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The evolving approach to the evaluation of low-gradient aortic stenosis☆,☆☆

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ABSTRACT

Severe aortic stenosis (AS) is typically identified by a low valve area (≤1.0 cm^2) and high mean gradient (≥40 mm Hg). A subset of patients are found to have a less than severe mean gradient (<40 mm Hg) despite a low valve area. These latter types can present as either low ejection fraction with low-gradient AS (stage D2) or normal ejection fraction with low-gradient AS (stage D3). Determining the true severity of disease within these categories has proved difficult. In this review we illustrate both traditional and novel techniques that can be used for further valvular assessment. We also propose a simple algorithm that can be used to evaluate low-gradient AS.
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1. Introduction

Calcific aortic stenosis (AS) is the most common valvular disease encountered in developed countries [1]. Based on American College of Cardiology/American Heart Association (ACC/AHA) guidelines, AS is categorized into stages by symptoms and valve hemodynamics. AS is identified as stage "D" once symptoms develop. Patients are further subdivided into stages D1, D2, or D3 depending on mean trans-aortic gradient and left ventricular ejection fraction (LVEF) [2]. Evaluation and treatment of those in the D1 category (symptomatic severe AS with low area/high gradient [≥40 mm Hg]) is fairly straightforward. Managing low-gradient (<40 mm Hg) severe AS can be more complicated. Stage D2 patients present with low-gradient severe AS in the setting of a low ejection fraction (LVEF, <50%), while stage D3 patients present with low-gradient severe AS in the setting of a normal LVEF and low stroke volume index (SVI <35 ml/m^2). According to the most recent guidelines, if these less straightforward stages are felt to be true severe AS and symptoms cannot be explained by other etiologies (coronary artery disease, cardiomyopathy, other valve disease, pulmonary hypertension, arrhythmia, chronic lung disease,

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anemia, etc), then aortic valve replacement (AVR) is indicated (IIa recommendation). Until recently, tools for evaluating the true severity of AS in low-gradient cases have been limited. We first present the workup of a complicated case of stage D3 AS recently encountered at our institution. We then review the pathophysiology and traditional evaluation of stage D2 and D3 AS, and discuss newer techniques that have been utilized to assist in AS severity classification. Finally, we propose a new algorithm for the assessment of patients with low-flow, low-gradient AS.

1.1. Case

A 70-year-old man with a history of coronary artery disease, coronary artery bypass grafting, moderate to severe AS, and hypertension presented to our clinic with worsening dyspnea on exertion and chest pain. Transthoracic echo showed LVEF of 50%, SVI of 33 ml/m^2 and an aortic valve area (AVA) of 0.8 cm^2 with a mean gradient of 30 mm Hg. The decision was made to further evaluate for true severe AS versus moderate AS (pseudo-severe aortic stenosis). An aortic valve calcium score assessment revealed a valve score of 2800 Agatson units. This value signified that severe AS was probable, therefore further evaluation was undertaken with an aortic valve study. Initial hemodynamics revealed an AVA 0.9 cm^2, mean gradient of 25 mm Hg, and SVI 34 ml/m^2. Because of inadequate valve assessment in the presence of a low-flow state, further provocative testing was undertaken with use of a nitroprusside challenge. Nitroprusside was infused at escalating doses (peak of 1 μg/kg/min), which increased the SVI to a peak of 46 ml/m^2 and AVA to 1.39 cm^2, indicating that our patient had moderate AS, and not true severe AS. An angiogram revealed a vein graft with an 80% stenosis that was felt to be the cause of his symptoms and thus was revascularized.

