PRECISION AND FUTURE MEDICINE

Symptomatic presentations of severe aortic stenosis

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ABSTRACT

Aortic stenosis (AS) is the most common type of valvular heart disease. A manifestation of ageing, the disorder is becoming more frequent as the average age of the population increases. Onset of cardinal manifestation of AS—angina, syncope, and heart failure—remains the major demarcation point in the disease's course. It has been well described that patients' survival is limited once they develop symptoms from AS and survival after the onset of a symptom depends on what type of symptom a patient develops. Knowing how the pathophysiology of AS causes typical symptoms and death is paramount to understanding the disease. We discuss these issues in this review.

Keywords: Aortic valve stenosis, Chest pain, Dyspnea, Echocardiography, syncope

INTRODUCTION

Aortic stenosis (AS) is the most common valvular heart disease in the elderly characterized by fixed aortic valve narrowing, left ventricular (LV) remodeling with hypertrophy, and progressive diastolic dysfunction [1]. The cardinal manifestations of AS include syncope, chest pain, and dyspnea. It has been well described that patients' survival is limited once they develop symptoms from AS and survival after the onset of a symptom depends on what type of symptom a patient develops [2]. Therefore, the onset or presence of these symptoms are the class I indication for surgical indication [3], but without any distinction among symptoms.

Is there any significant correlation between the severity of AS and development of symptoms? The development of symptoms in asymptomatic AS was predicted by aortic jet velocity at baseline, the rate of change in aortic jet velocity, and baseline functional status [4]. However, there was a large overlap between symptomatic and asymptomatic patients, consistent with the known heterogeneous response to the pressure load of AS [5]. Therefore, the occurrence and severity of cardiac symptoms may correlate poorly with the severity of AS (aortic valve area [AVA] and transvalvular pressure gradients), and symptoms often occur despite preserved LV ejection fraction (EF) [6,7].

THE EFFECT OF LEFT VENTRICULAR HYPERTROPHY ON SYMPTOMS STATUS IN AS

Hypertrophy is considered one of the major mechanisms of the myocardium for adapting to hemodynamic overload. More muscle mass provides more contractile elements for generating the extra work required by the overload. In pressure overload of AS, concentric LVH normalizes wall stress, a key determinant of ejection performance [8].

Afterload is often expressed as ventricular wall stress (δ). In this way, the high systolic pressure required to drive blood through a very stenotic aortic valve and it can be consistent with normal afterload and normal EF. Since afterload is a key determinant of ejection performance, its normalization is important in maintaining normal EF and stroke volume. LV pressure overload may induce LV hypertrophy. Unfortunately, hypertrophy is a double-edged sword. Although it helps to preserve ejection performance, hypertrophy also impairs coronary blood flow reserve inducing myocardial fibrosis, which in turn leads to increased chamber stiffness, delayed active LV relaxation, and compromised coronary flow reserve. All of these changes may affect diastolic and systolic function and be associated with increased mortality [9,10]. The magnitude of LVH did not by itself explain the presentations of symptoms of AS [7]. Pressure gradient nor AVA are not predictive of symptom onset because those factors alone do not by themselves control the myocardium's response to AS [11]. It is thus possible that the development of symptoms in AS reflects alterations in LV morphology and function, leading to increased filling pressures and left atrial (LA) dilatation, hemodynamic, and morphological changes that may occur without any change in LVEF.

ASYMPTOMATIC VERSUS SYMPTOMATIC AS

The basic question is which echocardiographic parameters differentiate the presence of symptoms in severe AS?

