

Surveillance for post-transplant coronary artery vasculopathy: Shifting gears from diagnosis to prognosis

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Coronary artery vasculopathy (CAV) developing in the allograft significantly limits event-free survival after heart transplantation. Some evidence of CAV can be detected by coronary angiography in 10% and 50% of patients 1 and 5 years after transplantation, respectively.¹ However, the disease is characterized by concentric and diffuse arterial hyperplasia in both proximal and distal coronary segments, and thus may be underestimated by coronary angiography. Furthermore, the diagnostic challenge is heightened by the absence of typical angina due to denervation of the transplanted heart. More sensitive detection techniques using intravascular ultrasound suggest that early evidence of CAV such as intimal thickening is prevalent in an even larger number of patients than detected by coronary angiography.² The pathogenesis of this intriguing and challenging condition is still somewhat speculative. The fact that patients without traditional risk factors, such as young patients transplanted for dilated cardiomyopathy, are at risk of CAV suggests a mechanism distinct from atherosclerosis. The involvement of allograft vessels with sparing of the host's native arterial system indicates that the disease is not solely caused by immunosuppressive therapy or systemic factors in the host.³ The current knowledgebase suggests that CAV is the result of immunological differences between the graft and host, leading to immunologically mediated arterial hyperplasia.⁴ Once the condition develops, no intervention has been shown to definitively reverse the process. The clinical course is

usually one of progressive myocardial ischemia leading to left ventricular dysfunction and heart failure. The diffuse nature of the arteriosclerotic process renders conventional coronary revascularization less useful, and re-transplantation remains the only definitive therapy. One-year survival is an abysmal 20% after a clinical ischemic event.¹ Thus, current clinical practice guidelines recommend annual surveillance coronary angiography in heart transplant recipients, the intent being early diagnosis of CAV. However, this approach is not optimal because of the associated patient risk and discomfort, and the performance characteristics of coronary "luminography," which are more suited for the detection of discrete rather than diffuse coronary involvement.

In this issue of the Journal, Alain Manrique and colleagues⁵ report on a study of 110 patients who had gated stress-rest SPECT myocardial perfusion imaging (MPI) using Tl-201 or Tc-99m sestamibi and surveillance coronary angiography within one month of each other, at least 18 months after heart transplantation. While prior studies have explored the utility of MPI in post-transplant patients, Manrique and colleagues used contemporary imaging methodology, i.e., *gated* SPECT imaging with mostly Tc-99m tracer, and thus had information on both perfusion and function. Abnormal coronary angiograms were classified into grade 1 (minor, diffuse irregularities or focal stenosis <50%) or grade 2 (obstructive disease) CAV. Outcomes measured consisted of cardiac events related to CAV: cardiac death, nonfatal MI, or re-transplantation, the primary endpoint, and late (>2 months after SPECT) revascularization, the secondary endpoint.

From a clinical perspective, the most relevant results pertain to the prognostic utility of SPECT in this population. It is noteworthy that 53% of SPECT performed an average of 66 ± 37 months (range 20-168 months) showed normal myocardial perfusion. While we are not told how many of these patients also had normal left ventricular function (stress ejection fraction $\geq 50\%$, and end-systolic volume ≤ 35 mL), we could perhaps infer that this number was high based on the good correlation between the summed stress score and left ventricular function. What is striking is the fact that in patients who had normal left ventricular perfusion *and* function on SPECT, the event free survival was 100% to at least

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27 months after the SPECT, and significantly better than patients with an abnormal SPECT. Multivariable analyses revealed that the presence of any CAV (RR = 8.816) and a stress perfusion defect >3 segments (RR = 5.607) were the only predictors of the primary end-point, and the latter the only predictor of late revascularization. A small post-hoc analysis performed by comparing outcome in the 17 patients who underwent late revascularization with non-revascularized patients matched for age and perfusion abnormality showed that revascularized patients were more likely to be re-transplanted, where as the predominant event in the matched, non-revascularized cohort was cardiac death. As expected, while parameters of abnormal myocardial perfusion and function were correlated with the presence of CAV, the diagnostic accuracy of MPI for the *detection* of CAV was only modest. However, there was a correlation between the degree of perfusion abnormality and the angiographic severity of CAV.

The diagnosis of CAV requires many unique considerations. The disease is characterized by diffuse involvement of proximal and distal coronary segments. Thus, coronary angiography, which relies on the presence of a normal reference segment to identify reductions in luminal diameter, does not have optimal performance characteristics for its diagnosis. Intravascular ultrasound is more sensitive for the detection of intimal thickening, an early manifestation of CAV, but is impractical for serial imaging.² Noninvasive coronary angiography using multi-detector x-ray computed tomography (CT), which visualizes the vessel wall, may have an advantage over the luminogram obtained by invasive coronary angiography in detecting intimal thickening.⁶ Limitations include the inability to sometimes visualize the distal branches, and the resting tachycardia prevalent in heart transplant recipients. Both invasive and CT coronary angiography require iodinated contrast with potentially deleterious effects in a population of patients with a high prevalence of compromised renal function due to toxicity from calcineurin inhibitor immunosuppressive therapy. In clinical practice, surveillance coronary angiography has to be avoided in a significant proportion of transplant recipients in an effort to preserve renal function. Thus, SPECT MPI, which is ubiquitously available, is an attractive option in this setting. The important question is whether it can replace coronary angiography as the surveillance imaging modality of choice. The study by Manrique and colleagues provides some important directions in this regard.