2. Discussion

2.1. Stage D2 patients

According to ACC/AHA guidelines, patients categorized as stage D2 AS have severe symptomatic AS with a valve area ≤ 1.0 cm^2, in the setting of a mean gradient that is not in the severe range (<40 mm Hg), in the presence of a low-flow state (LVEF <50%, SVI <35 ml/m^2) [2]. This is also known as “classical low-flow, low-gradient AS” [3], found in 5% to 10% of AS patients and typically associated with ischemic heart disease and LV dilatation [4]. Because of the low-flow state, it can be difficult to determine whether patients have true severe AS versus moderate AS (as the gradient is typically dependent on flow across the valve per beat) [5]. Historically, further evaluation of severity has been obtained with use of low-dose dobutamine testing via echocardiogram or heart catheterization to increase the stroke volume. The results of dobutamine provocation often allows for determination of true severe AS versus moderate AS. Dobutamine also has utility in determining whether a patient has *contractile reserve,* defined as an increase in stroke volume of ≥20% with peak infusion. The presence or lack thereof of contractile reserve allows patients to be further risk-stratified prior to AVR. In the pre-TAVR era it was long felt that the lack of flow reserve placed one at particularly high risk for operative mortality. With the advent of TAVR, more recent data suggests that lack of contractile reserve did not significantly impact clinical outcomes post TAVR [6]. Studies have also shown that utilizing the projected aortic valve area in stage D2 patients via dobutamine stress testing has utility in determining the severity of a patient's AS. Not only has this technique allowed one to better differentiate true severe AS vs moderate AS, it has also been found to have a strong association with mortality in those undergoing conservative management [7,8]. Unfortunately, this technique has its own limitations and has been found to be unreliable when there is no or minimum increase in trans-valvular flow (<15%), restricting its use to those who are found to have contractile reserve [7].

2.2. Stage D3 patients

D3 AS is defined as symptomatic severe AS with a low valve area (≤1.0 cm^2), but non-severe mean gradient (<40 mm Hg) in the setting of a normal EF (>50%) and low-flow state (SVI <35 ml/m^2) [2]. Some authors have previously dubbed this *paradoxical low-flow low-gradient AS* (with the paradox represented as a low-flow state despite a normal ejection fraction) [5]. Patients with similar valve characteristics and EF, but a normal flow state (SVI ≥35 ml/m^2) are not typically felt to have severe AS, and have outcomes similar to those with moderate AS [4,9]. In other words, patients with a normal stroke volume should have enough flow to generate a high gradient if severe AS is truly present. Those with stage D3 AS are often older and are found to have LV hypertrophy, small ventricular size, diastolic dysfunction, and systemic hypertension [2,10]. Not only is arterial compliance reduced, but vascular resistance is increased, further increasing afterload and limiting effective cardiac output. A measure of total LV hemodynamic load, valvulo-arterial impedance, is also known to be elevated in D3 patients compared with normal-flow severe AS patients [11]. Similar to stage D2, D3 patients should be thoroughly evaluated to ensure they have true severe AS rather than moderate AS. This proves difficult as the utility of dobutamine in the setting of a normal EF may be limited. Less traditional echo parameters are at times utilized to add further diagnostic information when stenosis severity is unclear [12]. One such measure is the dimensionless index, which is defined as the ratio of the left ventricular outflow tract velocity time integral (VTI) to the aortic valve VTI. Prior work has shown that in patients with preserved EF, the dimensionless index can be used as a reliable marker for AS severity [13]. This study found that from a prognostic point of view, a dimensionless index ≤0.25 is consistent with true severe AS. This measurement can also be prone to error, as ultrasound images are not always optimal for accurate doppler sample volume positioning which can lead to miscalculation of VTI values. This has set the landscape for finding newer techniques to further classify D3 patients. With the advent of multi-detector computed tomography (MDCT) for aortic valve calcium scoring and nitroprusside to assist with further defining AS hemodynamics, we are able to move closer to defining a pathway to help clarify these discordant findings.

