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EDITORIAL COMMENT

Establishing the Prognostic Value of Rb-82 PET Myocardial Perfusion Imaging

A Step in the Right Direction*

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In the last decade, positron emission tomography (PET) myocardial perfusion imaging (MPI) has emerged as a valuable clinical tool for the management of patients with known or suspected coronary artery disease (CAD). Compared with single-photon emission computed-tomography (SPECT), PET provides higher-quality images and superior diagnostic accuracy (1). Increased availability of PET scanners, Medicare approval of PET-MPI reimbursement, and greater access to the generator-produced perfusion tracer rubidium (Rb)-82 have increased utilization. However, despite the growth of Rb-82 PET-MPI, the literature showing its prognostic value has been limited (2–6). Small sample sizes (2,3), possible overlap in study populations (3,4), a focus on high-risk patients with known CAD (2), substantial patient exclusions (2–4,6), limited outcomes data (5), and smaller numbers of cardiac events (3) are some limitations of the existing literature. Furthermore, the majority of studies did not use current PET technology, which may include the application of computed tomography (CT) for attenuation correction (AC) and electrocardiographic (ECG) gating for measurement of left ventricular (LV) volumes and systolic function (LVEF).

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In this issue of *iJACC*, Dorbala et al. (7) report on the prognostic value of gated Rb-82 PET-MPI in 1,432 consecutive patients followed up for a mean of 1.7 years. The investigators carefully performed image acquisition, processing, and interpretation using contemporary, clinically relevant techniques, including CT AC, rest/stress ECG gating, and iterative reconstruction (7). In their study, the rates of both all-cause death and cardiac events increased with increasing extent and severity of Rb-82 PET-MPI findings. In Cox proportional hazards modeling, Rb-82 PET-MPI variables of ischemia and scar and the difference between LVEF at rest and stress (LVEF reserve) were found to be incremental to clinical variables and LVEF at rest for predicting both cardiac events and all-cause death. In addition, LVEF reserve had incremental prognostic value compared with perfusion image interpretation—a truly novel finding.

What are the potential weaknesses of this study? The study group is quite heterogeneous—31% had known CAD, 17% were studied for pre-operative evaluation, 48% had an intermediate likelihood of CAD. Both rest and stress LVEF were only available on 985 patients (69% of the study group); these patients were not formally compared with the remaining patients. The clinical models for cardiac events and all-cause mortality only included those variables that were statistically significant in the study group. However, experienced clinicians usually also incorporate the presence and severity of typical angina and diabetes not requiring insulin into their patient assessment; these variables should therefore be forced into prognostic models to better reflect clinical decision making. The annual all-cause mortality rate was high (3.5%) in patients with normal perfusion scans, suggesting a population with extensive noncardiac problems.

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On balance, we consider these weaknesses minor; this article makes a substantial contribution to the prognostic literature regarding Rb-82 PET-MPI. Should it inspire widespread use of LVEF reserve and broad application of PET-MPI? This seems premature. The recently published negative multicenter experience with echocardiographic parameters for predicting the outcome of cardiac resynchronization therapy underscores the importance of adequate multicenter validation before widespread clinical application of new imaging techniques (8). This is particularly important for PET, because it is under scrutiny (along with cardiac magnetic resonance and CT) because its (primarily noncardiac) utilization has increased dramatically in the past 10 years. Before LVEF reserve is used on a more widespread basis, its potential benefit must be further evaluated and compared with its cost/inconvenience. Most of the investigators' patients underwent dipyridamole stress, which requires more prolonged monitoring, and therefore more nurse/physician time, than adenosine stress. Although a small minority of their patients underwent adenosine stress, we are not certain that their results can be extrapolated to adenosine because its shorter half-life is likely to lead to less prolonged ischemia and more rapid LVEF recovery than dipyridamole. The investigators' receiver-operator characteristic curve analysis is statistically rigorous, but the clinical impact of such receiver-operator characteristic curve differences may be surprisingly modest (9). Ideally, one should demonstrate how many patients are reclassified, that is, how many patients are moved across thresholds that prompt a change in clinical management. The investigators' heterogeneous study group makes such an analysis very challenging. As mentioned, 31% of the investigators' patients had known CAD. The complex clinical decision making in such patients depends on their symptoms and their time since revascularization/myocardial infarction. An additional 17% of patients were studied as part of a pre-operative evaluation. Current clinical practice guidelines are far more restrictive regarding such pre-operative testing (10). Many of the investigators' patients were probably tested before publication of the latest national guidelines and might not merit testing in the current era. Thus, the clinical decision-making process in these 2 groups is likely much different than in patients with an intermediate likelihood of CAD, the largest group in this study.

How do the results of the current study compare with the existing literature on the prognostic value of PET-MPI? Overall, there is general agreement on the prognostic value of Rb-82 PET-MPI among studies. However, mortality and cardiac event rates vary widely (Table 1), likely reflecting the heterogeneous populations across studies (selection bias) and other methodological factors. The disparity in cardiac event rates among studies may be attributed to the profound susceptibility of this approach to misclassification bias (11). Variability in censoring related to revascularization (12) and uncertainty regarding the number of patients revascularized after Rb-82 PET-MPI can also contribute to the disparity. Finally, unlike SPECT-MPI, PET-MPI studies are characterized by less standardization in the reporting of imaging variables. PET-MPI studies have used different criteria for defining normal versus abnormal results; for classifying mild, moderate, and severe abnormalities; and for describing ischemia and scar (2,3,6,7).

What can an evidence-based physician conclude from this study? The incremental value of Rb-82 PET perfusion and function shown in the current study, combined with its previously reported higher diagnostic accuracy (1), interpretative certainty (1), lower patient radiation exposure (13), and similar Medicare charges in many parts of the U.S. compared with SPECT, support more widespread use of PET for patients in whom it has a clear advantage. Within our institution, we recommend it for men over 120 kg and women over 100 kg, in whom SPECT images are frequently of poor quality. We

Table 1. Approximate Annual Event Rates in Relation to Rb-82 PET-MPI Results

			All-Cause Death (%)				Cardiac Events (%)			
Author (Ref #)	n	Known CAD (%)	Normal	Mildly Abnormal	Moderately Abnormal	Severely Abnormal	Normal	Mildly Abnormal	Moderately Abnormal	Severely Abnormal
Marwick et al. (2)	657	>50*	0.8	2.5	5.8	5.7	3.2	4.3	7.0	5.6
Yoshinaga et al. (3)	367	40	NA	NA	NA	NA	0.4	2.3	7.0	
Lertsburapa et al. (6)	1,441	54	2.4		4.1	6.9	NA	NA	NA	NA
Dorbala et al. (7)	1,432	31	2.5	5.0	8.0	10.0	0.5	2.5	5.5	10.0

*Prior myocardial infarction: 48%, prior revascularization: 37%, and on medical therapy: >50%.
CAD = coronary artery disease; NA = not applicable; PET-MPI = positron emission tomography–myocardial perfusion imaging; Rb = rubidium.

believe that broader application of PET to other patients is not yet justified, because SPECT-MPI has a far larger and more robust prognostic database encompassing at least 40,000 patients in over 20 studies (14). To match these considerable data, carefully designed outcomes-based single-center studies and multicenter registries, such as the SPARC (Study of Perfusion and Anatomy's Role in CAD) trial, are needed. Such studies should help identify those patients who are most likely to benefit from PET-MPI and thereby justify more widespread use.

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