Severe Aortic Stenosis in Asymptomatic Patients: the Dilemma of Clinical *versus* Surgical Treatment

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Abstract

Aortic valve stenosis has become increasingly prevalent, in agreement with the aging of the population. Thus, it has become increasingly common to treat asymptomatic patients with severe aortic stenosis. Although the patients with asymptomatic aortic stenosis belong to the same group, they are heterogeneous from a clinical, laboratory and echocardiographic point of view. The treatment of these patients raises the dilemma of the clinical *versus* the surgical treatment: should we submit the patient to the risks of surgery or keep the patient under clinical observation, running the risk of irreversible myocardial damage or even sudden death? Under this perspective and based on the current literature, this study supplies tools that help to stratify the patients. The valvular area, degree of calcification, transvalvular aortic flow velocity, left ventricular hypertrophy and stress test alterations are the factors that place asymptomatic individuals with severe aortic stenosis in a group called very-high risk, in which the surgical approach starts to be considered.

Introduction

The prevalence of aortic stenosis (AoS) is growing, particularly that of degenerative etiology, mostly related to the aging of the population. The aging of the population is a worldwide phenomenon and it also occurs in Brazil. According to the estimates of the Brazilian Institute of Geography and Statistics (IBGE), by the year 2050, Brazilian individuals older than 75 years will represent 10% of the total population[1]. According to Lindroos et al[2], in an echocardiographic study of AoS prevalence, approximately 3% of the population older than 75 years presents severe AoS of degenerative etiology[2].

The epidemiological importance of AoS can be estimated by projecting the Brazilian population scenario for the year 2050. The country will have 260,000,000 inhabitants and of these, approximately 10%, or 26,000,000, will be older than 75 years[1].

Key words

Aortic valve stenosis; ventricular dysfunction, left/surgery; heart valve prosthesis implantation; symptoms, clinical.

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Considering the echocardiographic study by Lindroos, there will be 800,000 individuals older than 75 years with severe degenerative aortic stenosis. Adding these patients to those presenting AoS from the other age ranges and of different etiologies, this valvular disease can be considered a public health problem, further increasing the interest of its study.

In addition to the epidemiological aspect, another question raised regarding the AoS is the approach in case of asymptomatic patients with severe AoS. It is understood that the asymptomatic patient is the one who does not present the classic symptoms of AoS: dyspnea, angina and syncope, regardless of the age range and/or etiology. The asymptomatic patient with severe AoS has been the object of much debate between clinicians and cardiologists in recent years. According to the previous paradigm, based on the observations made during the 1960s and 70s, the asymptomatic patients with severe AoS can be followed clinically, as long as they do not present systolic ventricular dysfunction, as the survival curve in this group is similar to that of the general population[3].

However, the concept of "benignity" of the severe asymptomatic AoS has been contested in the last years, supported by two premises:

1. Asymptomatic patients are not always really symptom-free, as they very often progressively try to limit their activities, thus masking the symptoms (mainly elderly patients); they are actually "pseudo-asymptomatic" patients and therefore, present a worse prognosis.
2. The asymptomatic patients with severe AoS are not identical, i.e., even though they do not have symptoms and do not present left ventricular dysfunction, there are other variables that can increase or decrease the risk of these patients, making them, although part of the same group, a heterogeneous set of patients.

The objective of the present study, therefore, is to discuss, considering the current evidence, the best approach for the asymptomatic patient with severe AoS, by supplying tools that can help the decision-making of keeping the patient under observation or submitting him/her to the surgical treatment.

Aortic stenosis: relevant aspects

AoS is a valvular disease that affects the aortic valve and which is characterized by obstruction to the passage of blood flow from the left ventricular outflow tract to the aorta. Its main etiologies are rheumatic disease, degenerative disease, also called atherosclerotic etiology and congenital etiology[4].

Whatever the cause of the AoS, the final pathway is the calcification process and the progressive decrease in size of

the valve orifice. During the AoS evolution, this progressive decrease in the valvular area determines left ventricular (LV) hypertrophy (LVH), initially with maintenance of systolic function. The LVH allows the patient to remain asymptomatic for a variable period of time. In time, there is an imbalance between the muscle, interstitial and vascular compartments, resulting in ischemia and myocardial damage. Progressive ventricular dysfunction occurs, initially of the diastolic type; in the final phase, systolic ventricular dysfunction is observed.

Throughout the natural history of AoS, the onset of symptoms (dyspnea, angina and stress-induced syncope) is a marker of severity, with drastic implications on the survival curve of these patients[3,5].

