



Figure 2. Lipid-Rich Cardiac Allograft Vasculopathy

IVUS (A), angiography (B), and NIRS (C) scans of the medial right coronary artery (RCA) in a 24-year-old male patient. The **white arrow (B)** indicates the location of the presented IVUS cross-sectional image. **White lines (B and C)** represent a region of the angiogram corresponding to the NIRS scan. **Yellow lines (C)** represent 2-mm blocks. The patient underwent heart transplantation 19 years earlier after aortic root wrapping surgery for an aortic root aneurysm that resulted in severe left ventricular dysfunction. His medical regimen (tacrolimus, sirolimus, nifedipine, losartan, and aspirin) did not include any lipid-lowering therapy. Coronary angiography revealed a focal 80% lesion in the mid RCA, IVUS minimal lumen area = 3.5 cm², and a lipid core burden index in a 4-mm segment = 524 (**blue lines**). Abbreviations as in Figure 1.

yellow). Chemogram analysis enables one to divide the scan into 2-mm blocks and quantify the amount of lipid on a scale of 0 to 1,000, termed the lipid core burden index (LCBI).

Similar to Hou et al., we captured 2 distinct patterns of CAV by NIRS during the routine hemodynamic and angiographic assessment in long-term survivors after heart transplantation. Simultaneous gray-scale IVUS and NIRS scans in the 2 allograft recipients 11 and 19 years after the transplantation demonstrated fibrotic (Fig. 1) and lipid-rich plaques (Fig. 2), respectively. Interestingly, the NIRS chemogram showed lipid-rich regions, even for the angiographically normal-appearing vessel in the latter patient who did not receive statin therapy.

The 2 different NIRS scans of CAV in transplant recipients may correspond to the difference in elapsed survival time from transplantation and use of medical therapy. Autopsy studies have confirmed that in the first 5 years after transplantation, CAV plaques are mostly composed of fibrotic tissue, whereas lipid accumulation is seen later. Gray-scale IVUS studies have provided some insight into the etiology of CAV in survivors 1 to 9 years post-transplantation (4). They have revealed diffuse and circumferential lesions in mid and distal coronary segments, suggestive of the fibrotic tissue. Focal and noncircumferential lesions observed in the proximal segment of the vessel early after transplantation indicated pre-existing atherosclerotic lesions. Radiofrequency (RF) analysis by IVUS (virtual histology) suggested that lipid-rich regions in neointima increased and fibrosis decreased with time over 1 to 20 years after the heart transplantation (5). However, the accuracy of RF-IVUS in lipid-rich plaque determination has been questioned, and characterization of the IH by other imaging modalities should be confirmatory. Interestingly, the accelerated lipid-rich atherosclerotic process in CAV seems to be slower compared with vein coronary graft plaques and in-stent restenosis development. This insidious process is often a result of younger vasculature of the allografts, which is likely to be devoid of pre-existing disease. The immunosuppressive therapy could also contribute to the delay in the process; statin supplementation further enhances the immunosuppressive efficacy of calcineurin inhibitors.

New intravascular imaging modalities may improve CAV screening in allograft recipients. They would contribute to the

understanding of the disease process and help to better define management strategies. Allograft vasculopathy is not unique to heart transplantation and may occur similarly in all transplanted organs, and the knowledge gained from coronary screening may have wider implications.

**Raman Sharma, MD, Tomasz Roleder, MD, PhD,
Ziad Ali, MD, PhD, Bary A. Love, MD, Annapoorna S. Kini, MD***

*The Mount Sinai Hospital, Interventional Cardiology, One Gustave L. Levy Place, Box 1030, New York, New York 10029.

E-mail: annapoorna.kini@mountsinai.org.

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Please note: Drs. Sharma and Roleder contributed equally to this paper.

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Prognostic Value of Coronary CT Angiography

We read with interest the paper from Andreini et al. (1) that provided more evidence on the prognostic value of cardiac computed tomography angiography (CTA) in patients referred for evaluation of possible coronary

artery disease (CAD), an area of research in need of long term follow up studies like this one (mean follow-up >4 years).