SPECT MPI is very well-established for the assessment of atherosclerotic coronary artery disease. Although it has excellent diagnostic accuracy for the detection of obstructive coronary artery disease, the unique strength of the technique lies in its ability to

predict outcome. The report by Manrique suggests that the prognostic power of SPECT MPI could be applied with advantage to the post-heart transplant population. Their data indicate that a normal SPECT MPI (perfusion and function) predicts excellent event-free survival in the intermediate term (up to 2 years, approximately), even when performed an average of 5 years after heart transplantation. Furthermore, the presence of perfusion abnormalities predicts progressive disease leading to revascularization, which in turn is associated with a lower rate of cardiac death. These findings suggest that serial SPECT MPI could potentially be used in place of serial coronary angiography for the noninvasive surveillance for CAV.

The data presented in this analysis are preliminary, and subject to the usual flaws of a retrospective analysis. Importantly, selection bias is very likely to have occurred in this cohort of post-transplant patients, included in the analysis based on having had a clinically indicated SPECT and surveillance coronary angiography within one month of each other. We have no information on contemporary patients who did not undergo SPECT. Such bias in patient selection can have unpredictable effects on the data. Similarly, specific criteria for revascularization were not predetermined, and we are not told why patients with comparable perfusion defects in the matched cohort were not revascularized. Other considerations unique to SPECT should also be addressed, such as the prevalence of balanced ischemia, given the diffuse involvement of the coronary vasculature characteristic of CAV.

Despite these limitations and unanswered questions, this report by Manrique and colleagues establishes a good reason to further explore the utility of SPECT for the surveillance of CAV. The current practice of annual coronary angiography in these patients is cumbersome, and exposes patients to potential procedural and nephrotoxic risk. The use of a noninvasive imaging modality such as gated-SPECT in this setting offers many advantages, but the available literature pertaining to this is generally based on outdated imaging methodology.⁷⁻⁹ Therefore, before this approach can be implemented clinically, a prospective clinical study to confirm the results of Manrique and colleagues and to explore other relevant questions is essential. In designing such a trial, it would be important to remember that diagnostic sensitivity and specificity using coronary angiography as the gold standard may not be the best parameter to determine the utility of SPECT in this setting. Drawing an analogy from the paradigm shift occurring in the assessment and management of atherosclerotic coronary artery disease, it is perhaps time to shift gears from diagnosis to prognosis when evaluating post-transplant patients for CAV.

References

1. McCarthy PM. Surgical management of heart failure. In: Libby P, Bonow RO, Mann DL, Zipes DP, editors. Braunwald's heart disease. Philadelphia: Saunders; 2008. p. 665-83.
2. Kobashigawa JA. First-year intravascular ultrasound results as a surrogate marker for outcomes after heart transplantation. *J Heart Lung Transplant* 2003;22:711-4.
3. Libby P. The vascular biology of atherosclerosis. In: Libby P, Bonow RO, Mann DL, Zipes DP, editors. Braunwald's heart disease. Philadelphia: Saunders; 2008. p. 985-1002.
4. Libby P, Zhao DX. Allograft arteriosclerosis and immune-driven angiogenesis. *Circulation* 2003;107:1237-9.
5. Manrique A, Bernard M, Hitzel A, Bubenheim M, Tron C, Agostini D, et al. Diagnostic and prognostic value of myocardial perfusion gated SPECT in orthotopic heart transplant recipients. *J Nucl Cardiol* 2010. doi:10.1007/s12350-009-9166-x.
6. Iyengar S, Feldman DS, Cooke GE, Leier CV, Raman SV. Detection of coronary artery disease in orthotopic heart transplant recipients with 64-detector row computed tomography angiography. *J Heart Lung Transplant* 2006;25:1363-6.
7. Smart FW, Ballantyne CM, Cocanougher B, Farmer JA, Sekela ME, Noon GP, et al. Insensitivity of noninvasive tests to detect coronary artery vasculopathy after heart transplant. *Am J Cardiol* 1991;67:243-7.
8. Rodney RA, Johnson LL. Myocardial perfusion scintigraphy to assess heart transplant vasculopathy. *J Heart Lung Transplant* 1992;11:S74-8.
9. Ciliberto GR, Mangiacacchi M, Banfi F, Massa D, Danzi G, Cataldo G, et al. Coronary artery disease after heart transplantation: Non-invasive evaluation with exercise thallium scintigraphy. *Eur Heart J* 1993;14:226-9.