The diagnosis of AoS is based on anamnesis, physical examination and complementary assessment. The anamnesis must be thorough, aiming at establishing the patient's actual functional capacity and identifying the presence of symptoms related to the aortic stenosis. It is very common for patients to limit their activities after symptom onset[6].

At the complementary assessment, the role of the Doppler echocardiography (ECHO) procedure is a crucial one[7,8]. The ECHO allows the diagnostic confirmation and the stratification of the severity of the AoS, which can be mild, moderate or severe.

According to the American Heart Association[7], the severe AoS can be defined as that which presents a valvular area < 1.0 cm^2, mean aortic transvalvular gradient ≥ 40 mmHg, and/or peak systolic aortic jet velocity > 4 m/s. A sub-classification of AoS as very severe AoS has been suggested[9,10]: it would be the one in which the aortic valve area is ≤ 0.7 cm^2 and/or indexed valve area is ≤ 0.4 cm^2/m^2.

The definitive treatment of severe AoS, when indicated, is the surgical approach and the standard treatment, to date, consists in replacing the aortic valve with a prosthesis, which can be either biological or metallic.

The main indications for the surgical treatment are[7,8]:

- Severe AoS in symptomatic patients (dyspnea, angina and syncope)
- Severe AoS in patients that will be submitted to myocardial revascularization
- Severe AoS in patients that will be submitted to surgeries in the aorta or other valves
- Severe AoS in patients with ventricular systolic dysfunction

More recently, the technique of percutaneous aortic valve implantation[11,12] has been used. This procedure is carried out through the femoral vein and the biological aortic prosthesis is anchored on a wired structure that resembles a "large stent"; it is performed in centers that have experience with this procedure and it has not yet substituted the conventional surgical procedure, being reserved for selected cases with high surgical risk.

Severe aortic stenosis in asymptomatic patients: the great dilemma

The approach of patients with severe AoS initially allocates them in three groups:

- Symptomatic patients with severe AoS and/or LV systolic dysfunction. These patients have formal indication for surgical treatment and, as long as there are no factors/comorbidities that contraindicate surgery, the latter must be considered the treatment of choice.
- Symptomatic patients with severe AoS and/or LV systolic dysfunction, but with comorbidities that contraindicate the surgical treatment, or patients that refuse to be submitted to the surgical procedure. In these cases, the treatment is palliative, although there is a future perspective of the alternative possibility of treatment through the percutaneous aortic valve implantation[11,12].
- Finally, the third group, consisting of asymptomatic patients with severe AoS, with preserved ventricular function, the main object of this study. As mentioned before, although they belong to the same group, they comprise a heterogeneous set of patients. Therefore, the medical conduct must be individualized.

The therapeutic decision regarding the asymptomatic patient with severe AoS raises the dilemma: to keep the patient under clinical observation or submit the patient to a prophylactic surgery.

The strategy to submit all asymptomatic patients with severe AoS to a prophylactic surgery is not a viable one. Considering that the "prophylactic surgery" were the routine approach, we would be exposing 100% of the asymptomatic patients with severe AoS to a 3% to 4% risk related to the surgical procedure, added to a 1% risk a year related to the presence of valvular prosthesis, benefiting approximately 1% of this population who would present the risk of sudden death per year[5,13-15].

On the other hand, to keep all patients from this group under clinical observation can be hazardous. In fact, more recent observational studies related to the natural history of severe AoS in asymptomatic patients have shown that this group is not so "benign" as believed in earlier decades[16-21].

In 1997, Otto et al[18] presented a study of 123 asymptomatic patients with severe AoS that were followed prospectively for 2.5 ± 1.4 years. In this study, the probability of symptom-free survival for asymptomatic patients was 93% in the first year, 62% in the third year and 26% in the fifth year. The multivariate analysis showed that the aortic jet velocity, the increase in the aortic jet velocity and the change in the functional status were independent predictors of death or need for surgery. For the patient, the probability of remaining alive, without the need for surgery at 2 years of follow-up was only 21% for those presenting aortic jet velocity > 4 m/s at the study enrollment.

In 2000, Rosenhek et al[21] published the results of a prospective study in which 126 asymptomatic patients with severe AoS were followed for 22 ± 18 months. At the end of the follow-up period, the probability of survival calculated for the asymptomatic patients was 93% in the first year, 91% in the second year and 87% in the fourth year. The multivariate analysis showed that the degree of aortic valve calcification was an independent predictor of combined events that included the development of symptoms and/or death. The probability of symptom-free survival for the asymptomatic patients that

presented moderate or intense aortic valve calcification was 60% in the first year, 47% in the second year and only 20% in the fourth year.

