Risk factors for depression and anxiety in the patient with aortic valve stenosis
Factores de riesgo para depresión y ansiedad en el paciente con estenosis valvular aórtica

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Abstract:
Anxiety disorders and depression are common along with negative effects in different areas of the patient such as lower quality of life, lower adherence to treatment, negative perception of oneself combined with comorbidities and mortality. However, these disorders are usually considered as symptoms and not as an independent factor that require greater detection, care and early treatment. The following cardiovascular diseases are among the leading causes of mortality and morbidity in the world in which a subgroup of valvopathies stand out which can occur in young patients (congenital alterations) and in elderly patients (called calcific or degenerative aortic valve stenosis) consisting of calcium crystal formation and lipid accumulation. These processes damage the valve generating aortic sclerosis characterized by thickening of the leaflets. Valvopathies are usually asymptomatic during the first years after their onset, and several modifiable and non-modifiable factors have been related to the progression of the disease. Psychological alterations can occur in these patients before, during and/or after discharge, generating mood disorders such as anxiety and depression, which have an unknown prevalence. This review discusses the importance of the symptoms to promote a timely diagnosis and to generate future interdisciplinary interventions that may improve the quality of life in patients with aortic valve stenosis

Keywords:
Anxiety, depression, stenosis valve aortic, risk of factors, prevalence

INTRODUCTION
According to the World Health Organization (WHO), cardiovascular diseases cause about 17.9 million deaths per year worldwide, which means that four out of every five deaths are related to this condition, such as coronary heart disease and cerebrovascular events. It should be noted that they occur prematurely, that is, in people under 70 years of age, so it is estimated that by the year 2030 nearly 23.6 million people could die from some cardiovascular problem. These observations are related to Aortic Valve Stenosis (AVS) is present in developed countries and is considered the third most common cardiovascular disease and the most common valvulopathies along with ischemic artery disease and arterial hypertension there also data provided by the National...
Institute of Statistics and Geography (INEGI) of the 1,086,743 deaths registered in Mexico in the year 2020, 58% were men while 41.1% women.

On the other hand, in 2019 died about 72,768 women, while in 2020 rose about 121,556 women, men registered a death of 156,041 in 2019 while in 2020 rose to 218,704; that is, 62,663 more cases were due to ischemic problems (reduction of blood flow to the heart by partial or total blockage of the arteries) representing 76.3% with 166,874 cases (Figure 1), making it one of the main causes of death at the national level, together with COVID-19 and type 2 diabetes mellitus.1-3

Figure 1. Deaths from all-cause heart disease of heart such as ischemic (blood flow disorders) represented 166,874 cases (76.3%), hypertensive diseases represented 34,193 cases (15.6%), pulmonary circulation diseases and other diseases 17,053 cases (7.8%) and acute rheumatic fever diseases 584 cases (0.3%).

AORTIC VALVE STENOSIS

According to the American Heart Association (AHA) Aortic Valve Stenosis (AVS) is a narrowing of the aortic valve that through different physiological and hemodynamic processes develops calcification (calcium crystals). The heart contains four valves (mitral, tricuspid, pulmonary and aortic) that are responsible for sending all the blood flow around the body. The AVS is located in the left ventricle (LV) which allows the passage of blood into the aorta artery and the peripheral arterial system. The level of narrowing of the valve will need extra effort to be able to expel the greater amount of flow, and, as a consequence, a thickening of the ventricle develops known as ventricular hypertrophy. The severity of the disease will be constituted by the alterations of the valve itself, hemodynamics, symptomatology and forced LV exercise.4,5

ETIOLOGY

AVS can be caused by a congenital defect that produces an alteration in the valve, for example, bicuspid valve, which is associated with calcification and narrowing at early ages. It can also be acquired by infection with bacteria such as group A streptococci that are usually present in the throat and skin, which in turn activate proteins and cytokines together with T cells that cause inflammation of the cardiac tissue (rheumatic disease), it is worth mentioning that this infection is still prevalent in developing countries. On the other hand, there is a first phase of the disease called Aortic Sclerosis (AS) in which the leaflets are inflamed and calcium crystals are present, but there is still a normal valve area and blood flow, which does not generate any type of symptom for the patient.6

