EDITORIAL

Gated SPECT myocardial perfusion scintigraphy: a multi-faceted tool for the evaluation of heart failure

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Compared to the large volume of data available on the prognostic utility of myocardial perfusion scanning (MPS) in unselected patients referred for stress testing and several subgroups therein, there is only a relatively scant amount of literature pertaining specifically to the use of MPS to determine prognosis in patients with heart failure. One could be excused for being surprised at this state of affairs, since heart failure is widely prevalent, and frequently encountered by cardiologists, internists, and specialists in cardiac imaging, and MPS is one of the most widely utilized cardiac assessment tools.

In this issue of the Journal Candell-Riera and colleagues report on the prognostic value of clinically indicated Tc-99m gated SPECT MPS in a prospective cohort of patients with left ventricular ejection fraction (LVEF) $\leq$40%. Of 6114 patients referred to the authors' laboratory for MPS over a 6-year period, 365 had LVEF $\leq$40%. After excluding patients with nonischemic LV dysfunction and censuring patients who had early (with 60 days of MPS) revascularization, 167 patients with ischemic cardiomyopathy were followed up for an average of 2.3 ± 1.2 years to identify the variables associated with cardiac death. Thirty patients had stress testing precluded by severe heart failure and therefore, underwent only rest gated MPS. The mortality rate over this relatively short period of follow-up was substantial: 22% (36/167) all-cause mortality, of which 17% (29/167) were cardiac deaths. As expected, the majority of deaths in this population were from progressive heart failure (23), and most of the remaining were sudden cardiac deaths.

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MPS was read using a standard 17-segment LV model with visual, semi-quantitative scoring for perfusion and regional function. Residual myocardial viability was defined as preserved perfusion (normal to severe hypoperfusion) in $\geq$3 segments with severe dysfunction (severe hypokinesis, akinesis, or dyskinesis). For comparison with prior studies, this translates into an extent of viable but dysfunctional myocardium involving at least 18% of the LV myocardium, and approximates the threshold of critical mass that is generally accepted as clinically significant (i.e., predictive of recovery of function if revascularized, or of an adverse prognosis if not revascularized).[1] Perfusion assessment however, was based on visual rather than the quantitative (albeit relative) methods previously established as most accurate for detection of viability, and nitrate-enhancement was not performed.[2] On univariable analysis, patients who died from cardiac causes were older, less often able to undergo exercise testing, and had a greater prevalence of myocardial viability. Among patients who were able to undergo exercise testing, the survivors had greater exercise intensity and duration, with a lower prevalence of combined ischemia and viability, but not ischemia alone. Numerous other clinical and electrocardiographic criteria, *and notably all coronary angiographic criteria*, were similar between these groups. In a multivariable model that included the entire study group of 167 patients, myocardial viability and the inability to exercise were associated with cardiac death. In patients able to exercise, exercise intensity $<$75 W, exercise duration $\leq$5 minutes (cut-offs determined by ROC curve analysis), myocardial viability and ischemia were associated with cardiac death. The addition of the exercise MPS to the gated MPS variables significantly improved the chi-square of the model, thus establishing incremental prognostic value.

The Candell-Riera study, like any clinical study, has limitations when scrutinized for scientific rigor, and many of these are acknowledged by the authors. The results however are biologically tenable, and consistent with our understanding of the relationships between exercise capacity, myocardial viability, and outcome in heart failure. It is also one of the few prospectively conducted studies of the prognostic utility of MPS, for

even the large studies involving several thousands of patients that established the prognostic value of MPS were retrospective analyses.[3] Therefore, although these results are not unexpected, this study contributes important data to an otherwise sparsely populated field.

