EDITORIAL

Early insights of cardiac risk and treatment response with quantitative PET monitoring of coronary-specific endothelial dysfunction and myocardial perfusion reserve

Ronald G. Schwartz, MD, MS

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Quantitative measurement of absolute myocardial blood flow and myocardial perfusion reserve offers real promise in the assessment of heart disease.[1-6] Unlike cardiac CT and cardiac magnetic resonance imaging which can also provide non-invasive quantification of coronary blood flow in units of ml per min per gram tissue, positron emission tomography (PET) measurements of rest and stress coronary blood flow are based on kinetic modeling of true myocardial blood flow (MBF) which integrates flow of the entire coronary vascular tree and myocardial tracer uptake. Resting and pharmacologic vasodilator stress quantification of blood flow with Rubidium-82 and N-13 ammonia PET permit assessment of myocardial perfusion reserve, and these PET techniques are highly accurate for the detection of arteriographic stenoses[2,3,6].

Of greatest potential clinical value of quantitative PET is its ability to detect and track serial changes of early functional markers of cardiac risk and treatment response with coronary-specific endothelial dysfunction and total vasodilator reserve prior to the development of angiographically identifiable stenosis or microangiopathy and prior to the development of visible perfusion defects of routine rest and stress myocardial perfusion tomographic scintigraphy. Important long-term prognostic significance of reduced coronary flow reserve patients with normal N-13 ammonia PET perfusion images has been recently reported by Herzog et al.[4] The relatively mild degree and pervasive extent of endothelial dysfunction likely account for the absence of detectable perfusion defects by visual or semi-quantitative analyses of SPECT or PET images.[3,4] Alterations of coronary endothelial function with cold pressor testing (CPT) reflect upstream changes of coronary pathophysiology that precede symptoms, stress-induced ECG repolarization changes, and wall motion abnormalities that characterize traditional clinical recognition of the ischemia cascade associated with the development of coronary stenoses.[7-11]

Ample evidence exists of the pathogenesis of coronary artery disease associated with these measurable, pre-stenotic functional abnormalities of reduced vasodilator response by cardiac PET. While resting flow remains relatively intact, the magnitude of reductions of stress-induced blood flow correlate with the degree of cardiovascular risk. Numerous reports identify progressive reduction of stress-induced myocardial blood flow along the spectrum of cardiovascular risk in patients with hyperlipidemia,[12-14] diabetes,[15-18] cigarette smoking,[19] family history of a primary relative of a parent or sibling with a coronary disease event,[20] the presence of multiple coronary risk factors and increases in coronary vascular resistance,[21] chronic inflammation with coronary risk factors,[22] with increased risk of developing cardiovascular events,[23,24] with diffuse mild atherosclerosis prior to stenosis development with normal coronary angiograms,[25] in early atherosclerosis,[26] and in the regional segments without stenosis of patients with CAD.[27] The presence of microangiopathy as seen in diabetes, hypertrophic cardiomyopathy, and vasculitis also impairs total vasodilator reserve.[18] These scintigraphic reports correlate with contrast arteriographic observations of ''paradoxical'' vasospastic coronary vasomotor response in smooth coronary arteries induced by acetylcholine, adenosine, or CPT in patients with risk factors in the presence or in the absence of CAD.[28,29] The demonstration of the vasospastic response of the conduit coronary artery in response to endothelium-specific activation by CPT or by flow mediated dilation similarly identifies the presence of occult plaque, the subsequent development within 4 years of arteriographic stenosis,

From the University of Rochester Medical Center, Rochester, NY.
Reprint requests: Ronald G. Schwartz, MD, MS, University of Rochester Medical Center, Box 679-N, 601 Elmwood Avenue, Rochester, NY 14642-8679, USA; *ronald_schwartz@urmc.rochester.edu*.
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and the likelihood of a subsequent clinical cardiovascular event.[29] The stress-induced changes of myocardial blood flow and visible perfusion defects associated with the vasomotor response likely account for the consistent observation in the literature of their incremental value for prediction of clinical events when compared to clinical, exercise ECG, and arteriographic variables.[4,5,7-10]

Therapeutic reversibility of the stress-induced vasospastic response with statin and other lipid lowering therapy in patients with hyperlipidemia or CAD has been demonstrated by both angiographic[30] and scintigraphic data with PET[31-39] and SPECT,[40-43] as previously reviewed in the *Journal*.[44,45] In this issue of the *Journal*, Alexanderson et al[46] have extended these observations using N-13 ammonia PET with measurements of both coronary-specific endothelial dysfunction with CPT as well as adenosine-induced MFR reflecting total vasodilator capacity in patients with dyslipidemia treated daily for 8 weeks with the combination of simvastatin 40 mg and the intestinal cholesterol absorption inhibitor ezetimibe 10 mg. The investigators found reduced pre-treatment group mean values of CPT-derived Endothelial-Dependent Vasodilation Index (ENDEVI) and percent increase in MBF from baseline consistent with coronary endothelial dysfunction in patients with dyslipidemia compared to non-dyslipidemic controls. The expected treatment effects on all the components of the serum lipid profile were observed in the dyslipidemic group. With lipid treatment, substantial CPT-induced increases of ENDEVI and the percent increase of CBF from baseline were observed, consistent with an improvement in coronary-specific endothelial dysfunction. In contrast, the trend of improved total vasodilator reserve measured as MFR did not achieve statistical significance in the treated dyslipidemic group. Indices of coronary-specific endothelial dysfunction and total vasodilator reserve achieved normalized group mean values comparable to those of the control group, and the percentage of patients with coronary endothelial dysfunction decreased from 79% to 36% by the end of the 8-week lipid treatment period.