PATHOPHYSIOLOGY

The valve is composed of a ring and three leaflets (right coronary, left coronary and no-coronary) and is located between the lower left chamber of the heart and the main artery of the body (aorta) which allows to maintain the correct blood flow to the whole body, it is possible that people do not present symptoms for years. Meanwhile, it has been documented that the development of AVS is due to different factors such as congenital and/or anatomical: bicuspid, unicuspid or rarely quadricuspid valves that predispose to early calcification, clinical factors: increased lipids, blood pressure, glucose, cholesterol (LDL) and molecular factors: low infiltration of macrophages, lymphocytes and lifestyle factors: sedentary, diet, lack of exercise. During evolution of AVS, mild fibrocalcific changes originate a long-term asymptomatic AS, until more severe calcification develops during the considered final stage. At the severe stage of aortic valve stenosis, the calcification generates a considerable obstruction of LV flow injection resulting in clinical manifestations such as aortopathy or endocarditis and cardiovascular events.7-10

Table 1. Classification of the severity of aortic stenosis based on structural and functional parameters.

<table>
<thead>
<tr>
<th>Aortic Stenosis</th>
<th>Aortic Valvular Area (AVA)</th>
<th>Medium Gradient (GTEme d)</th>
<th>Maximum Speed (MS)</th>
<th>Hemodynamic Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slight</td>
<td>&gt;1.5cm²</td>
<td>&lt;25 mmHg</td>
<td>&lt;3 m/s</td>
<td>Early LV diastolic dysfunction</td>
</tr>
<tr>
<td>Moderate</td>
<td>1-1.5cm²</td>
<td>24 – 40 mmHg</td>
<td>3 – 4m/s</td>
<td>LV diastolic dysfunction, mild. LV hypertrophy, normal LVEF</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;1cm²</td>
<td>&gt;40 mmHg</td>
<td>&gt;4m/s</td>
<td>LVEF &lt;50%</td>
</tr>
</tbody>
</table>

LVEF: Left ventricular ejection fraction.10

CLASSIFICATION

The classification of the severity of valvular heart disease is based on certain criteria such as: symptoms, valve anatomy, hemodynamics, effects of valve dysfunction, ventricular and vascular function (Table 1). In other words, when there is a higher risk, the best option would be to perform a surgical intervention or percutaneous transcatheter replacement, and research has not yet found any other procedure and/or medication to reduce symptoms from early stages. All these observations are also related to the
psychoeducation provided to the patient before, during and after so that he/she can understand the complexity of the problem and be able to act and provide periodic follow-up to slow down or diminish the degenerative process.11

AS is a condition that becomes progressive and does not present symptoms or major events until an advanced stage appearing in the sixth, seventh and eighth decade, there is poor survival after the onset of the first symptoms (Figure 2).12

The main symptoms are dyspnea, angina pectoris and syncope. The appearance of these symptoms refers to clinically significant stenosis; however, in the severe population they may not present symptoms and only present some of them. On the other hand, some patients may have acute complications due to underlying disease or recurrent treatments. The classic finding is a hard, late systolic murmur and it is more tense in the second right intercostal space and travels to the carotid arteries. Attention at the primary level should be paramount among specialists and in the population that presents some type of cardiac anomaly such as irregular murmurs, in order to detect AVS early and provide adequate treatment to reduce the progression of the disease. Angina pectoris is a common symptom of ischemic heart disease, considered the leading cause of mortality and morbidity worldwide, which is an alteration in the supply and demand for oxygen during exercise stress that may be immersed in AVS.13,14,15,16

