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Coronary flow reserve in degenerative aortic stenosis and diabetes mellitus: An intriguing question

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Degenerative aortic stenosis (DAS) is the most common valvular heart disease in the elderly [1]. Since DAS shares many pathophysiologic mechanisms with coronary artery disease (CAD) [2], as much as 30%–80% of patients can suffer from both DAS and CAD, which is more frequent in patients with type 2 diabetes mellitus (T2DM). Surgical aortic valve replacement has been the standard treatment for DAS, although lately transcatheter aortic valve implantation (TAVI) has become the standard of care in fragile elderly patients with comorbidities. Therefore, the concomitant management of CAD has become a critical issue in patients undergoing TAVI.

Diabetes, atherosclerosis and degenerative aortic stenosis

Hypertension, hypercholesterolemia and T2DM are among the diseases/factors that have been seen to influence the progression of both atherosclerosis and DAS. T2DM accelerate the development of atherosclerosis, which is not only due to the hyperglycaemia but also to the associated insulin resistance, dyslipidaemia, etcetera. In addition, T2DM induces both a marked inflammatory response and an increase in lipid accumulation, which also affects DAS and CAD. The CANHEART aortic stenosis study [3] has shown the important influence of T2DM on the development of DAS, as well as on modifying risk factors associated with the burden of this disease. Indeed, in a long-term follow-up study of a Swedish population DAS

was 34% more frequent in patients with T2DM than in non-diabetic patients (3.42% vs. 1.68%; P <0.05) [4]. Furthermore, in Spain, the incidence of aortic valve replacement is 2.6 times higher in patients with T2DM than in non-diabetic patients [5].

T2DM is a progressive disease that develops from pre-diabetic stages to those of T2DM in which damage to the target organs is evident, usually due to macro and microangiopathy secondary to atherosclerosis. DAS and atherosclerosis share pathogenic mechanisms in the initial stages, although with some differences in the vascular wall, and the aortic valve begins to calcify in the later stages of the disease. Among other techniques, proteomics could help to further understand the pathogenic mechanisms of the different stages of the disease [2].

Indices of stenosis severity based on coronary flow and pressure

The concept of coronary flow reserve (CFR) was proposed by Gould et al. [6] as a physiologic measure of the severity of stenosis. In humans, CFR can be characterized by several noninvasive techniques capable of measuring coronary blood flow, such as cardiac magnetic resonance, positron emission tomography and single-photon emission computed tomography. The development of transducers that can be placed on the tips of catheters has enabled the measurement of distal pressure and flow in humans and has allowed the development of indices of severity of stenosis based on CFR and distal coronary pressure in coronary arteries at rest and after dilation. These techniques have helped to further understand the role of epicardial coronary artery stenosis and abnormalities in the control of coronary microcirculation that determine the limitation of coronary perfusion.

Pijls and Sels [7] used the measurement of pressure distal to a coronary stenosis as an indirect index of stenosis severity, based on the principle that the distal coronary pressure during vasodilation is directly proportional to the maximum vasodilated perfusion. Fractional flow reserve (FFR) is an indirect index that is determined by measuring the driving pressure for microcirculatory flow distal to the stenosis (distal coronary pressure minus coronary venous pressure) relative to the coronary driving pressure in the absence of a stenosis (mean aortic pressure minus coronary venous pressure). Mean pressure measurements averaged throughout the cardiac cycle are used. The simplified clinical FFR ratio of mean distal coronary pressure/mean aortic pressure (Pd/PAo), conceptually similar to relative CFR, results from the assumption that coronary venous pressure is zero, as well as the linearity of the pressure-flow relationship vasodilated.

FFR can immediately assess the physiologic significance of an intermediate (40%–70%) coronary stenosis to help guide decisions about the need for percutaneous coronary intervention

(PCI) and is not affected by flow disturbances at rest, which makes it very attractive for clinical use. Since FFR only requires vasodilated coronary pressure measurements, it can be used to assess the functional effects of a residual stenosis immediately after PCI. In addition, a considerable prognostic information is available for FFR. However, there are some limitations of this technique, such as the inability to assess restrictions in myocardial perfusion arising from abnormalities in microcirculatory flow reserve in coronary resistance vessels, as well as its critical reliance on achieving maximal pharmacological vasodilation (underestimating the severity of stenosis with submaximal vasodilation), among others.

