Quantitative coronary flow capacity for risk stratification and clinical decision making: Is it ready for prime time?

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Semi-quantitative evaluation of regional myocardial perfusion has been standard practice in nuclear cardiology for more than three decades. This approach has proven to be accurate and reproducible. Most importantly, semi-quantitative measures of total perfusion deficit and myocardial ischemia are powerful markers of clinical risk and have served as clinically relevant guides to patient management. However, the notion of ischemia-guided approach to management of stable coronary artery disease (CAD) is now being revisited and there is considerable debate regarding its role in patient management. Older observational data determined that a SPECT-defined threshold of ~10-15% ischemic myocardium was associated with equipoise between early revascularization and medical therapy among a large cohort of patients without known CAD, with increasing amounts of ischemia associated with enhanced survival after revascularization. These results were extended to other populations in subsequent studies. On the other hand, sub-studies from large randomized clinical trials comparing revascularization versus contemporary guideline-directed medical therapy (GDMT) for management of patients with stable CAD have reported conflicting results. In fact, the question of whether the presence of moderate-severe ischemia (>10% of the left ventricular myocardium) associates with a prognostic benefit from early referral to revascularization compared to GDMT is the subject of the ISCHEMIA trial, which recently completed enrollment.

Over the last 10 years, we have seen a growing interest in using quantitative myocardial blood flow (MBF) and flow reserve (MFR) as assessed by PET to improve diagnosis and management of CAD. It has been argued that such quantitative flow measurements provide a more accurate assessment of myocardial perfusion, thereby overcoming several important limitations of conventional semi-quantitative perfusion imaging including the underestimation of the extent of ischemia and obstructive atherosclerosis in the setting of multivessel CAD, and the inability to identify patients with clinically important non-obstructive atherosclerosis. Indeed, a growing body of data have demonstrated that quantitative MBF and MFR are unique phenotyping tools to assess vascular health and pre-clinical atherosclerosis which, in higher risk patients, can reveal flow-limiting coronary artery stenoses, thereby improving the accuracy of myocardial perfusion imaging in the diagnostic evaluation of known or suspected CAD. More recent data support the notion that coronary vascular dysfunction, as quantified by reduced MFR, is highly prevalent among patients with known or suspected CAD, increases the severity of inducible myocardial ischemia (beyond the effects of upstream coronary obstruction) and sub-clinical myocardial injury, and identifies patients at high risk for serious cardiac
adverse events, including cardiac death\textsuperscript{15-19} and heart failure\textsuperscript{20}. There is also emerging evidence that a reduced MFR may help identify patients who benefit most from revascularization\textsuperscript{21}.

In this context, the study by Gould et al in the current issue of the Journal [reference] sought to assess whether the measurement of the so-called coronary flow capacity (CFC), which integrates quantitative measurements of stress MBF and MFR, may provide incremental prognostic information that may potentially allow to direct care by selecting patients who would benefit most from revascularization. The study reports 3774 patients with known or suspected CAD referred to their center for rest and stress myocardial perfusion PET imaging for the evaluation of symptoms and/or to assess the physiologic significance of known coronary artery stenoses. Overall, 74% of patients were non-obese male with normal left ventricular function, 41% had known CAD and only 11% had anginal symptoms. Patients were followed for up to nine years with an average of 3 years for the occurrence of all-cause death, myocardial infarction (MI), stroke and revascularization excluding patients followed <90 days. The analysis was performed on a per-scan and per-patient basis with time dependent covariates for outcomes after each PET at different times in same patient or for different patients, indicating that the analysis included more than one PET scan and possibly more than one event per patient.

\textit{Does CFC severity predict risk?}

In risk adjusted analyses, they found that a severe reduction in CFC (i.e., CFR $\leq 1.27$ \textit{and} stress MBF $\leq 0.83$ cc/min/g) involving $\geq 1\%$ of the left ventricle was associated with a higher risk of major adverse cardiovascular events (MACE) including all cause death. This is not surprising given all prior data showing a prognostic association with both components of the CFC measurement\textsuperscript{15-19}. Importantly, a severe CFC was not associated with MACE after adjustment for revascularization as a time-dependent covariate (Supplemental table 1). Consistent with the extensive prior literature cited above\textsuperscript{15-19}, both regional and global reduction in MFR were also associated with the risk of MACE (Supplemental tables 2 and 3).

\textit{Does CFC severity predict prognostic benefit from revascularization?}

A major goal of the study was to assess whether a severe reduction in CFC by PET could help identify patients who may benefit prognostically from revascularization. Because of the observational nature of the study design, they developed a propensity score to account for differences between patients undergoing revascularization and those treated medically. The propensity score included a number of clinical, historical and some imaging variables including LV ejection fraction and resting perfusion defect
size. Surprisingly, it did not include the extent and severity of stress induced defects or ischemia—arguably the most important determinants of referral to catheterization and revascularization along with the severity of patient symptoms\(^1\). Their analysis showed a significant interaction between the extent of severe CFC reduction and revascularization within 90 days of PET imaging and reduced risk of all cause death during follow-up. No significant interaction was observed between the extent of mild-moderate reduction in CFC or other perfusion metrics including the extent and severity of regional perfusion defects, minimal regional stress MBF or MFR and revascularization.

Based on these data, the authors conclude that estimates of coronary flow capacity integrating regional MFR and stress perfusion in cc/min/g by PET provide an imaging marker of clinical risk which can be used to guide revascularization decisions and claim that such approach can help reduce the risk of death and MI by 54%. The strengths of the study include the relatively large number of patients with detailed quantitative PET myocardial perfusion data, the experience of the investigators in quantitative analysis of PET data, and the lengthy and robust follow up of their cohort.