Syncope, is an abrupt loss of consciousness and postural tone, which is usually followed by a rapid spontaneous improvement this symptom is observed in different underlying conditions or may be indicated by other symptoms such as dizziness, nausea, visual disturbances and lightheadedness. On the other hand, heart failure is a complex syndrome that is a structural and functional alteration bringing consequences such as hospitalizations and reduced life expectancy. The prevalence is 2% of adults and as age advances it increases to 10% in those over 70 years of age. In AVS this symptom is a late manifestation; that is, as the valvular obstruction worsens, it does not pump enough blood supply as it should, generating dyspnea.17,18,19,20

DEPRESSION AND ANXIETY: GENERAL ASPECTS

Depression is defined as an emotional state characterized by feelings of sadness, melancholy, irritability and accompanied by somatic and cognitive symptoms that affect the person as a whole and is considered a prevalent risk factor in the incidence of morbidity and mortality of cardiovascular diseases. The common feature of the affective disorders is the presence of episodes of a sad mood and/or irritable emptiness, somatic and cognitive changes that are determined by duration, frequency and/or presumed etiology. Clinically, depression shows patterns defined in four types: affective symptoms (low mood, sadness, discouragement), cognitive symptoms (negative thoughts about oneself, the world and the future, low self-esteem, hopelessness, remorse), behavioral symptoms (exclusion from social activities, decrease in habitual behaviors, motor lethargy) and physical symptoms (little or no appetite, changes in sleep habits, lack of energy).21,23

Anxiety is considered as a defense mechanism against an event which only promotes the survival style and from it an adaptive behavior. Thus, it is considered a common sensation that changes constantly throughout the existence, can occur in moderate amounts to which can facilitate motivation, performance, activation to a threatening situation. When anxiety is present in a situation that cannot be controlled, there is misinterpretation or perception of highly harmful events, resulting in responses of irritability, worry or restlessness. Finally, the presence of anxiety will be subject to changes in duration, severity, persistence, degree of distress and cognitive impairment in what could develop into an anxiety disorder; currently prevalent throughout the lives from 10 to 20% sharing comorbidities with mood disorders and substance abuse.24,25

STUDIES BASED ON DEPRESSION AND ANXIETY IN THE PATIENT WITH AVS

First, in the 1990s, it was possible to infer in some conclusions that personality traits (hostility) or psychological factors could be causal for acquired heart disease.26 It has been mentioned that an unusual pain of same disease and/or symptom can generate cognitive or emotional alterations precisely there are cognitive representations of the disease: identity (beliefs and symptomatology of the disease), consequences (quality of life and functional capacity), causes (beliefs that cause the disease), chronology (beliefs about the course of the disease and its duration) and control/cure (beliefs that the patient can control together with treatment) and negative emotional aspects such as: fear, anger, anguish.27-29 Emotional disturbances are often not recognized at first glance in heart disease, which is why depression and anxiety usually present themselves in different ways by chest pain that coexists with medical syndromes.30 In the literature, generalized anxiety disorder and major depressive disorder, commonly referred to as anxiety and depression, are the 2 main diagnosed and disabling mental health conditions in the USA prevailing in patients with cardiovascular disease and comorbidities. Such untreated conditions are poorly recognized risk factors with
highly variable results in different studies. Thus, preoperative and postoperative anxiety and depression are associated with a higher morbidity and mortality rate independent of the type of cardiac surgery. Research reports that having a cardiac function (functional class II and III) according to the New York Association (NYHA) is a risk factor for having anxiety/depression. Another point is this generates that these patients are more prone to develop psychosocial problems due to the concerns of medical follow-ups, types of treatments, negative thoughts, decision making, worries about possible surgeries, work, economic and family issues compared to the general population. All these observations are similar in studies of young and adult patients with congenital heart disease of various types, including AVS, and prevalence of 25% and 9% of anxiety and depression symptoms associated with less psychological support, anxiolytic/depressive medication, use of health services such as continuous visits to the physician, cardiology and emergency services, which present a higher risk of mortality compared to the general population. At the same time, geriatric patients who are candidates for TAVR (Transcatheter Aortic Valve Replacement) have been reported to have a 15.4% prevalence of baseline depression associated with an increased risk of postoperative mortality. The psychological implications of cardiovascular diseases including AVS tend to fluctuate among patients, but some relevant predictive factors that may increase the symptoms of anxiety and depression are: loneliness, family overprotection, transition to independent living (in the case of children and/or adolescents, which they consider a new challenge) fear or uncertainty of the negative evolution of oneself and the perceived state of physical health. For example, it has been found that patients with severe congenital diseases have low income, no psychological treatment, difficulty in finding a job and therefore in financing health insurance and outpatient treatment, which has negative consequences on their mental health. In summary, all these difficulties presented by the patient determine their behavior perception and way of coping with heart disease. All these observations are related to studies that highlight that women with coronary heart disease may be more likely to experience somatic symptoms of great intensity that generate anxiety and depression compared to men.