Thus, quantitative PET markers of coronary-specific endothelial function and total vasodilator reserve may provide a potentially important monitoring strategy to optimize lipid management. This report makes an important contribution to the seminal observations by Gould et al of reductions in extent and severity of Rb-82 PET perfusion defects with lipid lowering and lifestyle modification[31,32] and provides evidence of the incremental value of quantification of absolute flow and serial changes of indices of coronary-specific endothelial dysfunction with CPT for assessment of treatment effectiveness of dyslipidemia. Consistent with one prior report of rapid improvement in quantitative flow reserve with low fat diet and cardiac conditioning,[33] these findings document therapeutic responsiveness of prognostically important coronary vasomotor function well before the development of clinical events and substantially earlier than the observation periods noted in most prior reports with PET[31,32,38,39] and SPECT[40-45] techniques using visual and semi-quantitative analyses of extent and severity of defect resolution on statin therapy. This study also has important potential implications for primary and secondary prevention efforts to monitor treatment effectiveness. Thus, this evidence is a welcome addition to the literature and confirms expectations of improved coronary-specific endothelial function assessed with quantitative cardiac PET in pre-morbid dyslipidemic subjects treated with combination lipid lowering therapy.

Several limitations of the study should be considered. The study was relatively small and of short duration, and the study design did not permit direct correlation of measurements of coronary-specific endothelial function and coronary outcome events. The high cost and limited availability of PET imaging may discourage widespread use for optimizing individual treatment response. The number of subjects evaluated in their study was limited, and the independent effect of ezetimibe when compared to simvastatin was regrettably not addressed. Such a comparison of treatment effects of these two agents would be helpful to understand, given (1) the controversy surrounding the ENHANCE Trial,[47] which showed combined therapy with ezetimibe and simvastatin did not produce changes in intima-media thickness, as compared with simvastatin alone, despite decreases in levels of LDL cholesterol and C-reactive protein; (2) the lack of coronary outcome data with ezetimibe alone; and (3) understanding early in the course of management the physiologic effectiveness on coronary function of alternative treatment strategies of lipid lowering versus specific endothelial effects of statins. The authors suggest the importance of individualizing the treatment dose for the patient to achieve a normal coronary endothelial function as measured by quantitative PET, implicitly to improve outcome events. This suggestion is a testable hypothesis that merits further investigation. Whether monitoring coronary-specific endothelial dysfunction with N-13 ammonia PET offers advantages over brachial artery reactivity or other much simpler and less costly methods of assessing endothelial dysfunction in carotid or peripheral vascular beds is another important question, which requires additional study.

If verified by a substantial, multi-center clinical outcome study, the application of quantitative PET

analysis of coronary-specific endothelial function as reported by Alexanderson et al[46] could potentially reduce future costs of clinical trials and tailor individual treatment strategies regarding lipid management to maximize cardiovascular risk reduction. The approach could also help address therapeutic strategy questions. For example, whether statin sparing by ezetimibe has a clinical role when compared to other lipid treatments is currently unknown, and this approach of measuring coronary endothelial function may provide a means to assess efficacy of alternative treatments. Given the substantial therapeutic benefits of statins demonstrated consistently by randomized controlled trials in at-risk populations over the past two decades and the lack of evidence of therapeutic risk reduction beyond cholesterol lowering of ezetimibe, a role for statin sparing in lipid management may seen far fetched at the present time. However, several considerations suggest the value of confirming clinical benefit for the individual of lipid lowering therapy within 2 months of a potentially life long lipid lowering therapeutic strategy which include (1) subtantial residual risk remains and events occur even in the better treatment arm of randomized controlled trials; (2) controversy of the safety of ezetimibe ignited by the ENHANCE trial results; (3) the recent proposal of more widespread availability of ''Mac statin'' treatment to counteract unhealthy dietary choices[48] in an increasingly obese and sedentary population; (4) the potential for medication interactions, adverse muscular, and hepatic toxicities; and (5) the emerging uncertainty regarding the clinical significance of increased incidence of diabetes reported in randomized controlled trials of relatively short-term statin therapy lasting <5 years.[49-51] These considerations suggest the potential value of quantitative cardiac PET monitoring to confirm therapeutic benefit.

Alternative long-term lipid-modifying strategies of statin agent and dose, cholesterol absorption inhibitors, fibrates, niacin, fish oil regimens, anti-oxidant therapies, and the potential CETP inhibitors for treatment of cardiovascular risk confront the investigator and clinician. More controversial options currently exist for treatment of diabetes mellitus, as illustrated by the rosiglitazone controversy.[52] In the face of many challenging and questionable options of lifestyle and pharmacologic interventions, quantitative PET monitoring of coronary-specific endothelial dysfunction and myocardial perfusion reserve may offer unique timely and accurate physiologic insights of optimal treatment strategy in individuals with coronary risk in the presence or in the absence of dyslipidemia or previously recognized coronary artery disease.

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