

**“VICTOR BABES” UNIVERSITY OF MEDICINE
AND PHARMACY TIMIȘOARA
FACULTY OF MEDICINE
DEPARTMENT VI – CARDIOLOGY**

CIPRIAN NICUȘOR DIMA



DOCTORAL THESIS

**BICUSPID AORTIC VALVE
– HISTOPATHOLOGICAL STUDY –
THERAPEUTIC MANAGEMENT**

A B S T R A C T

Scientific Coordinator
PROF. UNIV. DR. LUCIAN PETRESCU

**Timișoara
2021**

CONTENTS

List of published papers	VII
List of abbreviations	IX
Index of figures	XI
Index of tables.....	XIII
Thanks	XV
INTRODUCTION	XVI
GENERAL PART	
1. Valvular morphopathology.....	1
1.1. Anatomy	1
1.2. Morphogenesis.....	3
1.3. Valvular haemodynamics	3
1.4. Aortic and mitral valvulopathies associated with genetic mutations	4
1.5. Valvular histopathology	5
2. AORTIC BICUSPIDIA	7
2.1. Anatomy	7
2.2. Diagnostics	9
2.2.1. Clinical aspects.....	9
2.2.2. Imagistics methods to explore bicuspid aortic valve	10
2.2.3. Complications associated with bicuspid aortic valve	12
2.2.3.1. Aortic stenosis	12
2.2.3.2. Aortic insufficiency	14
2.2.3.3. Aortic ascending aneurysm and dissection of aorta	15
2.2.3.4. Infectious endocarditis	18
2.3. THERAPEUTIC MANAGEMENT	18
2.3.1. Interventional procedure	18
2.3.1.1. Percutaneous valvuloplastia with baloon	18
2.3.1.2. Transcatheter aortic valve implantation	19
2.3.2. Surgical treatment.....	21
2.3.2.1. Prosthesis of aortic valve	21
2.3.2.1.1. Biological prosthesis versus mecanic	24
2.3.2.1.2. Surgical treatment versus interventional.....	26
2.3.2.2. Plastia of aortic valve	28
2.3.3. Conservator treatment	30
SPECIAL PART	
3. PATIENTS, MATERIALS AND METHODES	31

3.1. Patients selection	31
3.2. Imagistic methods	31
3.3. Surgical procedure	32
3.4. Postoperator monitoring	34
4. REZULTS	35
4.1. Statistics.....	35
4.2. Postoperator aspects	48
4.3. Discussion.....	50
4.4. Limits	53
4.5. Conclusions.....	53
5. HISTOPATHOLOGICAL STUDY OF THE BICUSPID AORTIC VALVE AND THE LOSS OF ELASTIC FIBERS FROM THE AORTA WALL LEVEL.....	54
5.1. Objectives	54
5.2. Methos	54
5.2.1. Patients selection	54
5.2.2. Histological evaluation	54
5.3. Rezults	57
5.4. Discussions	63
5.5. Limits.....	65
5.6. Conclusions.....	65
6. CHAMELEONIC APPERANCE OF CASEOUS CALCIFICATION OF THE MITRAL VALVE -STILL A PROBLEM FOR ITS APPROPRIATE MANAGEMENT	66
6.1. Discussion.....	74
6.2. Conclusions.....	76
7. TRANSCATHETER AORTIC VALVE IMPLANTATION STUDY	77
7.1. Patients selection	77
7.2. TAVI: procedure, valvular prosthesis.....	78
7.2.1. Ecocardiography 3D ETE	79
7.2.2. Computer-tomography	81
7.3. Rezults	84
7.4. Discussions	86
7.5. Limits.....	89
7.6. Conclusions.....	89
FINAL CONCLUSIONS	90
BIBLIOGRAPHY	92
ANNEXES	I

Keywords: bicuspid aortic valve, aortic stenosis, aortic insufficiency

INTRODUCTION

The theme of the paper starts from the approach of histopathological aspects of aortic bicuspid valves, the aortic bicuspid being one of the most common malformations of the valvular system of the heart, compatible with a relatively normal life of the patient, but also with various cardiovascular complications. Subjected to intense hemodynamic stress, bicuspid aortic valves may present various histopathological changes that must be identified clinically by the patient's symptoms, explored imagistically and treated accordingly. There is currently no treatment guide for patients with aortic bicuspid and developed complications, which is why we researched surgical treatment options and interventional methods. The topic is of deep interest at the international level, valvular implantation by transcatheterization being discussed as an alternative to surgical procedures. It is well known that open heart surgery is risky, with some patients not being eligible.