The instantaneous wave-free ratio (iFR) uses resting distal coronary pressure as an index of stenosis severity, based on the finding that a resting pressure gradient does not develop until stenosis severity reaches a threshold level that significantly affects peak perfusion during vasodilation and therefore iFR assesses the physiological impact of a coronary stenosis on the distal coronary bed. It reflects the relationship between the distal coronary pressure and the averaged aortic pressure during mid-diastole (i.e., the “wave-free period”). The “wave-free period” is defined as starting 25% into cardiac diastole and ending 5ms before the end of diastole. During mid-diastole, the distal coronary resistance is free of the compressive effects of systole and the phasic coronary flow, and the diastolic pressure gradient of the stenosis is maximal. Since at rest flow the stenosis pressure gradient is smaller and distal coronary pressure higher, the critical limit for iFR is a ratio of diastolic coronary to aortic pressure of 0.89 (vs. 0.80 for FFR). Because iFR does not require pharmacologic vasodilation, it can be obtained rapidly and is not affected by abnormalities in the coronary microcirculation, that can attenuate the vasodilatory response to adenosine. On the other hand, in circumstances where resting flow is abnormally elevated (e.g., anemia, left ventricular hypertrophy) iFR will overestimate the functional significance of a stenosis compared with FFR.

Large clinical trials have shown iFR to be non-inferior to FFR when used to defer PCI of hemodynamically insignificant lesions [8], although a meta-analysis suggests a borderline increase in the composite endpoint of death and MI with iFR versus FFR [9], which has not been confirmed by others.

Discordances between FFR and iFR

The diagnostic accuracy and clinical benefits of iFR and FFR are well established in the literature [7]. Despite the advantages of non-hyperemic pressure indices, approximately 20% of iFR and FFR measurements are discordant. Recent studies have identified many discordant factors including sex, age, bradycardia, artery stenosis location, elevated left ventricular end-

diastolic pressure, and diastolic disfunction [10]. As there is more interest in using iFR independent of FFR to guide PCI, emphasis has been placed on identifying factors that lead to discordance.

Discordance is said to exist when either FFR or iFR is positive and the other index is negative. Negative discordance is defined by a FFR <0.80 (significant lesion) and an iFR >0.89 (non-significant lesion), while positive discordance is the opposite: FFR >0.80 (no-significant lesion) and an iFR <0.89 (significant lesion). Managing lesions with discordant indices can be difficult, especially when iFR and FFR are numerically close to their cutoff values [4].

Elevated left ventricular diastolic pressure, usually present in aortic stenosis with left ventricular hypertrophy, is one of the most important causes of discordance between FFR and iFR, as 43% of these patients show this discrepancy [11]. T2DM can also show discordance of FFR and iFR, mostly due to the presence of microvascular dysfunction.

FFR and iFR in the assessment of myocardial ischemia in TAVI

FFR can underestimated CAD severity in patients with DAS, mainly due to modified coronary flow reserve for left ventricular hypertrophy [12]. On the other hand, it has been shown that coronary flow during the wave-free period does not change after TAVI, suggesting that iFR might be less affected by hemodynamic changes in this setting [13]. It has been postulated that the common threshold of 0.89 for determining lesion severity may not be valid in this population [7]. Scarsini et al. [14], studying a small number of patients, have proposed the use of a "hybrid approach" with the use of FFR only when iFR values are between 0.83 and 0.93.

In this issue of the *Kardiologia Polska* (*Kardiol Pol, Polish Heart Journal*), we can read the article by Dziewierz et al. [15] that go further evaluating the impact of T2DM on the performance of FFR in patients with severe DAS undergoing TAVI. They studied with iFR and FFR the functional significance of 416 angiographically intermediate coronary lesions in 221 patients (32.1% with T2DM) with severe DAS. The mean FFR was 0.85, and iFR was 0.90, with no differences between diabetic and nondiabetic patients. Good concordance between iFR and FFR was confirmed for non-diabetic (ICC, 0.83) and diabetic (ICC 0.82) patients. Among patients without T2DM, the optimal cutoff value for FFR to detect iFR ≤0.89 was 0.81, while the optimal cutoff value for FFR to detect iFR ≤0.89 for diabetic patients was 0.83. The authors concluded that in patients with severe DAS, FFR correlates well with iFR, although, more importantly, the optimal FFR threshold to identify significant ischemia (iFR ≤0.89 was used as the reference standard) in those patients may differ from the standard threshold of FFR ≤0.80 and may be affected by the diabetic status.

In our opinion, the article by Dziewierz et al. [15] provides good data that expands our knowledge of a frequent and complex clinical problem, such as the evaluation of the severity of CAD in patients undergoing TAVI, and that can help to shed light on this relevant clinical conundrum.

Article information

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