In 2001, Amato et al[16] reported the results of a prospective study that followed 66 asymptomatic patients with severe AoS. All patients were submitted to an ergometric test on treadmill, with the objective of stratifying them. There were four cases of sudden death during the follow-up and in these cases, the ergometric test had been positive and the aortic valve area was ≤ 0.6 cm^2.

In 2004, Bergler-Klein et al[22] studied the BNP and NT-proBNP as prognostic markers in patients with aortic stenosis. The focus was the analysis of symptom-free survival in asymptomatic patients. The BNP value < 130 pg/ml and NT-proBNP value < 80 pmol/l (678 pg/ml) were predictors of symptom-free survival for a period of six to nine months[22].

In 2005, the Pellikka et al[20] presented the results of a large study of 622 asymptomatic patients with severe AoS that were followed prospectively for 5 years. In this study, the probability of remaining symptom-free for patients not submitted to the surgical treatment was only 33% in 5 years, whereas the probability of survival without surgery was 25% in 5 years. The risk of sudden death, not preceded by symptoms, was approximately 1% a year. In this study, after 2 years of follow-up, the asymptomatic patient started to present a worse prognosis than that of the general population, even in the absence of symptoms. Age, chronic renal failure and aortic jet velocity were predictors of mortality[20].

More recently, Dr. Jean-Luc Monin´s group et al[17] carried out a study of 107 asymptomatic patients with severe AoS[17]. The objective was to develop a risk score that could be applied and that would be able to predict the chance of these patients to present adverse events over time. The patients were followed for 24 months and death or need for surgical procedure was considered adverse events. The independent predictors of adverse events found in this study were used to construct the score, which was then applied to a second population of 107 asymptomatic patients with severe AoS, with the objective of validating the score. The outcome predictor variables were female sex, peak systolic aortic jet velocity and initial BNP value. A formula was constructed to calculate the score:

> Score value = [peak systolic aortic jet velocity (m/s) x 2] + [(natural logarithm of BNP) x 1.5] + 1.5 (if female)

The values obtained for the score were grouped in quartiles: Q1 12.9; Q2 14.6; Q3 16.2 and Q4 19.7. The probability of event-free survival in 20 months was 80% among patients at the first quartile and only 7% among patients from the last quartile. Although the results of the study are significant, the systematic use of the risk score, proposed by Dr. Monin's group[17], still needs to be validated, in order to become of routine use[23].

If, on the one hand, the prospective studies that assessed asymptomatic patients with severe AoS have shown that the risk of sudden death in these patients is around 1% a year, on the other hand they have also shown that the group is indeed heterogeneous and that clinical, laboratory and echocardiographic parameters determine a higher or lower risk for these patients.

In addition to sudden death, the asymptomatic patients also present the risk of irreversible myocardial damage in cases when the surgery is postponed[23]. These risks must be taken into account when choosing between the conservative and the surgical strategies.

Therefore, what has been sought is a more refined stratification of this group of patients, with the objective of identifying, among asymptomatic patients with severe AoS, those at higher risk who, consequently, would benefit from the surgery. That objective is exactly to prevent sudden death and/or irreversible myocardial damage. In this sense and based on more recent guidelines and observational studies, the main risk factors would be[7,8,10]:

- Very severe AoS (aortic valve area ≤ 0.7 cm^2 or indexed valve area ≤ 0.4 cm^2/m^2
- Accelerated increase in the severity of the AoS (defined as increase in the aortic jet velocity > 0.30 m/s a year)
- Aortic valve calcification
- Presence of documented ischemia / coronary artery disease
- Ventricular systolic dysfunction (when present indicates surgery)
- LV dilation with systolic function impairment (afterload mismatch)
- Marked or rapidly progressive LV hypertrophy (12 to 14 mm in women and 14 to 16 mm in men)
- Age (> 60 years)
- Other non-cardiac comorbidities

The answer to the dilemma: individualized management

As shown before, although asymptomatic patients with severe AoS belong to the same group of patients, they are actually a heterogeneous set of patients from a clinical, laboratory and echocardiographic point of view. As a consequence, the prognosis also becomes dependent on these particularities and, therefore, the conduct for these patients must be individualized. At one extremity, for the low-risk patients, the conduct is a conservative, expectant one. At the other extremity, for the high-risk patients, the conduct is the surgical one, with aortic valve replacement.