The hemodynamic consequence of AS is LV pressure overload, causing morphological changes of the LV characterized by LV hypertrophy, concentric remodeling, and myocardial fibrosis. As a consequence of increased afterload [8] and LV
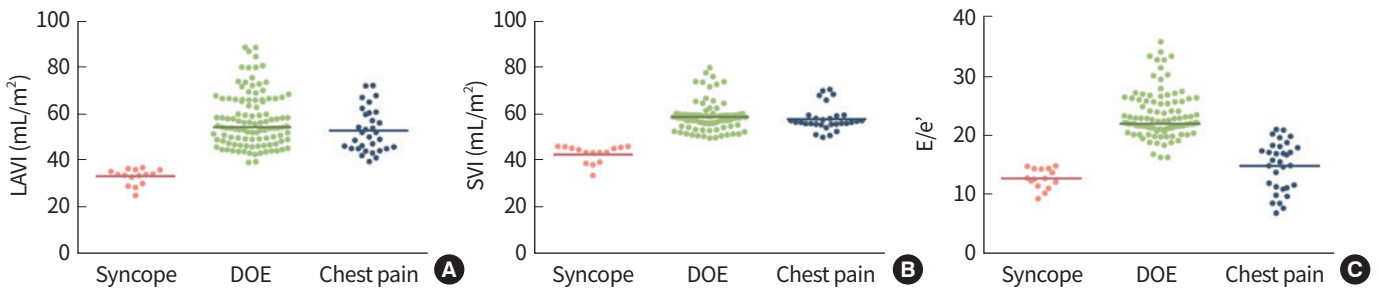

Fig. 1. (A) Left atrial volume index (LAVi), (B) stroke volume index (SVI), and (C) E/e' ratio in patients with different symptoms. Adapted from Park et al. [7]. DOE, dyspnea on exertion.
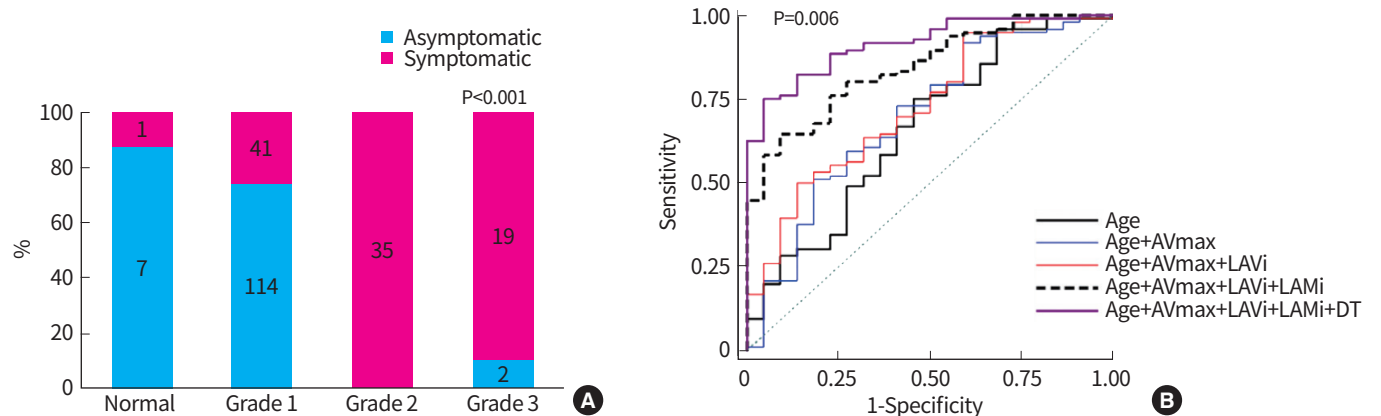

Fig. 2. (A) Symptomatic status as a function of diastolic grade, (B) Incremental information of age, maximum aortic valve velocity (AVmax), left atrial volume index (LAVi), LVMi, and deceleration time in predicting symptom status. Adapted from Dahl et al., with permission from Wolters Kluwer Health [17].

remodeling [12-14], AS will lead to LV diastolic dysfunction, increased filling pressures, and heart failure (HF) symptoms. The development of HF symptoms has previously been demonstrated to be associated with measures of AS severity and LV hypertrophy [15,16]. In contrasts, Park et al. [7] recently demonstrated that compared with the asymptomatic group, symptomatic patients were older and had lower cardiac output, and higher E/e' ratio while having a similar AVA and gradient in 498 severe AS and normal LVEF. Syncope group displayed smaller LV dimension, stroke volume, cardiac output, left atrial volume index (LAVi), and E/e' ratio. Conversely, dyspnea group was found to have the worst diastolic function with largest LAVi and highest E/e' ratio (Fig. 1). Dahl et al. [17] also compared clinical characteristics and echocardiographic parameters in 99 symptomatic and 139 asymptomatic patients with severe AS and normal LVEF. This study demonstrated that symptomatic status was associated with LVH, concentric remodeling, diastolic dysfunction, and dilatation of LA. An LV diastolic grade of 2 or 3 was highly associated with the presence of symptoms and model including age, maximum aortic valve velocity, left ventricular mass index (LVMi), LAVi, and deceleration time provided incremental information on symptomatic status (Fig. 2).