TREATMENT OF ANXIETY AND DEPRESSION IN THE PATIENT WITH AVS

Treatment for depression and anxiety in cardiovascular diseases including AVS suggest include pharmacotherapy, for example selective serotonin reuptake inhibitors (SSRI) which can even reduce recurrent cardiac events, in contrast, the use of benzodiazepines has been documented to produce new cardiac alterations, damage to the central nervous system and development of dependence which reduces the efficacy of these anxiolytics. There are also alternatives such as psychotherapy which consist of cognitive reconstructive, discussion of emotions and thoughts about disease as well as relaxation techniques to reduce stress levels, psychoeducation (knowing the origin, risk factors, treatment of the disease), development of social skills, and one of the most researched interventions is “Mindfulness” which has bad positive effects on depression and anxiety in patients with cardiovascular events.

EPIDEMIOLOGY OF ANXIETY AND DEPRESSION

It is estimated that % of the world population has depressive disorders according to the global study of diseases, injuries and risk factors conducted in 2017. At the same time in the population, the prevalence of major depression in Europe is estimated at 6.6-6.9% while in the USA in adults >65 years of age it is 9.1%, while in the population with coronary heart disease it is 15-30%, which means that one in three older patients who undergo surgical or percutaneous valve surgery have prolonged depressive symptoms that prevent them from getting an adequate improvement, increased adverse effects and consequently lower quality life. On the other hand, patients are more likely to adopt unhealthy behaviors such as smoking, physical inactivity, poor nutrition and less adherence to treatment. To mention congenital heart disease, it is estimated that between 17% and 27% suffer from major depression related to New York Heart Association (NYHA) class IV classification together with a 3-fold higher mortality rate. There are systematic reviews showing that depressive symptomatology and diagnosed depression predict heart disease and aggravate prognosis, while epidemiological studies indicate that panic attacks, phobias and generalized anxiety can worsen the development of heart disease. To mention some studies, an American survey was conducted with older adults with heart disease and found that 42% presented elevated anxiety symptoms and 12% depression. While a German study found that mood disorders 30% and anxiety 28% were higher than in the population without heart disease Included AVS. A similar finding occurred in another German study of patients with percutaneous intervention and found that depression exceeded 30% and was closely associated with high mortality rates.

