UPDATE

Cardiovascular Disease in Women (VI)

Valvular Disease in Women

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There are very few studies on valvular heart disease in women. There is a sex influence in the prevalence of some types of valve disease: it is well known that rheumatic mitral stenosis is very common in women but degenerative valve disease affects both sexes in a similar way.

In degenerative aortic stenosis several physiopathological differences have been reported in women: the amount of calcium is lower than in men and the left ventricle generates higher gradients and hypercontractile response in women.

Regarding prognosis it is well accepted that women have higher mortality rates than men in cardiac surgery, both in coronary surgery and in valvular surgery. The ultimate reasons for this increased mortaliy are not known.

Pregnacy can be a difficult situation in women with valvular disease. In women with significant valve lesions it is wise to correct the valve disease before pregnancy is attempetd. Pregnancies in women with mechanical prosthesis carry an increased risk of prosthetic thrombosis as well as the risk of fetal embriopathy when oral anticoagulants are used in the first trimester.

Key words: *Valvular heart disease. Female sex. Cardiac surgery.*

Patología valvular en mujeres

Hay pocos estudios que hagan referencia, específicamente, a las valvulopatías en mujeres. Se conoce la influencia del sexo en la prevalencia de alguna de sus formas: la estenosis mitral reumática es una enfermedad más frecuente en las mujeres, mientras que las valvulopatías degenerativas parecen afectar a ambos sexos por igual.

Se ha descrito una serie de diferencias en la fisiopatología de la estenosis aórtica degenerativa en relación con el sexo: las mujeres tienen menores grados de calcificación y sus ventrículos responden con mayores incrementos de gradiente e hipercontractilidad ante valores similares de reducción del área valvular.

En cuanto al pronóstico, se acepta que el sexo femenino tiene una mayor mortalidad en la cirugía cardiaca, tanto en cirugía coronaria como en cirugía valvular. Las razones de esta mayor mortalidad no están del todo aclaradas.

El embarazo supone un problema importante en las mujeres con valvulopatía. En caso de lesiones significativas, es aconsejable tratarlas antes de un eventual embarazo. En caso de embarazo en pacientes portadoras de prótesis mecánicas, el tratamiento anticoagulante supone un grave problema, ya que hay un riesgo aumentado de trombosis protésica y un riesgo de embriopatía fetal si se utilizan anticoagulantes orales durante el primer trimestre de embarazo.

Palabras clave: *Valvulopatías. Sexo femenino. Cirugía cardiaca.*

INTRODUCTION

Valvular heart diseases have undergone highly significant changes in recent decades. In industrialized countries, the incidence of rheumatic valve disease has decreased dramatically, but the overall incidence of valve disease does not appear to have varied, mainly due to the increasing prevalence of degenerative valve disease and, to a much lesser extent, to the detection of new types of valve disease.[1]

In fact, these new valvular diseases constitute clinical rarities and include those caused by the chronic ingestion of certain drugs, such as ergotamine or methysergide, and those associated with certain types of systemic disease, such as antiphospholipid syndrome.[2,3] It was also feared that the acquired

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TABLE 1. **Etiology of Native Valve Disease in Europe (Euro Heart Survey)**

	Aortic Stenosis (n=1197)	Aortic Insufficiency (n=369)	Mitral Stenosis (n=336)	Mitral Insufficiency (n=877)
Degenerative, %	81.9	50.3	12.5	61.3
Rheumatic, %	11.2	15.2	85.4	14.2
Congenital, %	5.4	15.2	0.6	4.8
Others, %	1.5	19.3	1.5	16.2

TABLE 2. **Demographic Characteristics of Patients With Valve Disease in Europe (Euro Heart Survey)***

	Number of Patients	Age, Mean (SD), y	Patients Over 70 Years of Age	Female Sex
Aortic stenosis	1197	69 (11)	668 (56%)	512 (43%)
Aortic insufficiency	369	57 (16)	91 (25%)	96 (26%)
Mitral stenosis	336	57 (12)	61 (18%)	272 (81%)
Mitral insufficiency	877	65 (14)	384 (44%)	421 (48%)

*SD indicates standard deviation.

immunodeficiency syndrome might constitute a frequent cause of endocarditis and the resulting valve lesions. It seems, however, that valve involvement is uncommon in this syndrome.[4]

The recent Euro Heart Survey[5] on valve diseases collected data on 5001 patients with valvular heart disease, infective endocarditis or previous valve intervention from 25 European countries. In this registry, aortic stenosis and degenerative mitral insufficiency were the most common valve diseases, while the prevalence of rheumatic valve disease and other valve diseases was considerably lower (Table 1).