GENERAL PART

Valvular diseases occur in ~ 30% of cardiovascular malformations, including complex heart disease. Valve changes can be myxomatous and fibrous. Changes in fibrous degeneration cause valvular stenosis.

Bicuspid aortica is one of the most common congenital heart disease, affecting 0.5-1.4 of the general population predominating in men in a ratio of 3: 1. BA is associated with several cardiovascular malformations including aortic coarctation and Turner syndrome. In general, patients with aortic bicuspid disease are asymptomatic in childhood, being diagnosed due to the appearance of symptoms in adulthood.

50% of patients with aortic bicuspid disease have aortic stenosis. Degeneration of the bicuspid aortic valve is due to fibrosis, calcification and is closely related to the patient's age. Patients with aortic bicuspid valve require aortic valve replacement ~ 5 years earlier than patients with tricuspid aortic valve. Both calcifications and fibrosis of the bicuspid aortic valve occur much faster than the tricuspid aortic valve.

Factors that may influence accelerated calcification in the aortic bicuspid are:

- large spikes
- presence of raffle
- valve anatomy

Patients with severe aortic stenosis and multiple comorbidities have an increased risk for surgical treatment, being optimal candidates for interventional treatment.

In most patients with aortic bicuspid and symptomatic severe aortic stenosis, surgical treatment (valve prosthesis) is of choice. If coronary heart disease or other concomitant cardiovascular disease is associated, they should be resolved at the same time as the aortic valve prosthesis according to surgical guidelines.

The operative indications for aortic valve replacement and ascending aortic replacement in patients with aortic bicuspid are:

- asymptomatic or symptomatic patients with aortic bicuspid and ascending aortic diameter ≥ 5.5 cm- valvular prosthesis and ascending aortic replacement
- asymptomatic patients with aortic bicuspid and ascending aortic diameter of 5-5.5 cm and with risk factors for aortic dissection (family history of aortic dissection, rate of increase in ascending aortic diameter > 0.5 cm / year) - valve prosthesis and replacement of the ascending aorta
- patients with aortic bicuspid with indication of valvular prosthesis and an ascending aortic diameter ≥ 4.5 cm- aortic valvular prosthesis and ascending aortic replacement
- patients with aortic bicuspid who have criteria for replacement of the ascending aorta, but have a normofunctional aortic valve (replacement of the ascending aorta and / or prosthesis / plastic aortic valve)
- asymptomatic patients with low surgical risk aortic bicuspid, with ascending aorta of 5-5.5 cm, without risk of aortic dissection (replacement of the ascending aorta and / or prosthesis / plastic aortic valve).

Patients requiring aortic valve prosthesis (biological / mechanical) should be properly informed about the advantages and disadvantages of these valve prostheses. The surgeon must also take into account the patient's choice, to discuss the indications and risks of anticoagulant therapy and the possibility of surgical reoperations in both mechanical prostheses and biological prostheses. Patients < 50 years of age who have no contraindications to anticoagulant therapy should have a mechanical prosthesis. In patients aged 50 to 65 years who have no contraindications to anticoagulant therapy, the most appropriate option should be considered in terms of both valve type and type of intervention. Patients over the age of 65 should be the ideal candidates for valve prosthesis with a biological prosthesis.

In symptomatic patients with severe aortic valvulopathy aged between 65 and 80 years, who do not have anatomical contraindications for transcatheterization with valve

implantation, both surgical and interventional treatment is recommended, taking into account the patient's life expectancy.

The real challenge in bicuspid aortic valve surgery with severe aortic regurgitation is aortic valve plasty.

Approximately 50% of patients with aortic bicuspid and aortic regurgitation will develop an ascending aortic aneurysm, which will also need to be surgically corrected with a severely regurgitating aortic valve.

Drug treatment is recommended for patients who are not candidates for cardiac surgery. Patients who have had surgery but still have signs of heart failure, heart arrhythmias, high blood pressure are recommended treatment with angiotensin converting enzyme inhibitors, angiotensin receptor blockers and beta-blockers.

In patients with aortic bicuspid, aortic root dilation and / or ascending aortic aneurysm, administration of beta-blockers and losartan may slow the aortic root dilation and decrease the risk of aortic complications.

SPECIAL PART

PATIENTS, MATERIAL AND METHODS

The study was performed at the Institute of Cardiovascular Diseases Timișoara, a hospital that serves the western part of Romania. The study was conducted over a period of 5 years, between 2015-2020 and included 105 hospitalized patients with aortic bicuspid.