DYSPNEA

Onset of dyspnea and other symptoms of HF presage the worst outlook for the patient with AS [18]. The first question is what causes the dyspnea in severe AS? In the patients with severe AS who develop dyspnea, markedly altered LV diastolic function with increased filling pressure was present (Fig. 1) [7]. Left-sided filling pressures seem to have a good correlation with the symptom [19]. Diastolic dysfunction, which increases LV filling pressure, predicted dyspnea in severe AS patients. The second question is what causes the diastolic dysfunction in severe AS? Diastole is typically divided into two parts, early active relaxation and passive filling [10]. Early relaxation is described by LV pressure decay time, whereas passive filling is characterized best by the diastolic pressure-volume relationship of the LV. During active relaxation, calcium is pumped back into the sarcoplasmic reticulum, causing the contractile interaction between actin and myosin to diminish. In pathologic LVH, early active relaxation is delayed, reflecting abnormalities in the calcium handling that pumps calcium back into the sarcoplasmic reticulum, reducing actin-myosin interaction [20]. This slowing of active relaxation delays the diastolic fall in LV pressure during isovo-

lumic relaxation, in turn delaying mitral valve opening and shortening the time for the LV to fill. Passive filling in pathologic LVH is characterized by a shift in the diastolic pressure-volume relation of the LV upward and leftward, thus requiring increased filling pressure to fill the LV to any given volume because the LV is stiffer than normal. Increased LV stiffness in pathologic LVH accrues both from intrinsic and extrinsic factors. Intrinsically, myocytes are thicker and filled with a denser than normal cytoskeleton [21], in turn causing the myocyte to be stiffer than normal. Increased chamber stiffness is also due to increased extracellular components including the collagen network that holds the LV together and that connects the myocyte to the chamber [22]. In severe AS patient, at least four factors—LV thickness, active relaxation, myocyte structure, and extracellular matrix—can vary from patient to patient. Those four factors can alter diastolic function [11]. This complexity and augmented diastolic dysfunction leads to pulmonary congestion and dyspnea in severe AS.

SYNCOPE

Syncope is one of the most urgent clinical symptoms, occurring suddenly without warning. Syncope occurs when there is inadequate systemic blood pressure to support cerebral blood flow. Three mechanisms have been suggested to explain exertional syncope in patients with AS: (1) cardiac arrhythmias, (2) sudden failure of an overloaded LV during the stress of exercise, (3) peripheral vasodilatation occurring suddenly and inappropriately in the face of fixed cardiac output [23]. Inappropriate vasodilation, the result of reflexes triggered by LV baroreceptors [24] and occurring during or just after exercise, is thought to be the mechanism in most cases [25]. The exact mechanism of syncope in AS still remains unclear.

The prevalence of AS has increased with aging. The main cause has markedly changed from rheumatic pathogenesis to arteriosclerosis [26]. Almost all current clinical studies of AS discuss patients aged >70 years [15,27,28], contrary to the average age of 48 years at clinical presentation reported by Ross and Braunwald [2]. It is natural to think that the perception from clinical studies of the past would not apply to the new condition in recent years. However, only few recent studies have investigated on syncope in patients with AS [25,29,30].

Park et al. [7] demonstrated that the group with syncope had the lowest stroke volume along with the smallest LV
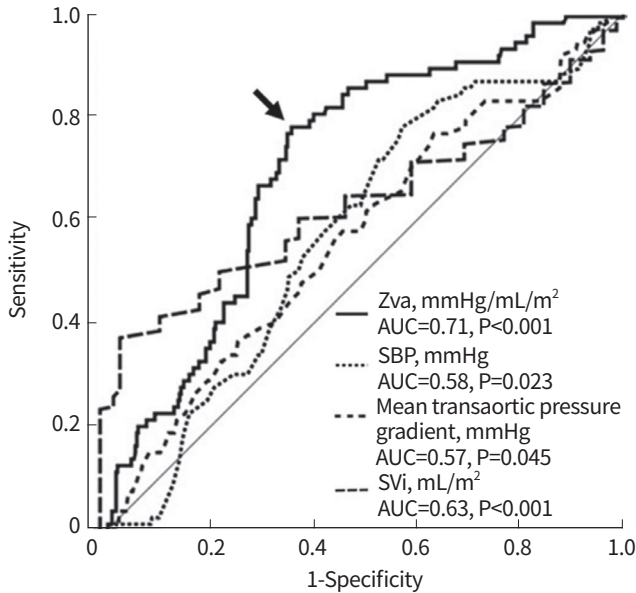
Fig. 3. Receiver operating characteristic curve analysis of the ability of valvuloarterial impedance (Zva), systolic blood pressure (SBP), mean transaortic pressure gradient, and stroke volume index (SVi) to predict syncope in patients with aortic stenosis. Adapted from Harada et al., with permission from Wolters Kluwer Health [31]. AUC, area under the curve.