The differentiating features of valve disease in women have not been very widely studied. The influence of gender on the prevalence and characteristics of rheumatic valve disease has been recognized for years, but there is very little data concerning the prevalence in other types of valve disease. The data specifically related to the prognosis of valve disease according to sex is also very limited.

DISTRIBUTION ACCORDING TO SEX IN THE DIFFERENT TYPES OF VALVE DISEASE

Rheumatic mitral stenosis predominantly affects women. This classical observation, reported many years ago, has remained unchanged in all the countries in which rheumatic fever continues to be a public health problem. It is also widely known and accepted that when the rheumatic involvement takes the form of mitral insufficiency or aortic valve disease, the incidence in men and women is more or less the same. In their classical study, Roberts and Virmani[6] analyzed the presence of Aschoff bodies in patients with rheumatic valve disease and found that, in mitral valve disease, the proportion of women was 70%, whereas in aortic valve disease and aortic and mitral valve disease, it was 21% and 35%, respectively. The reasons for this female predominance in rheumatic mitral valve disease have not been studied.

A greater proportion of women than men has also been reported for mitral valve prolapse.[7] This was substantiated in population-based studies, like that carried out in the county of Olmsted, in the state of Minnesota,[8] which demonstrated that 62% of the cases of prolapse in that community had been diagnosed in women. However, other studies in different types of populations reported a similar incidence in the 2 sexes (1.8% and 1.6% in women and men, respectively).[9] While there may be doubts about the greater or lesser female predominance in mitral valve prolapse, what appears to be clearly established is the fact that, in men, this condition is associated with greater progression and the need for surgery.[10]

Calcification of the mitral annulus is especially frequent in older women, and it has been associated with cardiovascular risk.[11,12] Although mitral annulus calcification does not usually produce functional anomalies, it can occasionally cause severe mitral insufficiency and even significant mitral stenosis.

Among the patients with congenital aortic valve disease and, particularly, bicuspid aortic valve, men clearly predominate. In the classical pathological series of the Mayo Clinic, of a total of 542 cases of surgically confirmed tricuspid aortic valve, 69% of the patients were men.[13] This finding explains the fact that, in the middle-aged population, aortic stenosis is observed predominantly in men. Likewise, the prevalence of isolated aortic insufficiency is significantly lower among women than among men.[14]

While there is a clear male predominance in rheumatic aortic stenosis and congenital aortic stenosis, there is no evidence of the influence of gender in degenerative aortic stenosis. Population-based studies suggest a higher incidence among males. The Cardiovascular Health Study, in which echocardiography was employed to investigate the prevalence of aortic sclerosis and stenosis in a sample of 5201 patients over 65 years of age, demonstrated that male patients had a 2-fold higher risk of aortic valve involvement than female patients.[15] However, the greater longevity of women means that, in older age groups, aortic stenosis is observed with the same frequency in both sexes. Table 2 shows the distribution by sex and age of the valve diseases most prevalent in the Euro Heart Study.[5]

DOES GENDER HAVE AN INFLUENCE ON THE PATHOPHYSIOLOGY OF DEGENERATIVE AORTIC STENOSIS?

Recent studies have shown that men present a higher degree of valve calcification than women. Analyzing the calcium content of a total of 187 stenotic aortic valves obtained during valve replacement, Ortlepp et al[16] demonstrated that for similar degrees of valve stenosis, that is, for established based on mean gradients, women present less valvular calcification. In their study, they found no relationship between the degree of calcification and cardiovascular risk factors. However, they did observe that gender and genetic polymorphisms were associated with the extent of valve calcification. On the other hand, Roberts and Jong investigated the relationship between the weights of stenotic aortic valves obtained from patients undergoing valve replacement and transvalvular gradients. In their study, they observed that, for each valve weight, women presented higher pressure gradients than men.[17] Another aspect that has been little studied is whether the adaptive pathophysiological response of left ventricle to aortic stenosis is the same in both sexes. In this respect, Carroll et al[18] observed that, for similar aortic valve areas, women presented significantly higher gradients, smaller end-systolic chamber size and a high proportion of supranormal ejection fractions.

SEX AND PROGNOSIS

The mortality rate associated with cardiac surgery is higher in women. This fact has been clearly demonstrated in coronary surgincal coronary revascularization. In a series of 2129 consecutive patients undergoing coronary surgery in Sweden, female sex was an independent factor of surgical mortality and of perioperative complications, although the outcome and the long-term benefits of surgery were similar.[19] More recent studies, like that involving 15 440 patients who underwent coronary artery bypass grafting in Midwest hospitals, also showed female sex to be an independent predictor of surgical mortality, even when adjustments were made for all the comorbidities and body surface area.[20] As a result of these studies, scoring systems like the Eusoscore include female sex as a risk factor.[21] There are fewer studies that specifically analyze gender-related surgical risk in valve surgery but, very recently, the American Society of Thoracic Surgeons published the results of 409 904 surgical procedures in patients with valve disease and, in the analysis of factors predictive of mortality, female sex was considered an independent factor in this prediction, with an odds ratio of 1.37.[22]

The ultimate causes for the higher mortality rate in women are unclear since, both in coronary artery bypass surgery and valve surgery, the higher risk associated with the female sex appears to be independent of age and the presence or absence of comorbidity.

