Oxygen-sensitive magnetic resonance imaging: a non-invasive step forward for diagnosing vasculopathy in the cardiac allograft

Editorial to Iannino N, Fischer K, Friedrich M, Hafyane T, Mongeon F-P, White M. Myocardial vascular function assessed by dynamic oxygenation-sensitive cardiac magnetic resonance imaging long-term following cardiac transplantation. Transplant 2020; doi:??

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In this issue of Transplantation, Iannino et al. (1) explore the use of oxygen-sensitive cardiac magnetic resonance (OS-CMR) for noninvasive detection of cardiac allograft vasculopathy (CAV) after orthotopic heart transplantation (HTx). CAV still remains the third leading cause of late mortality posttransplant (2) and accounts for more than half of all cases hospitalized for graft failure. (3) Using a phenotyping approach based on unsupervised latent class mixed models, Loupy et al. recently identified four trajectories of CAV in a multicenter prospective cohort of HTx recipients followed by serial coronary angiography for detection of CAV. It is good news that the majority of these study participants never developed intraluminal pathology compatible with CAV (56% in the European part of the cohort and 74% in the U.S. part of the cohort), while fewer participants exhibited early-onset CAV with intraluminal pathology (6 and 13%, respectively). (4)

More recently, conversion to sirolimus was shown to mitigate progression of CAV and to decrease mortality in HTx recipients on standard immunosuppression. (5) However, this beneficial effect was only obvious when conversion was realized in early-stage CAV, which was detected in that study by intravascular ultrasound (IVUS) imaging of the epicardial coronary vessel wall. This result underlines the need of an imaging tool appropriate for detection of early-stage CAV. However, this imaging tool should not only visualize structural or functional change with early-stage CAV but, ideally, also provide a precision of measurement that enables the detection of small-scale progression, which is necessary to timely identify those patients with an adverse trajectory of CAV disease. Both IVUS and optical coherence tomography (OCT) fulfill these requirements and result in a high-resolution depiction of the coronary arteries. However, they both require the injection of contrast media, restricting their application to HTx recipients without more advanced kidney disease. Furthermore, these imaging tools are both invasive and therefore less adequate for serial investigation at short interval. (5,6)

This brings in non-invasive imaging techniques such as cardiac magnetic resonance (CMR) imaging, in particular because of its precise depiction of soft tissues. In the last decades, perfusion MRI with pharmacological vasodilator and gadolinium-based contrast agent (GBCA) injections has been well established for the assessment of the coronary circulation. Routine perfusion CMR can be used to measure the myocardial perfusion reserve (MPR), a

surrogate and semi-quantitative marker of myocardial blood flow in epicardial and microvascular coronary systems. Chih et al. assessed the feasibility of using the MPR to for the detection of CAV. (7) However, that study showed an imperfect correlation between the MPR and IVUS-based CAV assessment in epicardial coronary segments (7), since microcirculatory resistance, which is specific for the microvascular function, can remain normal even though early-stage CAV is present in epicardial segments. (8) These observations question the significance of structural changes in epicardial segments of the coronary vessel for assessment of CAV, while underlining the importance of MPR testing.

In their study, Iannino et al. used OS-CMR for the assessment of the change of myocardial oxygenation during a 30 seconds breath-hold, which had been preceded by an episode of hyperventilation maintained for one minute. (1) Breathhold-associated hypoxemia induces in the healthy coronary artery a vasodilatory response resulting in transient hyperemia, associated with increase or maintenance of oxyhemoglobin. However, pathological vasoreactivity, such as in CAV, restrains the hyperemic response, resulting in a continuous deoxyhemoglobin increase during the breath-hold and thus a decrease of the OS-CMR signal. Using the ratio of the OS-CMR signal intensity at the beginning and the end of the breath-hold therefore enables semi-quantitative assessment of coronary and microcirculatory vasoreactivity. The main advantage of the technique presented here is that it requires neither a pharmacological stressor that heart transplant recipients might be sensitive to (9), nor a GBCA that is contraindicated with more severe kidney disease. Furthermore, the magnitude of the response to the breathing maneuver is larger than what is normally obtained with a pharmacological vasodilator. A final advantage is the comparison between the rest and the stress state within a single measurement, while pharmacological MPR measurement needs two separate measurements, which are time-consuming and susceptible to change of the clinical conditions.

Iannino et al. observed that the OS-CMR signal change after the hyperventilation-breathhold maneuver was considerably different in HTx recipients from that in healthy volunteers. Furthermore, the OS-CMR signal was more decreased in moderate+severe CAV when compared with none+mild CAV as graded by coronary angiography. The number of patients with moderate and severe CAV (n=5+1) was rather small in this study as noted by the

authors, so it will be exciting to see this technique applied in a larger cohort. Furthermore, the OS-CMR signal was less strong in HTx recipients with increased interstitial fibrosis as quantified by extracellular volume mapping. This observation is in accordance with a recently reported positive association between interstitial fibrosis and intimal-media thickness of epicardial segments of the coronary artery as assessed by OCT. (6) This can indicate that interstitial fibrosis may also serve likewise as a marker for clinically relevant CAV on the basis that CAV-related hypoxia results in increased expression of hypoxia-induced factor 1 (HIF-1) and HIF-1 response elements, which by themselves induce expression of the pro-fibrotic cytokine TGFβ. (10) This suggests indirect relation of myocardial perfusion with structural change of the coronary vessel wall compatible with early-stage CAV, which can explain the imperfect correlation observed by Chih et al.

A final point of interest will be to see how the 91% of patients that could hold their breath for the full 30s in this study translates into a larger group, and how this compares to the percentage of patients that cannot participate in or complete an exam with a pharmacological vasodilator. Such a larger cohort will also allow for a sensitivity analysis of the technique, which may indicate if there is an OS-CMR cutoff indicating the presence of early-stage CAV, which appeared challenging in this study. Such a diagnostic indicator of early-stage CAV - especially without any injected compounds - would be of great clinical interest for the reasons discussed above.

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