RISK FACTORS FOR AVS

AVS has a myriad of multifactorial factors (Figure 3) that act together at different times of life: birth, productive age and during old age, which unfortunately in the latter, life expectancy is considerably reduced as symptoms become more severe. As mentioned above, the prevalence is 21 – 31% in population >65 years and 12.4% in population >75 years. AVS is expected to double by 2040 and triple by 2060. Due to the accelerated aging of the population, but even mortality in this age group is present despite not having aortic stenosis but due to other cardiovascular diseases. The reviews show atherosclerosis that becomes a passive degenerative process creating fatty deposits along with calcium crystals in the valve tissue and diabetes that if left untreated causes an inflammatory process and increases minerals in different tissues including heart valves specifically aortic, hyperglycemia develops proteins that generate calcification and prevalence of 30 and 41% have been reported together with traditional factors such as arterial hypertension, obesity and dyslipidemias underlining this last established factor and it is estimated that more than 50% of the adult population in the world has dyslipidemias, thus in live models they mention that at earlier age they initiate dynamic processes to sclerosis and later calcification.
insulin resistance that coexists with hypertension, so that it has been observed that in normotensive patients the degree of calcification is lower, although it is worth mentioning that aortic flow velocity increases the risk of stenosis.\textsuperscript{3,5}\textsuperscript{5} A similar thing happens with chronic kidney disease along with the metabolism of minerals such as serum calcium and phosphate where calcification progresses and emphasizing that mortality increases despite receiving an aortic replacement.\textsuperscript{56-58} Obesity considered a multifactorial disease that may also contribute along with IMC or waist circumference further complicates the risk of stenosis.\textsuperscript{59} Simultaneously the metabolic syndrome involving abdominal adiposity together with insulin resistance increases the risk of adverse events and is associated with mechanical and structural changes in the valve independent of traditional factors.\textsuperscript{60} Male gender has been associated with a 56% higher probability of developing aortic stenosis compared to female gender.\textsuperscript{61} Therefore, there is a higher probability of generating sclerosis independent of other clinical factors.\textsuperscript{62} Smoking has been considered another factor for the occurrence of stenosis, however, not with progression (calcification).\textsuperscript{63} There are findings of genetic factors on a large scale, for example studies mention two genes in particular: PALMD together with TEX41 associated with stenosis with malformations in bicuspid valves.\textsuperscript{64,65} It should be added that the functionality of the ventricles and pulmonary circulation of these patients tend to have irreversible alterations increasing the probability of sudden death.\textsuperscript{66} Finally, another factor considered emerging and no less important is the family history or kinship observed in a Swedish study where 4.8% of patients with stenosis has a sibling with the same problem increasing three time more likely to develop it compared to 0.5% of the general population.\textsuperscript{67} A study conducted in Mexico showed that factors such as physical inactivity, hypertension, dyslipidemia, high insulin levels, male sex, and obesity increase the likelihood of AVS.\textsuperscript{68}

**Figure 3. The development of aortic valve stenosis is common in the elderly population and is largely related to known and unknown risk factors. Calcification of the tricuspid aortic valve occurs throughout the tissue while the leaflets present stiffness and later stenosis, which prevents proper blood flow.**\textsuperscript{48}

**DIAGNOSIS AND TREATMENT OF AVS**

The presence or absence of symptoms, as well as the severity of valvular narrowing and LV response to overload will be key factors in clinical decision making in patients with AVS. In the presence of symptoms, echocardiographic studies and cardiology consultation should be performed for all patients with mild exercise, dizziness and nausea, indicating that there is some alteration, especially in mild, moderate or severe stages. However, the symptomatology is varied and can be misinterpreted with other diagnoses or in the worst-case comorbidities in advanced stages. In order to know the variety of symptoms, one of the recommended studies should be performed, such as the stress test, where alterations in blood pressure can be found. So far, the only effective treatment is transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR). On the other hand, there are patients who need a replacement, but cannot receive it for this reason, it should not be considered as abandonment of medical care considering that it has been documented that there are situations that involve coping responses, from despair to hope.\textsuperscript{69,70}

**PROGNOSIS**

The prognosis of postoperative aortic valve replacement patients will depend on age (>65 years), two or more comorbidities, valvular hemodynamic factors, irreversible myocardial damage, left ventricular hypertrophy and studies prior to surgery. Patient survival ranges from 7 to 8 years, with the most frequent causes of death being stroke, cancer, pulmonary failure and acute myocardial infarction.\textsuperscript{71,72}

**CONCLUSIONS**

Mental disorders coexist with chronic degenerative diseases and likewise patients have little or no knowledge of their existence. More research is needed on psychological variables since they are seldom recognized and related to adverse outcomes; that is to say, they go unnoticed in any diagnosis. An improvement is needed for the early detection of symptomatology of the two main mental health disorders (depression and anxiety) and the efficacy of addressing psychosocial needs to optimize the health care service. These advances are required to improve the prognosis at the beginning of any surgical or percutaneous procedure.

**CONFLICT OF INTEREST**

The author declares that there is no conflict of interest and that he was not financed by any institution or company for the writing of this article.

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