In patients with aortic insufficiency, a valve disease in which the decision to undergo surgery is based on the presence of symptoms or ventricular dysfunction, established on the basis of the ejection fraction and a given degree of ventricular dilation, in these patients the results of surgery have been found to be poorer in women. It could be that the criterion for ventricular dilation considered to indicate surgery (end-systolic diameter ≥50 mm) is not applicable in women.[23] For this reason, we advocate the utilization of diameters indexed by body surface area.

PREGNANCY AND VALVE DISEASE

It is a well-known fact that the most important cardiovascular changes occurring during pregnancy are an increase in blood volume, a decrease in peripheral resistance and an increase in heart rate. Thus, cardiac output increases by nearly 50% after the fifth month of pregnancy and is not restored to normal until several days after childbirth. On the other hand, during pregnancy there are a series of changes in hemostasis that contribute to a state of hypercoagulability and a higher risk of embolism.[24,25]

The valve diseases that are associated with the greatest risk of hemodynamic decompensation are those involving stenosis, particularly mitral stenosis, the disease that most frequently produces clinical problems and severe aortic stenosis.[26] Regurgitant lesions usually tolerate pregnancy well, provided that systolic function is not especially affected. Another risk situation is pregnancy in patients with Marfan syndrome associated with dilated ascending aorta since there is a high risk of dissection during pregnancy.[27]

For these reasons, preventive correction of moderate or severe mitral stenosis should be carried out in asymptomatic patients or those who wish to have children, especially those who are candidates for percutaneous valvuloplasty.[28] Much more problematic is the approach to patients with mitral valve lesions that can not be repaired using percutaneous valvuloplasty, or with severe asymptomatic aortic stenosis who want to get pregnant, since they require the implantation of a valve prosthesis.

The decision as to the type of prosthesis to implant in a young woman who wants to have children is difficult.[29] In patients with mechanical prostheses, pregnancy increases the risk of prosthetic valve thrombosis and, thus, of embryopathy associated with the administration of oral anticoagulants during the first trimester of pregnancy. These risks should be taken into account, together with the risks of an eventual future reoperation should a biological

prosthesis be implanted. Although, obviously, the decision must be made in agreement with the patient, most groups at the present time may are inclined to recommend a bioprosthesis since, in a young patient, the risk of an eventual reoperation may be lower than the real risk of embryopathy and prosthetic valve thrombosis that, during pregnancy, is associated with mechanical prostheses. In the case of aortic stenosis, some authors consider aortic surgery using the Ross procedure to be clearly indicated.

Patients with valve disease who are already pregnant when they first visit the cardiologist should undergo strict cardiological monitoring, especially in the case of moderate or severe stenotic lesions. The use of beta-blockers to slow the heart rate is especially indicated in patients with mitral stenosis, as is a low-sodium diet and diuretics if congestive symptoms develop. When there is severe hemodynamic deterioration that does not respond to rest or medication, percutaneous valvuloplasty can be attempted. The medical literature provides sufficient evidence in support of the application of this approach in pregnant women with mitral stenosis.[30] The experience in percutaneous aortic valvuloplasty in pregnant women is much more limited.[31] In any case, it must be kept in mind that bypass surgery during pregnancy is associated with a very high risk of fetal loss.

Finally, pregnant patients with mechanical prostheses, especially in the mitral position, pose an especially difficult problem. In this situation, the woman presents a considerable risk of prosthetic valve thrombosis if anticoagulation is not administered very carefully. On the other hand, there is risk, albeit low, of embryopathy if coumarins are used during the first trimester of pregnancy. This risk of teratogenesis appears to be zero if the required dose of warfarin is less than 5 mg/day (data concerning other anticoagulants are not available). Thus, if adequate anticoagulation is achieved at these doses, the safest strategy for the fetus and the mother is to maintain the anticoagulation until the end of pregnancy and change to heparin at the time of vaginal birth.[32,33] If it is decided to administer heparin during the first trimester, to avoid embryopathy, it is necessary to maximize the monitoring of anticoagulation to ensure its adequacy, regardless of whether unfractionated or low molecular weight heparin is utilized.[34] It must be kept in mind that the majority of prosthetic valve thromboses associated with pregnancy have occurred with heparin treatment.

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