To individualize the risk in asymptomatic patients is also the suggestion of the main guidelines. According to the European consensus, asymptomatic patients with severe AoS that present preserved ventricular function, exuberant aortic valve calcification, rapid increase in the aortic jet velocity or stress test alterations would be candidates to surgery, as well as those that will be submitted to other concomitant cardiac surgery, such as associated myocardial revascularization[8].

The American consensus indicates surgery for patients

who, albeit asymptomatic, present exuberant aortic valve calcification or rapid increase in the aortic jet velocity[7]. The national experience emphasizes the importance of the stress test in patient stratification[16].

Based on the exposed facts, we propose the following approach for the asymptomatic patient with severe AoS:

1. Confirmation of severe AoS diagnosis

The physical examination, complemented by the echocardiography, allows the confirmation of AoS and the assessment of its severity. According to the echocardiographic parameters, severe AoS can be defined as the one presenting mean aortic pressure gradient > 40 mmHg, aortic valve area < 1 cm^2 and/or peak systolic aortic jet velocity > 4 m/s. It has been suggested that very severe AoS is the one in which the aortic valve area is < 0.7 cm^2 or the indexed valve area is < 0.4 cm^2. When there are doubts about the severity of the AoS, a good alternative is to carry out a hemodynamic assessment, using manometry and detecting the transvalve aortic pressure gradient.

2. Clarification of the actual functional status. Is the patient really asymptomatic or is the patient self-limited?

The anamnesis of these patients must be detailed and thorough, focused on the patients' routine activities. It is very common for patients who walked without any problems to present now, at a more limited state, restricted to housework activities, and even so, declare that they feel fine, when they have actually ceased to perform at the previous level of effort.

A good complementary alterative, in an attempt to clarify the question of functional status, would be to submit these patients to a functional assessment, such as the ergometric test[24]. The test can supply important data and select the so-called pseudo-asymptomatic patients. The test also helps in cases of isolated syncope (without angina or dyspnea). The isolated syncope, as the only clinical manifestation of AoS, is unusual [25,26]. In these cases, the presence of syncope during the test defines the symptom-exertion association, indicating the need for surgery. It is also worth mentioning that the stress test can also be associated to the echocardiography[27]. The stress-echocardiography is another method of functional stratification of these patients.

Although the stress test is infrequently performed in clinical practice[28], in a recent meta-analysis[29], which analyzed the role of the ergometric test in the assessment of asymptomatic patients with severe AoS, the authors emphasized that the test is safe and effective to identify patients at high risk for adverse cardiac events and sudden death. The test can be used for risk stratification and to define the best moment to submit patients to the surgical procedure.

The stress test is increasingly growing in recognition and whereas its recommendation is class IIb in the 2006 American guidelines for the management of patients with valvular heart disease[7], the European Society of Cardiology in 2007 considers it beneficial and effective and included the test in the decision-making algorithm for asymptomatic patients with severe AoS[8].

3. Left ventricular function assessment

The echocardiography allows the assessment of the systolic ventricular function[30]. In patients with severe AoS, even asymptomatic ones, if there is systolic ventricular dysfunction, the surgical treatment must be considered.

4. Definition of clinical or surgical conducts for asymptomatic patients with severe AoS, with preserved ventricular function

For these patients, the conduct must be individualized[10,31]. Some parameters can classify the patient as being very-high risk and among the aforementioned factors, the ones that define very high risk are:

- Positive stress test (with evident symptoms or stress-induced hypotension)
- Aortic valve area ≤ 0.7 cm^2 or indexed valve area ≤ 0.4 cm^2/m^2. The body-surface indexed area is important due to the anthropometric differences observed in several patients.
- Rapidly progressive increase in aortic jet velocity, with an annual rate of increase > 0.30 m/s a year.
- Moderate to intense aortic valve calcification, if associated with a rapid increase in aortic jet velocity.
- Marked ventricular hypertrophy, another marker of severity, especially when added to the reduced valvular area. The ventricular hypertrophy, on the one hand, allows the maintenance of cardiac output in the presence of the pressure overload caused by the AoS. On the other hand, it alters the diastolic function, decreases the coronary perfusion and is related to an increase in mortality[32].

