increases in the summed stress score on MPI may have yielded similar results. Still, if the CFR results can be further validated, this parameter has the potential to alter decisions specifically regarding revascularization.

Conversely, in patients with normal perfusion, a normal CFR was considered to yield a warranty period of 3 years compared with those with abnormal CFR. The small sample size limits detection of differences beyond this point. This abnormal CFR may represent a biomarker of microvascular dysfunction due to effects of CAD risk factors (19), which may contribute to the pathogenesis of disease that will later lead to myocardial ischemia and events, thus representing potential therapeutic targets (9). Although this mechanism is proposed by the authors, there is no coronary anatomy correlation to confirm this hypothesis. Do we know for certain for a given patient whether global flow reserve reduction is due to balanced 3-vessel CAD versus microvascular disease or both? The presence or absence of relative perfusion abnormalities may favor the former or latter, respectively. The severity of reduced CFR may also help. However, none of these features would be definitive, so coronary anatomy definition may become necessary. In patients with abnormal CFR without other high-risk features on imaging, CT angiography (either independent or as part of hybrid imaging) may play a valuable role.

How certain are we of the potential added value of flow quantification in this study? The work of Herzog et al. (2) has limitations that require consideration in this regard. The study was observational and data were retrospectively acquired. So, there is selection bias. Furthermore, although the statistical methods are appropriate for defining independent predictors, the sample size does not permit full use of interaction testing to help define the relationship between perfusion score and CFR. In Table 2 and Figures 2 and 3 of Herzog et al. (2), we see that overall, there is an effect of CFR on outcomes for abnormal perfusion but, in fact, not for normal perfusion patients. To be confident that the CFR added prognostic value in a subgroup, the interaction must be considered. The authors state that there is no interaction effect of perfusion and CFR. However, the study was not powered to be confident that no interaction exists. Without an appropriately powered interaction analysis, it is difficult to be definitive about the subgroup findings (20). Future studies should consider the guidelines proposed by Wang et al. (21) so that interaction tests used to ensure the differences between and within subgroups are considered when investigating the value added of one predictor over another.

Other unresolved issues include the prognostic value of regional CFR that is not evaluated (acknowledged by the authors) and the selection of a cut-off value of CFR <2. Others have suggested 2.5 (22). If 2 SDs from the mean in a normal population is selected, cut-points of 1.8 or lower would be selected (8,23). In the current study, patients with a CFR <2 are at increased risk for major adverse cardiac events and cardiac death, but more likely there is a continuum of risk. Larger studies will be needed to ascertain such incremental risk.

There is also uncertainty as to the best index of PET quantitative flow analysis. CFR is most commonly used, but the myocardial stress-rest flow difference (or absolute reserve) and hyperemic MBF have also been proposed (8–10).

Finally, although 13NH3 is well validated, it is a short t1/2, cyclotron product, thus limiting its availability. The wider application of CFR will likely require different tracers. Recent data indicate that PET rubidium-82 (82Rb) is feasible to obtain accurate flow values (24,25), but the added prognostic value of CFR using 82Rb PET has not been assessed. Novel 18F-labeled PET perfusion tracers are promising (26–28) given the potential for wide distribution, but have not been validated in humans. Animal studies using gallium complexes (29) present the potential for long t1/2 generators. It is uncertain whether flow quantification with these new radiotracers will be possible. The importance of quantifying flow has been realized, spawning investigation using other noninvasive technologies, magnetic resonance imaging (30), computed tomography (31), and SPECT (32), with PET as the gold standard for comparison (8). Clinical utility is highly suspected but not yet proven.

Herzog et al. (2) have brought us to the foot of the final path and taken a major step forward. The full clinical utility of PET flow quantification will require larger prospective studies using more widely available tracers to determine its impact on decisions that affect outcomes, quality of life, or costs. As noted by DeMaria (33), “Additional data on comparative effectiveness should help us make better clinical decisions and result in better care for our patients.” The journey continues, with the end of the trail in sight.

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