2.3. Aortic valve calcium scoring to classify aortic stenosis

Increased aortic valve calcium burden is essentially pathognomonic for the development of worsening AS. Therefore, it has long been felt that quantifying aortic valve calcium may assist with defining the severity of a patient's AS. Utilizing MDCT, aortic valve calcium can be measured on a non-contrasted study with use of the Agatson method. Calcification is defined as 4 adjacent pixels with a density > 130 hounsfield units, and can easily be measured with commercially available software [14]. Early studies showed that aortic valve calcium as measured by MDCT correlated well with valve hemodynamic characteristics. This was true not only with normal-flow severe AS, but with D2 patients as well [15]. The use of MDCT for evaluation of D3 patients has also been validated. Prior work has shown that at least half of D3 patients have aortic valve calcium burden in the severe range. Results also showed that those D3 patients with and without aortic valve calcium in the severe range were older (76 vs 71 years, $P = 0.03$) and presented with different mean gradients (32 vs 27 mm Hg, $P < 0.0001$) [16]. Absolute aortic valve calcium burden was also found to be independently predictive of mortality. In fact, regardless of the presence or absence of hemodynamic parameters consistent with severe AS, higher aortic valve calcium density was associated with increased mortality [17]. These findings have prompted newer guidelines/recommendations to include MDCT as part of the workup for severe AS

with discordant hemodynamic parameters. As of 2017, the European Society of Cardiology (ESC) now recommends using MDCT to help further classify those who present with stage D3 AS (once low-flow status is confirmed) [10]. A recent report published by the United States appropriate use criteria committee now also recognizes aortic valve calcium burden as a supportive tool to help determine the appropriateness of AVR. In both D2 and D3 patients, the committee now supports AVR when MDCT shows a high calcium burden, and supports no intervention when the calcium burden is low [18].

2.4. The nitroprusside challenge

As previously mentioned, determining whether a patient who presents with D3 characteristics has true severe AS versus moderate