Based on the current literature, we suggest that asymptomatic patients with severe AoS who present very-high risk factors be considered candidates to surgical treatment. The surgical risk is relatively low, when compared to the risk of rapid development of symptoms and sudden death, specific for this group of very-high risk patients. Although there have been no randomized studies on the clinical *versus* surgical conduct in these patients, the strategy of not delaying the surgical treatment is being increasingly acknowledged, considering that the myocardial damage can be irreversible, the symptoms can develop rapidly without the patient's correct perception and the risk of sudden death can increase drastically.

A special consideration must be given to the elderly population. When we analyze guidelines and consensuses, there is no reference to the age-limit that contraindicates the surgical treatment. In fact, what the studies reveal through series of cases is that the surgical treatment, even in the elderly patient, is better than the expectant conduct, when indicated[33]. Concerning the elderly patient, one must seek the very-high risk factors, but always taking the following equation into account: life expectancy x quality of life x risk of the surgical treatment, so that the best therapeutic decision can be achieved.

Examples of clinical situations

We will exemplify what has been discussed throughout this article through three clinical situations:

Situation 1

Fifty-three-year-old executive man, hypertensive and dyslipidemic, who was asymptomatic in his daily life, plays soccer with his friends twice a week. During a consultation with his cardiologist, a murmur suggestive of AoS is detected. The echocardiogram disclosed normal-sized cardiac chambers, septal and posterior wall thickness of 11 mm, normal biventricular function, calcified aortic valve with severe aortic stenosis, mean aortic pressure gradient of 45 mmHg, aortic jet velocity of 4.1 m/s and aortic valve area of 1 cm^2. There are no alterations in the other valves. BNP level is 70 pg/ml. The cardiologist advises the patient to stop playing soccer and requests a stress test, of which results are normal and repeats the echocardiogram every six months, of which result is identical to the initial assessment. The indicated conduct is the expectant, conservative one. The patient is asked to return every six months or earlier in case of symptom onset.

Situation 2

Seventy-five-year-old retired man, asymptomatic in daily life, walks regularly. During a consultation with his cardiologist, a murmur suggestive of AoS is detected. The echocardiogram discloses normal-sized cardiac chambers, septal and posterior wall thickness of 12 mm, normal biventricular function, calcified aortic valve with severe AoS, mean aortic pressure gradient of 45 mmHg, aortic jet velocity of 4.2 m/s and aortic valve area of 0.9 cm^2. There are no alterations in the other valves. BNP level is 100 pg/ml. The cardiologist requests a stress test, of which results are normal. The initial conduct is the expectant one and asks the patient to return in six months. At the return (6 months) the patient remains asymptomatic and a new echocardiogram disclosed septal and posterior wall thickness of 14 mm, normal biventricular function, calcified aortic valve with severe AoS, mean aortic pressure gradient of 58 mmHg, aortic jet velocity of 4.9 m/s and aortic valve area of 0.7 cm^2. A rapid six-month evolution of the AoS is observed (increase in septal and wall thickness, decrease in aortic valve area, increase in aortic pressure gradient and jet velocity). The patient is classified as very-high risk due to the rapid evolution of the aortic stenosis and the surgical conduct is indicated.

Situation 3

Sixty-two-year-old woman, no diagnosed diseases, asymptomatic in daily life, retired. The daughter has observed that the mother seldom leaves the house and that her activities are being increasingly restricted to domestic activities. The cardiologist detects a murmur suggestive of AoS. The echocardiogram discloses normal-sized cardiac chambers, septal and posterior wall thickness of 13 mm, normal biventricular function, calcified aortic valve with severe AoS, mean aortic pressure gradient of 58 mmHg, aortic jet velocity of 4.8 m/s and aortic valve area of 0.8 cm^2. There are no alterations in the other valves. BNP level is 200 pg/ml. The cardiologist indicates a stress test to evaluate the actual functional status of the patient: at the second minute of the test the patient presents hypotension with pre-syncope sensation and the test is interrupted, followed by the patient's total recovery. The cardiologist interprets the case as a very-high risk one, considers that the patient probably self-limited and indicates the aortic valve replacement surgery.

Conclusion

The asymptomatic patients with severe AoS belong to a heterogeneous group of patients from the clinical, laboratory and echocardiographic point of view. Within this group, a number of patients classified as being very-high risk are noteworthy. The very-high risk criteria are: stress test alteration, aortic valve area $\leq$ 0.7 cm^2 or indexed valve area $\leq$ 0.4 cm^2/m^2, rapidly progressive transvalve aortic jet-velocity, moderate to intense aortic valve calcification, marked ventricular hypertrophy. For very-high risk patients, the surgical approach must be considered, in opposition to the conservative approach.

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