Editorial

Coronary Blood Flow and Flow Reserve in Aortic Stenosis: Effect of Aortic Valve Therapy

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The two components of coronary blood flow (CBF), lumen area and CBF velocity, are principally determined by different physiological factors. Although lumen area is closely related to left ventricular muscle mass, CBF velocity is mainly determined by the rate-pressure product, a surrogate of the instantaneous myocardial oxygen demand. Long-term adaptation to flow is achieved by an increase in lumen area, whereas short-term myocardial oxygen requirements are satisfied by changes in resting (baseline) CBF velocity.[1]

However, the precise mechanisms of CBF regulation are not fully understood. Myocardial perfusion pressure, extravascular compressive forces, and coronary resistance vessel (microcirculation) tone are the most significant determinants in CBF regulation.

The microcirculation (defined as vessels <200 μm in diameter) not only consists of a channel of passive networks but also is an active site of blood flow control. This is achieved by arterioles that have smooth muscles with a strong and immediate myogenic response (autoregulation). At rest (baseline), the capability for blood flow regulation is high, as 60% of total myocardial vascular resistance is offered by arterioles. However, when hyperaemia is induced, smooth-muscle vasodilation results in dilation of the arterioles and venules with no change in the capillaries. The total myocardial vascular resistance decreases and capillary resistances now comprise 75% of the total myocardial vascular resistance. Thus, capillaries offer the most resistance to CBF during hyperaemia and provide a ceiling to hyperaemic blood flow. Consequently, conditions that are associated with fewer capillaries are associated with reduced coronary flow reserve (CFR), despite the absence of coronary stenosis.

Coronary resistance vessel tone results from the accumulation of vasodilator and vasoconstrictor influences (including neurohormones, endothelial and myocardial factors).

The development of left ventricular hypertrophy in patients with aortic valve stenosis is an adaptive response that attempts to reduce wall stress in the left ventricle. However, the increased ventricular mass and intra-myocardial pressure, particularly at the level of subendocardial layers, affects myocardial oxygen requirements and leads to CBF augmentation at baseline. In addition, the relatively low aortic pressure during both systole and diastole, the prolongation of systole with relative shortening of diastole, the increased ventricular mass with relatively fewer capillaries per gramme of myocardium,[2] and the pathological changes, including myocardial fibrosis and reduced density of resistance vessels,[3] affect coronary resistance vessel integrity, leading to CBF reduction at maximal hyperaemia.

Consequently, CFR, defined as the

ratio of CBF at maximal hyperaemia to CBF at baseline, is impaired in patients with aortic stenosis, as has been confirmed in a number of published studies.[4,5] CFR was found to be more severely impaired in the subendocardium and the severity of impairment was related to aortic valve area, haemodynamic load imposed and diastolic perfusion, rather than to left ventricular hypertrophy. Going one step further, as shown in the recently published TOPAS study,[6] we can use CBF measurements as an additional diagnostic tool for discrimination between truly-severe and pseudo-severe aortic stenosis. In truly-severe aortic stenosis baseline CBF is higher and CFR is lower compared to the corresponding values in pseudo-severe aortic stenosis.

Aortic valve therapy (either surgical aortic valve replacement or percutaneous aortic valve implantation), via removal of pressure overload and regression of left ventricular hypertrophy, could be accompanied by a reversal of CBF alterations and CFR improvement.

Single-centre studies including small numbers of patients and early follow up (six months) showed CFR improvement after aortic valve replacement,[7,8] but these changes were not directly dependent on regression of left ventricular mass. Reduced extravascular compression and increased diastolic perfusion time have been proposed as the main mechanisms for improvement in CBF and CFR. Also, a marked heterogeneity in the response of the patients has been observed.

Longer-term follow-up studies confirmed recently that, despite a small initial improvement of CFR after aortic valve replacement,[9] CFR deteriorates further at 1 to 3 years of follow up.[9,10] Although patient-prosthesis mismatch and aortic valve design (stented versus stentless valves) have been proposed as an explanation[11] for the persistence of CBF abnormalities, CFR impairment has been documented recently, even in patients with aortic valve calcification before valve stenosis develops.[12,13] Calcific aortic valve disease is an active disease process characterised by lipid accumulation, inflammation, and calcification,[14] with many similarities to atherosclerosis, and has been associated with increased morbidity and mortality.[15] Therefore, microvascular-endothelial dysfunction is present during the early stages of the disease and deteriorates further in the later stages.

In addition, persistent intraventricular conduction abnormalities and requirements for pacemaker implantation are common after aortic valve therapy. Especially after percutaneous aortic valve implantation, left bundle branch block has been observed in 55% of patients and pacemaker implantation was required in 18%.[16] Left bundle branch block has been clearly associated with impairment of the early diastolic CBF in the left anterior descending coronary artery and microvascular dysfunction with reduced CFR in the same vascular territory;[17] abnormalities of CBF and CFR impairment are to be expected in these patients. Similarly, permanent ventricular pacing is associated with perfusion abnormalities and reduced CFR in the dominant coronary artery,[18] so impairment of CFR may also be expected.

Consequently, a combination of factors produce CBF and CFR abnormalities in patients with aortic stenosis and most of them are not reversed by the current aortic valve therapies. Nevertheless, the main issue is that CFR of normal to mildly diseased arteries is an independent predictor of the long-term prognosis of atherosclerosis within the next decade.[19]

Data on long-term survival after aortic valve therapy is limited by so-called valve-related complications, such as thrombosis, and mechanical and structural valve deterioration in biological substitutes. After aortic valve replacement, although at 5 and 9 years the actuarial freedom from valve-related death is approximately 95% and 85%, the actual survival is 75% and 40%, respectively. After percutaneous aortic valve implantation the mortality rate is 15% at one year[20] and is expected to be 30-40% at 2 years. Although these deaths were due to cardiovascular disease in all patients, no evidence of valve dysfunction has been confirmed.

By definition, the development of heart failure and sudden cardiac death is not considered to be related to the implanted aortic valve, although these complications occur in as many as 24% of the patients within 10 years after surgery.[21,22] This incidence is significantly greater than in the general population; therefore, a connection between aortic valve therapy and the risk of development of heart failure and arrhythmias can be postulated. Both might be related to inadequate myocardial perfusion because, as we already mentioned, CFR has been defined to be a strong independent predictor of adverse cardiovascular events.[19] In addition, according to the microvascular ischaemic hypothesis, chronic myocardial hypoperfusion and/or repetitive ischaemia as the result of impaired microvascular flow cause progressive left ventricular dilation and systolic dysfunction; this in turn may affect coronary blood flow in a vicious circle and lead to further deterioration of left ventricular function and progression of heart failure.[23]

In conclusion, CFR may be an important parameter of long-term survival after aortic valve therapy (either aortic valve replacement or percutaneous implantation) in patients with aortic stenosis. CBF abnormalities and reduced CFR may contribute to more cardiovascular events and greater rates of mortality in these patients.

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