The selection criteria in the study targeted patients with aortic bicuspid during hospitalization in the Institute of Cardiovascular Diseases between January 2015 and January 2020.

Patient data were obtained with the consent of the hospital management from the observation sheets, having at their disposal the clinical consultation, imaging records, surgery report and subsequent histological results.

Patients with Marfan syndrome, coronary heart disease, other congenital heart disease, ischemic heart disease, and conditions that could be associated with and significantly reduced life expectancy, such as cancer patients, were excluded from the study.

Patients were imaged by angiocoronarography to rule out coronary heart disease and angioCT to evaluate the aorta as a whole and various anatomical variants.

Transthoracic and / or transesophageal echocardiography was performed in all patients with aortic bicuspid, preoperatively and / or intraoperatively.

The surgeries were performed by surgeons with experience in extracorporeal circulation, median sternotomy was performed, the ascending aorta was clamped at the emergence of the brachiocephalic arterial trunk, and a solution of cardioplegia was administered at repeated intervals of about 20 minutes. Intraoperatively, the aortic valve was replaced with a mechanical or biological prosthesis and the ascending aorta was replaced. The dimensions of the valve prosthesis were chosen according to the measurements performed on echocardiography.

For patients with aortic bicuspid and ascending aortic aneurysm with aortic lumen diameter ≥ 5.6 cm, the ascending aorta was replaced with tubular prostheses made of synthetic material (Dacron). The tissue samples were excised from the wall of the ascending aorta where the maximum dilation of the lumen was, and the excised samples were fixed in 10% formalin.

Patients with aortic bicuspid and ascending aortic aneurysm with aortic lumen diameter of 5-5.5 cm underwent reductional plasty, which involved resection of an oval portion of the ascending aortic wall, with subsequent double suture Prolene aortofix 4-0. The aortic lumen was reduced to a maximum of 4 cm.

Intraoperatively, the size of each valve was selected based on measurements with specific testers for each valve type, the dimensions chosen intraoperatively corresponding to preoperative echocardiographic measurements. Bicuspid aortic valves have been replaced with mechanical or biological prostheses

RESULTS

The results of this study show that most patients with aortic bicuspid and ascending aortic aneurysm who underwent valvular replacement and reductional plasty of the ascending aorta (4 of 7) underwent aortic redilation over time, while none of the same group of patients who had undergone valve replacement and replacement of the ascending aorta did not show relapse.

There were differences between patients with aortic bicuspid regurgitation enrolled in this study with ascending aortic aneurysm and aortic stenosis compared with those with ascending aortic aneurysm and aortic regurgitation, in patients with aortic bicuspid, ascending aortic aneurysm and redilation earlier than patients with aortic bicuspid, ascending aortic aneurysm and aortic stenosis after reductional plastic surgery.

DISCUSSIONS

In patients with aortic bicuspid and ascending aortic aneurysm, surgical treatment is a challenge and there are currently controversies about the therapeutic act. There is a wide phenotypic variety in the bicuspid aortic. Therefore, the surgical method must be adapted to the pathogenic mechanisms of different aortic bicuspid phenotypes. A review published in 2017, following the collection of clinical and scientific data from the literature published over a year, shows that clinical trials comparing the results of patients with aortic bicuspid after exclusive aortic valve replacement agree on the increased risk of severe aortic complications in patients with aortic insufficiency compared with those with aortic stenosis.

Surgical techniques for replacement of the ascending aorta in patients with aortic bicuspid are supported by arguments that aortic bicuspid aortopathy is more similar to Marfan syndrome aortopathy than to aortopathy secondary to degenerative diseases of the tricuspid aortic valve

CONCLUSIONS

For patients with bicuspid with an ascending aortic aneurysm, reductional plasty of the ascending aorta is effective in the short term, but redistribution occurs over time, which provides a justification for the need for long-term monitoring.

None of the patients with aortic bicuspid, ascending aortic aneurysm and aortic regurgitation or aortic stenosis developed aortic redilation after ascending aortic replacement during the 3-year monitoring period; however, most of them developed redilation after aortic reductional plasty in the same period.

After reductional plasty of the ascending aorta, redilatation is faster in patients with aortic bicuspid, ascending aortic aneurysm and aortic regurgitation compared to patients with aortic bicuspid, ascending aortic aneurysm and aortic stenosis. better long-term in patients with aortic bicuspid, ascending aortic aneurysm and aortic regurgitation.