However, we noticed that the mean pre-test probability of CAD in the study population was 42.5%, with one-quarter of the patients having a high CAD probability, which is not in line with the most favored low-to-intermediate probability population referred for CTA for the exclusion of possible CAD (2), and that could explain the higher-than-expected hard event rate for a stable CAD population (almost 1 out of 2 patients with obstructive CAD dying or having a nonfatal myocardial infarction [MI]) in the follow-up (3). This could have been the result of having included patients admitted to the hospital because of new-onset chest pain (43%), a subset that could be considered as possible acute coronary syndrome (ACS) unstable angina/non-ST-segment elevation MI) and can explain the higher than expected rate of major (death/MI) events in the follow-up (event-free survival of 54%). In how many cases was an ACS diagnosis confirmed? If any, the authors should have excluded these patients from the study. We fully agree that CTA can provide useful prognostic information beyond the exclusion of obstructive CAD, but the inclusion of patients with possible ACS and high CAD probability could have lead to an overestimation of the prognostic power of CTA.

Another striking point was the fact that 45% of patients had hypercholesterolemia but only 26% were treated with statins. Further, statins turned out in multivariable analysis to be independent predictors for hard events. Likewise, 26% of the population (with suspected CAD) was taking aspirin, which is not generally recommended as primary prevention. Use of aspirin was also an independent predictor of all cardiac events. It would have been interesting to know if the use of these drug groups is allocated to a more severe subset of patients (more frequently used in obstructive vs. nonobstructive vs. normal patients) and in this way are just a surrogate marker of higher disease burden. Likewise, it would be of interest to know if patients were already taking these drugs before the CTA or if they were just started after significant disease was identified and, in this way, they could not have had enough time to come out with its protective effects in a more severe CAD subgroup of patients.

The Framingham risk score (FRS) was used to estimate the cardiovascular risk of this Italian cohort of patients; it could have been more accurately estimated with the European-based HeartScore (4). This could have also influenced the results, as the multivariable analysis models were adjusted for the FRS.

It is not mentioned that the events were independently adjudicated and that the adjudication event committee is an experienced one with acceptable intra-committee reproducibility for the adjudication of events. This point is of utmost relevance in a report of this nature. In addition, regarding *revascularizations*, we agree that early revascularizations should be excluded to avoid the influence of CTA results in patient management but most of the previous studies considered early as 30 days (5) and not 6 months like in the paper from Andreini et al. (1). This could have also influenced the results, as revascularizations in obstructive CAD group are likely to have happened sooner after the CTA and in this regard could have underestimated the prognostic value of obstructive versus nonobstructive CAD. Further, it is not mentioned whether the revascu-

larizations were ischemia-driven (i.e., only for obstructive lesions) or not.

Despite the fact that authors have scored hierarchically the plaque type per segment (i.e., in case of presence of 2 plaques, calcified and noncalcified, only one was scored and labeled as calcified) which underestimates the frequency of noncalcified plaques, in the univariate analysis, these were found to be independent predictors of hard events. This methodology seems to us to be counterintuitive, since it has been reported many times that high-risk plaques (i.e., plaques prone to rupture and associated with an event) are those noncalcified or mixed, which could have come out as strong predictors also in the multivariate analysis if the authors had not underscored them.

Undoubtedly, this is a report with an important message, but we feel that the above-mentioned points should be further explained to strengthen the conclusions.

**Pedro de Araujo Goncalves, MD,
Hector M. Garcia-Garcia, MD, PhD***

*Thoraxcenter, Erasmus Medical Center, Interventional Cardiology, Z120, 's-Gravendijkwal 230, Rotterdam, Zuid Holland 3015 CE, the Netherlands. E-mail: hgarcia@cardialysis.nl OR h.garciagarcia@erasmusmc.nl

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REPLY

The comments of Garcia-Garcia and Goncalves are relevant and allow us to expand on some results of our study (1). First, we found