mass and LV volumes and LA volume. Additionally E/e', a guide to filling pressure, was also lowest in this syncope group. These data suggest that patients with syncope have remodeled in such a way as to have smaller hearts that generate less cardiac output, possibly compounded by lower LV filling pressure further limiting cardiac output [11].

The important question is which echocardiographic parameters predict the development of syncope in severe AS. Recently, Harada et al. [31] suggests that valvuloarterial impedance ≥ 4.7 mm Hg/mL per m^2 may have clinical significance because it may represent not only the cutoff value of syncope prediction, but also an afterload level that surpasses the capabilities of the LV compensatory mechanism. In this study, conventional parameters of AS severity, including mean transaortic pressure gradient and AVA, were unable to independently predict syncope (Fig. 3).

ANGINA

The incidence of angina pectoris in patients with AS has been reported to range between 30% and 40% in the absence of associated obstructive coronary artery disease [32-35]. The pathophysiological mechanism of angina is not clear but seems to be due to unbalanced myocardial oxygen supply and demand. Oxygen demand is proportional to heart rate

and systolic wall stress, and the latter can be elevated in cases of AS when hypertrophy is inadequate to normalize stress [8]. After aortic valve replacement (AVR), there is marked regression of hypertrophy that may occur over the next several months to years [36], but angina is relieved immediately. Relief of angina immediately after AVR is probably due to the combination of sudden decreased oxygen demand after removal of pressure overload and increased oxygen supply of improved perfusion [37].

On the oxygen supply side, it is well known that coronary flow reserve is reduced in AS patients [38]. This phenomenon has been revealed by invasive coronary catheterization [38] and imaging modalities such as positron emission tomography [39] and cardiac magnetic resonance (CMR) [40,41]. Julius et al. [42] demonstrated patients with angina had a lower LV muscle mass, an increased LV peak systolic pressure, and increased wall stress than those without angina. Vessels of the left coronary artery were smaller and coronary flow reserve was lower in patients with angina than in those without angina. Inadequate LV hypertrophy with an increased wall stress was found in patients with angina but not in patients without angina. However, there is no difference in the flow reserve of patients with versus those without angina. Thus, this factor must in some way contribute to the potential for ischemia to develop in severe AS.

Myocardial ischemia in patients with severe AS can occur in the absence of coronary artery disease and appears to be due to inadequate LVH with high systolic and diastolic wall stresses and a somehow reduced coronary flow reserve.

In the absence of significant coronary stenosis, this finding is indicative of microvascular dysfunction, but it remains unclear whether the reduced myocardial perfusion reserve seen in severe AS without obstructive coronary artery disease (CAD) leads to angina during stress stimuli.

Adenosine-stress CMR can detect stress-induced abnormal hypoperfusion with signs and symptoms of ischemia without CAD [43,44] and this is the almost the only noninvasive clinical method that allows assessment of the transmyocardial distribution of coronary blood flow and myocardial perfusion reserve index. Among severe AS patients with angina but no obstructive CAD, Park et al. [7] demonstrated a reduced myocardial perfusion reserve, which is indicative of microvascular dysfunction, compared with severe AS patients without any symptoms [45]. Park et al. [7] suggests that angina in patients with severe AS without obstructive CAD might be attributed to LVH, which can cause myocardial ischemia by coronary microvascular dysfunction (Fig. 4).