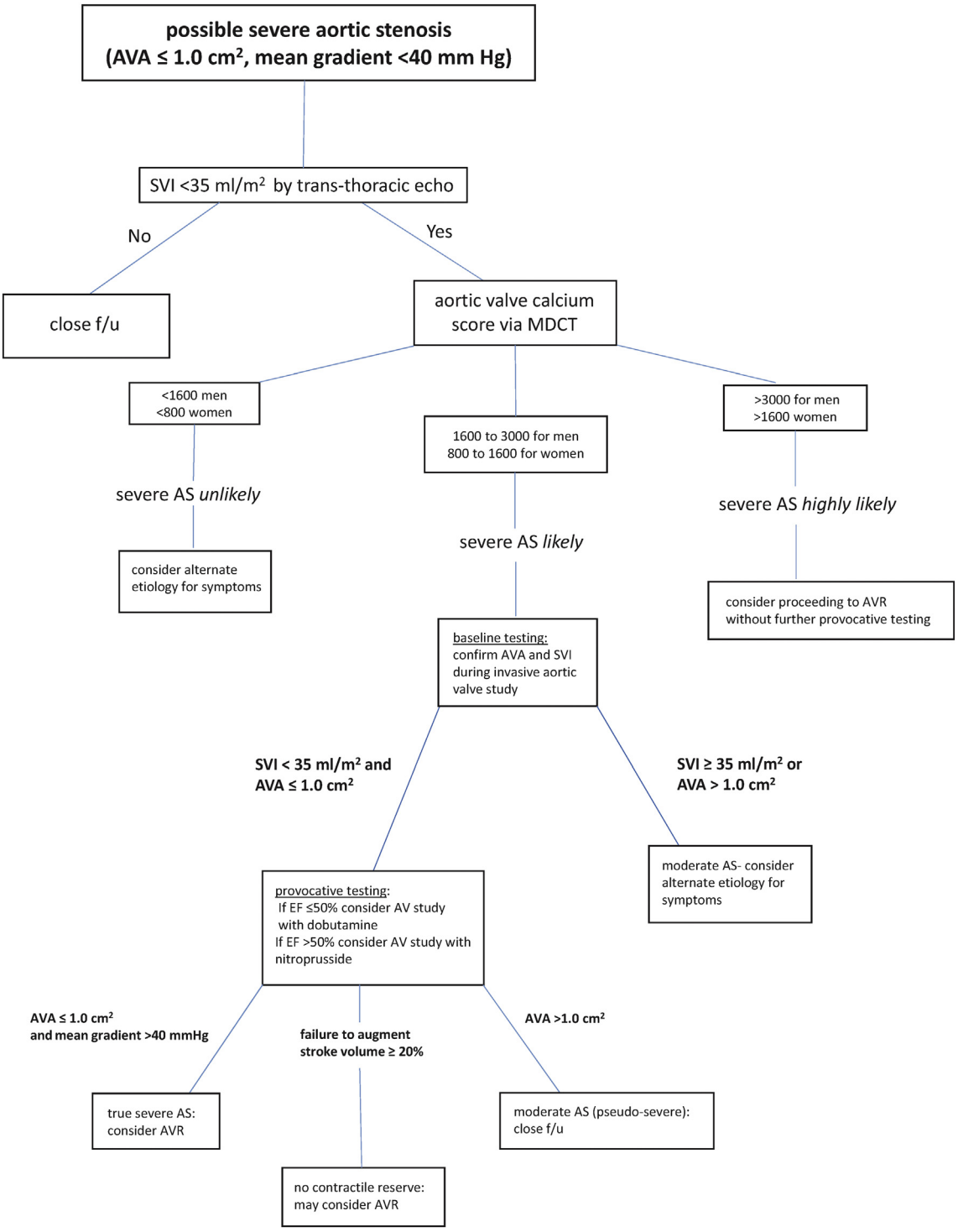

Fig. 1. Proposed new algorithm for the evaluation of discordant aortic stenosis (AS) patients. AVA, aortic valve area; AVR, aortic valve replacement; EF, ejection fraction; MDCT, multidetector computed tomography; SVI, stroke volume index.

AS can be difficult. Dobutamine has been used in D2 patients with success; however its utility with D3 patients is limited. Its effects are typically limited to increased inotropy/chronotropy, which in turn leads to a higher cardiac output. D3 patients have a normal EF and higher markers of increased vascular resistance/afterload. As such, increased inotropic/chronotropic effects may not be effective when attempting to increase outputs in discordant AS patients. Targeting these increased resistance/afterload patterns has begun to garner significant research interest, with the utilization of vasodilators leading the way. Unfortunately, this practice may be met with skepticism, as it has long been felt that in the setting of severe AS, one should avoid the use of vasodilators as they may lead to a rapid fall in coronary and cerebral perfusion. Fortunately, recent work by the Mayo Clinic has shown that use of nitroprusside for provocative testing in AS patients can be safe and useful [19]. Their study evaluated patients with normal EF and low-gradient AS. Patients were excluded if mean arterial pressure was <60 mm Hg or SBP was <100 mm Hg. Nitroprusside was administered in a fashion similar to that of provocative studies with dobutamine (initial dose 0.5 μg/kg/min, increased by 0.5–1 μg/kg/min q5 min until dose of 10 μg/kg/min reached, AVA >1.0 cm2, mean gradient >40 mm Hg, mean arterial pressure <60 mm Hg, or the onset of intolerable side effects). Results showed that SVI improved more with nitroprusside in those with low flow compared with normal flow, and overall the change varied inversely with baseline SVI. This led to an increase in AVA in some low-flow patients, allowing 25% to be reclassified to moderate AS. There was also a significant increase in mean gradient after administration of nitroprusside in low-flow patients and a significant decrease in measures of total LV afterload as measure by valvulo-arterial impendence in low-flow patients. These results show that D3 patients may respond more favorably to vasodilator therapy rather than dobutamine which may be in part due to increased sensitivity to afterload. Although not evaluated in this study, nitroprusside use for the evaluation of patients with low-EF discordant AS (D2 patients) may also be beneficial. When evaluating for contractile reserve and attempting to re-classify D2 patients, escalating doses of dobutamine has the potential to induce ischemia, leading to an inability to substantially increase stroke volume. This is likely more common than appreciated as D2 patients often have significant coronary artery disease [3]. Perhaps in the near future nitroprusside will be more widely used during valve studies to allow for a more accurate assessment of AS severity.

