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EDITORIAL COMMENT

Imaging in Aortic Stenosis—Let the Data Talk*

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Physiology plays an increasingly clinical role in cardiology. In this issue of *iJACC*, Steadman et al. (1) reflect this trend with their report on myocardial perfusion in aortic stenosis (AS) using cardiac magnetic resonance.

Noninvasive imaging transformed the assessment of AS. Echocardiography with Doppler quantification of valve function has replaced invasive hemodynamic catheterization as the primary clinical guide to management. Invasive measurements remain important for complex cases, confirmation, or physiological insights (2), but do not quantify myocardial perfusion or transmural perfusion gradients critical to understanding the pathophysiology of AS.

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In the developing era of transcatheter therapy for AS, we ask if noninvasive imaging can transform AS again for better understanding and clinical management. As the basis for this potential, we briefly review 3 physiological principles (3,4) for noninvasive physiological imaging in AS necessary for this second transformation to occur.

High pressure load, left ventricular mass, and myocardial flow. As pressure-work rises along the spectrum of AS, left ventricular (LV) thickness and, hence, mass increase to normalize LV wall stress. High pressure-work needs more coronary blood flow even at baseline conditions so that rest flow per unit mass (cc/min/g) increases.

Coronary flow reserve (CFR), the ratio of hyperemic to baseline flow, therefore falls as rest flow increases if maximal vasodilatory flow remains constant. This fall in CFR differs from the reduced CFR seen in structural microvascular dysfunction associated with impaired maximum vasodilatory flow. The association among LV thickness or mass, rest flow, and CFR, therefore, reflects these secondary changes in rest flow due to the primary pressure-work disturbance of AS, not primary structural microvascular dysfunction limiting maximum vasodilatory flow. This reduced CFR as secondary to high resting demand, not primary structural microvascular disease, has been recently confirmed by invasive coronary flow velocity and pressure wave analysis before and after transcatheter aortic valve replacement (2).

Diastolic perfusion time. Coronary perfusion primarily occurs in diastole. At rest, most patients even with critical AS meet myocardial flow demand, reflecting adequate diastolic perfusion time. However, with activity or tachycardia, the situation changes substantially. Rising heart rates both increase myocardial demand and decrease diastolic perfusion time. The result is supply/demand mismatch leading to subendocardial ischemia with potential angina, heart failure, syncope, and/or fatal arrhythmia.

As well documented (2,5), stress diastolic perfusion time closely relates to impaired maximum flow and flow reserve, particularly of the subendocardium. Recent work has also documented the immediate improvement after transcatheter aortic valve replacement of the coupling between heart rate and coronary physiological reserve (2). The improvement in coronary reserve paralleling diastolic perfusion time immediately after transcatheter aortic valve replacement indicates that pri-

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mary structural microvascular dysfunction is not the cause of reduced CFR in AS but rather limited diastolic perfusion time during stress or tachycardia.

Transmural perfusion gradient. Normally flow to the subendocardium slightly exceeds that to the subepicardium (6). However, this transmural gradient becomes reversed in severe AS particularly during stress tachycardia as shown by quantitative positron emission tomography perfusion imaging (5). Perfusion imaging techniques with high short-axis spatial resolution such as computed magnetic resonance imaging and computed tomography have yet to study this gradient in humans.

Clinical challenge. The clinical challenge for selecting patients for surgical or transcatheter aortic valve procedures lies in those who are apparently asymptomatic. Imaging has a potential vital role in teasing out a subset of seemingly asymptomatic patients with severe AS by echocardiography who will benefit from a procedure.

Current national guidelines recommend treadmill exercise for patients with severe AS who appear asymptomatic. Treadmill-induced symptoms or a fall in blood pressure are class IIb indications for valve replacement. However, these recommendations are Level of Evidence C (expert opinion, case studies, or standard of care) only (7). No imaging data currently exist on how these clinical manifestations relate to the pathological triad of increased rest flow, decreased exercise diastolic perfusion time, and predominantly subendocardial hypoperfusion. Such data might lead to unmasking of patients without treadmill-induced symptoms or signs who nevertheless need a valve procedure.

Alternatively, if demonstrated by additional data, the clinical implications of stress diastolic perfusion time being the primary limitation to functional capacity might suggest heart rate slowing. Agents such as beta-blockers or pure ion-channel antagonist drugs like ivabradine could potentially improve subendocardial perfusion, reduce subendocardial ischemia during exercise, and thereby increase exercise capacity and reduce angina and sudden arrhythmic death in AS. Imaging alone could provide the data for, and study the effects of, such medical interventions for severe AS with borderline indications for a valve procedure.

Where no catheter can go. Echocardiography replaced invasive catheterization for AS because of equivalent hemodynamics with lower risk and cost. The future of imaging for AS may come by another mechanism. Namely, no catheter or flow wire can determine transmural flow gradients. As such, imaging offers potentially unique insight as opposed to replacing an existing yet invasive tool.

Let the data talk. Perhaps we should summarize our scientific thinking process for the reader. For discovering new insights, we examine whatever is known or whatever pilot data we have or is in the literature for inconsistencies, some odd signal that has been missed (sometimes obvious once seen) or clues that do not fit what we thought we knew. We look at data like an unknown foreign language that makes no sense at first. But after days, months, sometimes years of repeatedly thinking about it, the data begins to tell us a physiological story.

This principle of "letting the data talk to us" requires a thorough knowledge of background physiology tempered by the flexible skepticism that any part of it could be wrong. The first step of scientific progress is both accepted knowledge and continual, instantaneous willingness to admit that what we believed true earlier was wrong and needing replacement by a view more consistent with new data. Once we "let the data talk to us" to suggest a physiological hypothesis, then we apply a physiologically based statistical model that usually proves the initial hypothesis wrong in part or entirely. However, it provides the clues and refinements for evolving hypothesis testing until the final correct physiological hypothesis, the statistical model, and the data fit together.

We echo the call by others for cardiology—including cardiac imaging—to place physiology again as its cornerstone (8,9).

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