Prognosis in heart failure is intricately related to etiology. We know from epidemiological and clinical trial data that 60-70% of patients with heart failure have coronary artery disease (CAD), and fare worse than patients with heart failure which is unrelated to CAD.[4] However, it must be emphasized that the mere presence of CAD in patients with heart failure implies neither a causal relationship nor adverse prognosis. This was elegantly demonstrated in a study by Felker et al[5] of heart failure patients in the Duke database. When these patients were followed up, it became clear that patients with LV systolic dysfunction and single-vessel CAD have a prognosis similar to patients with LV dysfunction and no CAD, which was distinctly better than patients with LV dysfunction and extensive CAD (defined in that study as at least two-vessels with >70% stenosis, single vessel disease of the left main stem or proximal LAD, prior myocardial infarction, or coronary revascularization). This prognostic distinction between patients with ischemic LV dysfunction and patients with limited CAD co-existing with nonischemic LV dysfunction is important, since recent studies seem to indicate that the performance characteristics of MPS are excellent for the detection of extensive CAD (as defined in the Felker study) in new-onset heart failure patients, but only modest for limited CAD.[6] The Candell-Riera study adds further proof to the concept that gated SPECT MPS can reliably detect prognostically significant CAD in patients with heart failure. The study fell short of demonstrating a significant difference in outcome between patients who were treated medically and those who underwent revascularization. It was probably underpowered to do so, and not randomized to treatment strategy. The literature on the interaction of myocardial viability, treatment strategy, and patient outcome is limited by a conspicuous lack of randomized clinical trials. However, a meta-analysis of several observational datasets suggested that compared to medical therapy alone, coronary revascularization affords a survival benefit to heart failure patients with significant amounts of viable myocardium, but not to patients with predominantly non-viable myocardium.[7] The mechanistic basis of this relationship was demonstrated in a study by Senior et al[8] who showed that revascularization of viable myocardium results in an improvement in the sphericity index of the left ventricle, indicative of reverse remodeling, and a decrease in the LV end-systolic volume. These changes were associated with improved survival.

Thus, the composite of currently available data in the literature suggests that heart failure patients with extensive myocardial perfusion abnormalities are likely to have etiologically related and prognostically significant CAD and are therefore likely to benefit from coronary revascularization, while patients with normal MPI are unlikely to have prognostically significant CAD.

One important clinical question which remains is whether MPS can be reliably used in place of coronary angiography to exclude clinically important CAD in patients presenting with new-onset heart failure. While the growing evidence base increasingly suggests that this might be the case, a large prospective trial is needed to answer this question definitively. An important concern is that of balanced ischemia which is particularly relevant to the heart failure population. While the prevalence of balanced ischemia is likely to be low in heart failure patients without angina, stress induced ECG changes or perfusion abnormalities, this has not yet been demonstrated conclusively in a prospective clinical study. Therefore, given the critical importance of excluding significant CAD in this population, patients with new-onset heart failure continue to undergo coronary angiography for the exclusion of CAD.

MPS has also been applied to heart failure patients for indications beyond the assessment of CAD. A particularly promising use is for the assessment of LV dyssynchrony using phase analysis.[9] Preliminary studies suggest that dyssynchrony parameters derived from gated MPS may be useful to predict response to cardiac resynchronization therapy.[10] The high reproducibility of this completely automated application is likely to be a significant advantage over echocardiography, which is currently the most widely used imaging modality for this purpose, but limited by poor reproducibility.[11]

Another potentially useful application of gated MPS in heart failure is for the derivation of the LV shape index (the ratio of the short and long axis dimensions of the LV) analogous to the sphericity index derived from echocardiography, which is a measure of the degree of LV remodeling.[12] Extrapolating from the data on sphericity index, the LV shape index may predict prognosis, and functional response to interventions such as coronary revascularization and CRT. In preliminary studies, the LV shape index has been shown to correlate with symptoms and hospitalization for congestive heart failure,[13] and with response to beta blocker therapy.[14]

Thus, the many facets of information derived from gated-SPECT MPS including rest and stress myocardial perfusion, viability information, LV volumes, shape indices, and phase analysis can all be applied with advantage to the evaluation of patients with heart failure. In this environment of burgeoning and competing

new imaging modalities, these developments in the field of MPS are encouraging. For, as recent times have shown us, it is robust science and supporting data that drive the utilization and reimbursement of medical technology. The continuing evolution of supporting data for the use of MPS ensures that its future is bright, even scintillating!

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