3. Suggested approach

With the advent of these new techniques, it is time to re-assess the typical methods used to classify low-gradient AS patients. Despite the limitations of dobutamine stress testing, low-gradient AS patients have historically been further evaluated with this method of provocation. Recent data has demonstrated the utility and safety of MDCT and nitroprusside administration in low gradient AS patients, allowing authors to integrate these studies into their practices [20]. Fig. 1 illustrates a suggested algorithm that can be useful for the evaluation of stage D2 and D3 patients. The most important step is to determine if the patient has a *true* low-flow state (SVI <35 ml/m^2). This is first suspected via two-dimensional echocardiogram. If a normal flow state is found, it is more likely that moderate AS is present, as low-gradient severe AS with a normal flow state does not make sense by fluid dynamics principles [4]. Once a low-flow state is confirmed, the next step in evaluation should begin. We propose that an aortic valve calcium score should be determined next. Based on the calculated aortic valve calcium score, patients are further classified as 1) AS *not likely*, 2) severe AS *likely*, and 3) severe AS *highly likely*. This classification scheme has been adapted from the most recent ESC guidelines [10]. Different cut-offs have been established for men and women as severe AS progresses sooner in women despite a lower aortic valve calcium score. This is likely due to the presence of more fibrosis, which is not readily visualized via MDCT imaging [3]. If the aortic valve calcium score indicates that severe AS is *not likely*, then AVR should be deferred and patients should be followed closely. If the AVC score lands in the *highly likely* category, then we feel it may be reasonable to proceed with AVR without further valve provocation studies. Aortic valve study should be considered if an intermediate AVC score is obtained. During this study your low-flow state and valve area should be confirmed. If the SVI is ≥35 ml/m^2 or AVA >1.0 cm^2 then further testing can be deferred and the patient should be treated as moderate AS and monitored closely. If hemodynamics confirm your initial echo findings (SVI <35 ml/m^2 and AVA ≤ 1.0 cm^2) then further testing should be completed. If LVEF is <50%, a provocative study with dobutamine should be completed. If LVEF is normal, we suggest using a nitroprusside protocol to assist in further evaluation of the severity of AS.

4. Conclusion

Classification of AS patients can often be difficult, especially when discordant findings are noted between valve area and gradient. Traditional techniques (transthoracic echocardiogram/dobutamine stress testing) can have limited utility at times, especially in stage D2/D3 patients. Nitroprusside valve studies and MDCT both provide new, safe, and accurate methods to further evaluate AS severity. As invasive aortic valve studies are not without risk, initiating evaluation with aortic valve calcium scoring allows one to limit the risk imposed upon those who may not have severe AS. When diagnosis remains questionable, utilizing nitroprusside or dobutamine in the catheterization laboratory not only can confirm the diagnosis, but will allow the operator to determine which patients are more likely have moderate AS and are not necessarily in need of more urgent AVR.