Compared to randomized clinical trials, observational studies have several advantages including the ability of following larger, unrestricted cohorts with robust data collection for long periods of time. However, such study design requires robust statistical methods to overcome both potential confounding as well as the lack of treatment randomization\(^2\). Observational studies such as this one are difficult to interpret when confounding and bias are unaccounted or partially accounted for, more the case when complex analyses are attempted\(^2\). Thus, the current study’s internal validity is undermined by numerous methodological issues related to both multivariable model derivation and interpretation. First, seven survival models are presented, two modeling all cause death, the remainder modeling the composite of death/MI/stroke. In these models, CFC severe is often—but not always—a significant predictor of outcome and in one (Table 2) appears to be protective from events.

Second, the authors appropriately develop a propensity score but do not include key PET information available to referring physicians and a critical determinant of revascularization (i.e., extent of ischemia), calling into question the adequacy of this score. In fact, the revascularization group had very large stress perfusion defects involving nearly a third of the LV mass (28%) with little or no rest defects (indicating a large ischemic burden) compared to those who were treated medically (5%). In addition, the authors included it in only one model (Table 4) despite including revascularization use in all seven models. Given
the thresholds used to define a severe reduction in coronary flow capacity outlined above, it would be
difficult to imagine that those critical flow abnormalities would not be associated with a severe
perfusion deficit which is not only straightforward to see and measure, but it may also undermine the
incremental value of the quantitative flow capacity information and the claim of such a large prognostic
benefit from revascularization, which has not been realized in any of the large contemporary
randomized clinical trials in stable CAD. There are other methodological limitations including model
overfit based on the relatively limited number of deaths and limited statistical power (Table 4), lack of
accounting for medical therapy that impacts all components of the MACE endpoint, inclusion of multiple
and highly inter-related PET measurements of perfusion in their models without evidence that
collinearity was examined, and repeat testing without adequate statistical adjustment. In fact, from the
p values in the manuscript, adjusting their results for this repeat testing would eliminate the significance
of the study’s primary findings.

Third, correct model interpretation is important as well. To determine whether imaging results (CFC
severity) associate with a treatment benefit from an intervention (revascularization), a significant
interaction between the imaging metric of interest and the intervention use must be present as part of
the model. In the absence of this interaction, the statistical significance of revascularization use (with a
hazard ratio <1) indicates that risk is reduced by revascularization irrespective of the values of all other
variables. Hence, all but one model indicate that PET data was unnecessary to identify treatment benefit
with revascularization. Hence the claim that “...the threshold of any CFC severe (blue) remains as the
statistically significant association with reduced death, MI or stroke after revascularization within 90
days after PET by multiple Cox regression modeling...” seems unsupported. The models demonstrating
statistical significance for both PET data and revascularization use do not indicate that the PET data
associates with a treatment benefit after revascularization.

Quantitative thresholds of ischemia for guiding revascularization

As discussed above, prior data has suggested a threshold of ~10-15% ischemic myocardium as a point of
equipoise regarding the relative benefit of revascularization versus GDMT in patients with stable CAD23.
This has informed the design of the ISCHEMIA trial, which is testing whether revascularization of
patients exceeding this ischemic threshold offers a measurable outcome benefit compared to GDMT
alone. The finding of insignificant hazard ratios at every level of severe CFC extent (Supplement Figure 2)
further complicates the interpretation of the study results as does the inability to identify a threshold of
severe CFC extent associated with a survival benefit. This threshold is critical to inform prospective clinical trial design to test the effectiveness of this approach and, ultimately, translate the current findings into practice. Also, the current thresholds of stress MBF and MFR used in this study to define a severe CFC appear to be extremely low, which is in part related to the fact that they were derived from the development of clinical ischemia (ST segment depression and chest pain) during vasodilator-stress testing that is typically seen in patients with coronary steal in the setting of critical stenosis. In fact, the authors used the presence of a new stress defect as part of their definition of low flow ischemia in the CFC measurement. This suggests that if the CFC thresholds for revascularization benefit are that severely low, the incremental contribution of quantitative flow data may be more modest than described in this paper. Other studies have reported higher thresholds, which suggests that more research is necessary to define this very important point.

Coronary flow reserve, stress myocardial blood flow, or integrated coronary flow capacity
Stress myocardial blood flow and flow reserve measures are clearly inter-related and highly correlated and agree with each other (concordant abnormal and concordant normal) in a large number of patients. Calculated as a ratio, MFR is sensitive to unusually high or low resting flow values. These two clinical phenotypes (unusually low and high resting flows) are precisely the groups with the largest discrepancies in risk stratification between stress MBF and MFR. In such scenarios, the concept of coronary flow capacity, coined by the authors, is useful to understand pathophysiology and, more importantly, associated clinical risk. Patients with low stress flow but relatively preserved MFR are predominantly male and have a low risk of cardiac death (<1%/year), while those with preserved stress flow but reduced MFR are predominantly women with a substantially higher risk of cardiac death (1-3%/yr.). The differentiation of these two prognostically different groups is difficult as they were lumped as mild-moderate CFC reduction in the current study. The lower risk attribution of such patients in the study is likely related to the fact that they studied a predominantly male population. It is unclear that the risk thresholds and findings described in the study are also applicable to female patients.

In summary, despite its significant limitations the study provides provocative data that should motivate further research in this area as outlined above. Ultimately, the clinical value and role of quantitative coronary flow capacity or any other quantitative flow measurement to guide management of stable CAD will have to be tested in properly designed randomized clinical trials, which remain the best level of evidence we have to support clinical practice.


