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EDITORIAL COMMENT

Diagnosing Cardiac Allograft Vasculopathy

Focusing on the Little Things…*

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It has long been an axiom of mine that the little things are infinitely the most important.

—Arthur Conan Doyle,
The Memoirs of Sherlock Holmes (1)

Coronary artery disease, by common definition, refers to disease of the epicardial coronary arteries, conductance arteries that serve to transport blood. Much of cardiovascular medicine is focused on the investigation and management of epicardial coronary disease, perhaps in part because clinicians are able to straightforwardly, and accurately, interrogate the epicardial arteries (we measure what we can measure).

The coronary microvessels (extramyocardial prearterioles and intramyocardial arterioles) match blood flow to the requirements of myocytes by continuously modifying their resistance (resistance arteries) (2). With the exception of a few specific conditions, the coronary microcirculation has, until recently, been largely ignored, certainly clinically. With the advent of invasive techniques that specifically interrogate the microvasculature (e.g., index of microcirculatory resistance), and noninvasive imaging techniques, the prognostic importance of microvascular coronary disease has become apparent across several conditions, including coronary artery disease (3).

Cardiac allograft vasculopathy (CAV) continues to represent the main limitation to the long-term survival of transplanted hearts (4). CAV is an exemplifier of a disease that affects the epicardial and microvascular coronary compartments. Importantly, epicardial and microvascular disease occur independently, and both are independently predictive of prognosis (5). Thus, whereas transplant cardiology is relatively niche, CAV may serve as a model for coronary pathophysiology, its assessment and clinical implications, more widely.

SEE PAGE 255

In this issue of *iJACC*, Erbel et al. (6) demonstrate that semiquantitative myocardial perfusion reserve and early diastolic strain rate, both measured using cardiac magnetic resonance (CMR), are independently associated with microvascular disease, as determined histologically in 63 patients post-heart transplantation. Furthermore, myocardial perfusion reserve index and early diastolic strain rate, measured using strain encoding (7), were both associated with clinical outcome, albeit with a limited number of events included in the analysis because of the small sample size. The work is noteworthy in particular for the histological correlation of microvascular disease with imaging parameters.

An increasing number of CMR and positron emission tomography–based studies have demonstrated evidence of microvascular dysfunction across a range of conditions, although few have included reference standards. Although there are some notable omissions from their multivariable analyses (e.g., hypertension, diabetes, body mass index), Erbel et al. (6) now provide histological support for the microvascular dysfunction detectable on CMR. This ability to detect microvascular disease noninvasively potentially opens the window on the "black box" (2). Being able to quantitatively assess microvascular function, and change in microvascular function (as also demonstrated), potentially paves the way for the development and evaluation of specific coronary microvascular disease modulators.

The study also serves to reinforce that myocardial blood flow is dependent on microvascular function. Thus, accurate assessment of the diagnostic accuracy

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of functional imaging techniques (with visual or quantitative analysis) requires a reference standard that takes account of the microvasculature. Indeed, as demonstrated in CAV (8) and highlighted more generally (9), fractional flow reserve, which by definition is normalized (i.e., brought closer to 1) by microvascular dysfunction, does not provide a meaningful correlate for measurement of myocardial blood flow. It is also interesting that semiquantitative perfusion assessment performed well in the study by Erbel et al. (6), whereas we and many others in the CMR field have invested considerable effort in absolute quantification of myocardial blood flow (10,11).

The relationship between diastolic function and microvascular disease is in keeping with previous invasive work. Chronic subendocardial ischemia leading to impaired ventricular function may represent a mechanism of chronic graft failure, responsible for up 25% of deaths beyond the first year post-transplant (4). It will be interesting to see how techniques that measure deformation parameters (strain) directly from CMR cine images, which require shorter breath-holds and potentially allow more effective contour tracking, perform in this setting (12,13).

A major limitation of the study is the use of invasive coronary angiography to confirm the absence of epicardial disease, indeed a generous threshold of up to a 69% epicardial stenosis was permitted. It is well documented that significant (both anatomically and prognostically) epicardial CAV frequently exists in the context of apparently normal or mild angiographic disease. If clinicians are to further advance the understanding of CAV and evaluate the potential impact of interventions, angiography as a meaningful assessment of epicardial CAV must no longer be accepted, at least in the research setting.

Furthermore, in keeping with most studies involving heart transplant recipients, the size of the cohort precludes meaningful conclusions to be drawn with regards to clinical management. Indeed, given the small number of events, the study lacks power to detect important prognostic factors and the outcome data should be interpreted with caution. Larger, multicenter studies are required to better define the optimal CMR parameter cutoff values for detecting microvascular disease, and for evaluating their prognostic value.

Nevertheless, this study further demonstrates that noninvasive tools exist to quantitatively interrogate the microvasculature; perhaps clinicians can now start to focus on the little things. The challenge is developing effective therapies that can prevent or reverse the early features of microvascular disease.

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