CENTRAL ILLUSTRATION Coronary Microvascular Dysfunction: Mechanism of Occurrence of Angina

Progression of Aortic Stenosis

Development of Left Ventricular Hypertrophy

Decrement of MPRI

Occurrence of Angina

Ahn, J.-H. et al. J Am Coll Cardiol. 2016; 67(12):1412-22.

In patients with severe aortic stenosis (AS) without obstructive coronary artery disease, angina is related to the decrement of MPRI (impaired coronary microvascular function) along with development of left ventricular hypertrophy (LVH). LVMI = left ventricular mass index; MPRI = myocardial perfusion reserve index.
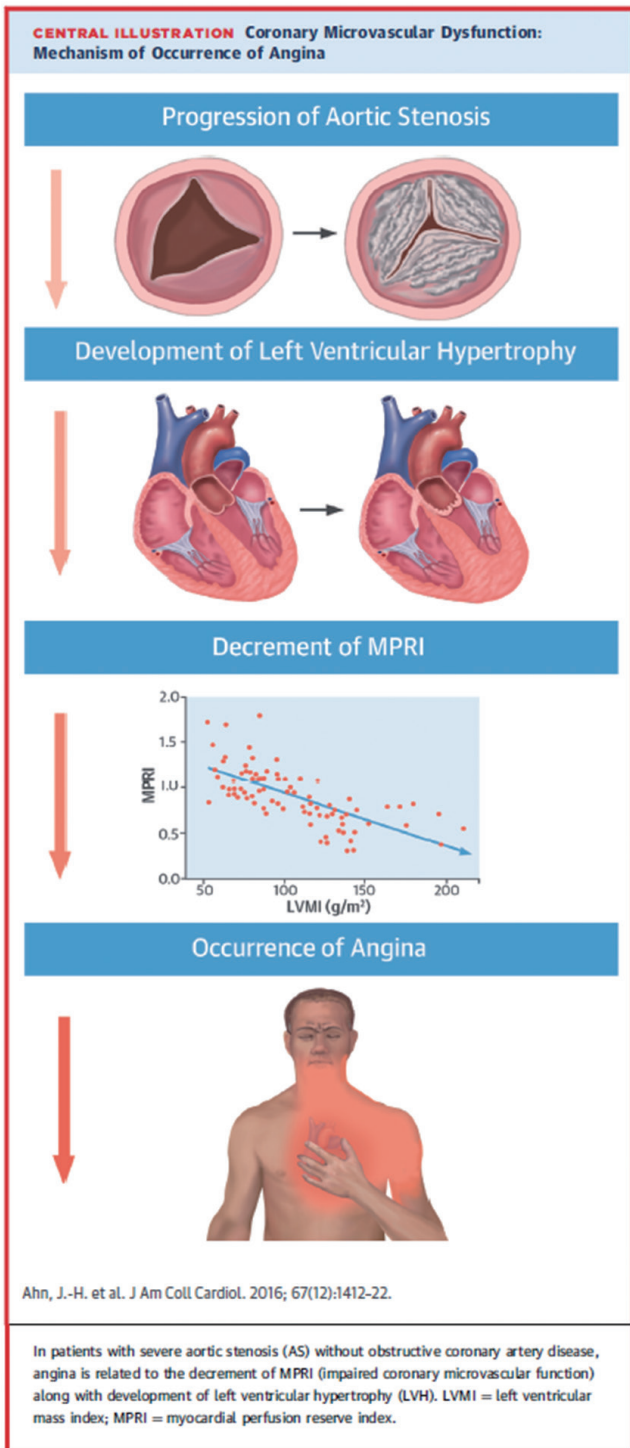
Fig. 4. Coronary microvascular dysfunction: mechanism of occurrence of angina. Adapted from Ahn et al. [45]. MPRI, myocardial perfusion reserve index.

CONCLUSION

Diastolic dysfunction is important in the natural history and its role in presenting symptoms of patients with severe AS. In patients with normal EF, diastolic dysfunction is a key driver of development dyspnea. Smaller LV volumes reduce cardiac output, predisposing the patient to syncope. Angina can occur in the absence of coronary artery disease and appears to be due to inadequate LVH with high systolic and diastolic wall stresses and a somehow reduced coronary flow reserve. Future prospective studies should be conducted to clarify the pathophysiologic mechanisms of presentation of specific symptoms in severe AS.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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