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References

[1] Osnabrugge RL, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, et al. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. J Am Coll Cardiol 2013;62:1002–12.
[2] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin III JP, Guyton RA, et al. 2014 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57-185.
[3] Clavel MA, Burwash IG, Pibarot P. Cardiac imaging for assessing low-gradient severe aortic stenosis. JACC Cardiovasc Imaging 2017;10:185–202.
[4] Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging 2017;18:254–75.
[5] Pibarot P, Dumesnil JG. Low-flow, low-gradient aortic stenosis with normal and depressed left ventricular ejection fraction. J Am Coll Cardiol 2012;60:1845–53.
[6] Ribeiro HB, Lerakis D, Gilard M, Cavalcante JL, Makkar R, Herrmann HC, et al. Transcatheter aortic valve replacement in patients with low-flow, low-gradient aortic stenosis: the TOPAS-TAVI registry. J Am Coll Cardiol 2018;71:1297–308.
[7] Clavel MA, Burwash IG, Mundigler G, Dumesnil JG, Baumgartner H, Bergler-Klein J, et al. Validation of conventional and simplified methods to calculate projected valve area at normal flow rate in patients with low flow, low gradient aortic stenosis: the multicenter TOPAS (true of pseudo severe aortic stenosis) study. JASE 2010;23:380–6.
[8] Annabi MS, Touboul E, Dahou A, Burwash IG, Bergler-Klein J, Enriquez-Sarano M, et al. Dobutamine stress echocardiography for management of low-flow, low-gradient aortic stenosis. J Am Coll Cardiol 2018;71:475–85.
[9] Eleid MF, Sorajja P, Michelena HI, Malouf JF, Scott CG, Pellikka PA. Flow-gradient patterns in severe aortic stenosis with preserved ejection fraction: clinical characteristics and predictors of survival. Circulation 2013(16):1781–9.
[10] Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739–91.
[11] Hachicha Z, Dumesnil JG, Bogaty P, Pibarot P. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. Circulation 2007;115:2856–64.

[12] Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the european association of cardiovascular imaging and the american society of echocardiography. J Am Soc Echocardiogr 2017;30:372–92.
[13] Rusinaru D, Malaquin D, Maréchaux S, Debry N, Tribouilloy C. Relation of dimensionless index to long-term outcome in aortic stenosis with preserved LVEF. J Am Coll Cardiol Img 2015;8:766–75.
[14] Clavel M. How does CT fit into the evaluation and management of patients with AS? Cardiosource. http://www.acc.org/latest-in-cardiology/articles/2016/06/13/10/01/how-does-ct-fit-into-the-evaluation-and-management-of-patients-with-as; 2016, Accessed date: 5 March 2018.
[15] Cueff C, Serfaty JM, Cimadevilla C, Laissy JP, Himbert D, Tubach F, et al. Measurement of aortic valve calcification using multislice computed tomography: correlation with haemodynamic severity of aortic stenosis and clinical implication for patients with low ejection fraction. Heart 2011;97:721–6.
[16] Clavel MA, Messika-Zeitoun D, Pibarot P, Aggarwal SR, Malouf J, Araoz PA, et al. The complex nature of discordant severe calcified aortic valve disease grading: new insights from combined Doppler echocardiographic and computed tomography study. J Am Coll Cardiol 2013;62:2329–38.
[17] Clavel MA, Pibarot P, Messika-Zeitoun D, Capoulade R, Malouf J, Aggarval S, et al. Impact of aortic valve calcification, as measured by MDCT, on survival in patients with aortic stenosis: results of an international registry study. J Am Coll Cardiol 2014;64:1202–13.
[18] Bonow RO, Brown AS, Gillam LD, Kapadia SR, Kavinsky CJ, Lindman BR, et al. ACC/AATS/AHA/ASE/EACTS/HVS/SCA/SCAI/SCCT/SCMR/STS 2017 appropriate use criteria for the treatment of patients with severe aortic stenosis: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, European Association for Cardio-Thoracic Surgery, Heart Valve Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. J Am Coll Cardiol 2017;70:2566–98.
[19] Lloyd JW, Nishimura RA, Borlaug BA, Eleid MF. Hemodynamic response to nitroprusside in patients with low-gradient severe aortic stenosis and preserved ejection fraction. J Am Coll Cardiol 2017;70:1339–48.
[20] Saybolt MD, Fiorilli PN, Gertz ZM, Herrmann HC. Low-flow severe aortic stenosis: evolving role of transcatheter aortic valve replacement. Circ Cardiovasc Interv 2017;10:e004838.