HISTOPATHOLOGICAL STUDY OF THE BICUSPID AORTIC VALVE AND THE LOSS OF ELASTIC FIBERS FROM THE AORTA WALL LEVEL

The study has a dual purpose, to identify the degree of alteration of elastic fibers in patients with aortic bicuspid and ascending aortic aneurysm associated with stenosis or aortic insufficiency and aims at the type of surgery to prevent late complications such as aortic redilation.

The second goal is to evaluate the pathological aspects of the bicuspid valve that underlie the developed pathology. The surgical method of reductional plastic surgery or AAA resection with ascending aortic replacement was associated with the degree of alteration of the elastic fibers and patients were monitored in the medium and long term to follow the adverse effects mainly of aortic redilation, so the aim of the study is to achieve clinical-histopathological correlations that can lead to the identification of risk factors in patients with BA that result in an impact on clinical practice guidelines by offering therapeutic options.

Of the 105 patients with bicuspid and aortic stenosis or aortic regurgitation, 14 patients developed ascending aortic aneurysm. In these patients, surgical interventions were performed, the type of intervention being established according to the clinical-imaging and functional aspects.

Damage to the elastic fibers in the wall of the ascending aorta has been histologically graded in three degrees (mild, moderate, severe), similar to recent studies in the field of aortic atherosclerotic lesions.

Our study shows that the changes are due to loss of elastic fibers and are more severe in patients with aortic bicuspid, ascending aortic aneurysm and aortic regurgitation compared to patients with aortic bicuspid, ascending aortic aneurysm and aortic stenosis, thus demonstrating the different pathogenic mechanisms. distinct therapeutic.

Patients with aortic bicuspid, ascending aortic aneurysm and aortic stenosis who underwent aortic valve replacement and reduced ascending aortic plasty developed aortic dilation over time, unlike patients with aortic bicuspid, ascending aortic aneurysm who suffered ascending aorta and stenosis ascending aorta and did not develop redilation over time.

In our study we noticed that the changes in the valves are represented by the appearance of a dense fibrous connective tissue with randomly arranged collagen bands and dystrophic calcifications or a loose connective tissue with a rich vascular network, the type of connective tissue can be correlated with severity. clinical aspects.

The current study shows that patients with aortic bicuspid, ascending aortic aneurysm and aortic regurgitation have a more pronounced loss of elastic fibers compared to patients with aortic bicuspid, ascending aortic aneurysm and aortic stenosis. Also structurally, the bicuspid aortic valve has early degenerations (fibrosis and calcifications) that underlie the aortic valve pathology.

Histological examination of samples collected from the excised aortic wall revealed interlamellar degeneration with mucoid replacement, as well as fragmentation and reduction of elastic fibers.

Immunohistochemical investigations showed that in areas with sclerotic tissue of the heart valves no myofibroblasts and macrophages were identified but were present in large numbers in areas with loose connective tissue.

The areas of the bicuspid aortic valve rich in fibrous connective tissue, hyalinized have calcification areas and collagen bands, these can be correlated with a reduction of vascularity and elastic fibers.

In our study, 50% had aortic stenosis, and bicuspid aortopathy was predominant in men (78.6% of cases).

TRANSCATETER AORTIC VALVE PROSTHESE IMPLANTATION STUDY

Implantation of a transcatheter aortic prosthesis (TAVI) is an alternative method to surgical methods for the treatment of aortic stenosis by implanting a biological prosthesis. It is a method for patients with high surgical risk, serving as an alternative to open heart surgery. Proper measurement of the aortic ring leads to the selection of a suitable prosthesis and is essential for the success of TAVI.

From January 2018 to January 2020, 25 patients at high surgical risk with severe aortic stenosis and severe symptoms were subjected to the TAVI procedure at the Institute of Cardiovascular Diseases in Timisoara. The surface area of the native aortic valve was 0.7-1 cm². Some patients experienced significant comorbidities, such as porcelain aorta, anterior chest irradiation procedures, old age, obesity, pulmonary fibrosis, and hematologic disease.

Patients were examined prior to the TAVI procedure using computed tomography, echocardiography to measure the aortic annular diameters required for sizing the valve prosthesis. All 25 patients were selected for this study. The selection criterion was the presence of both aortic CT and ultrasound ring measurements.

For the transfemoral approach, it is important to know the presence of pre-existing factors such as abdominal aneurysm, aortic dissection, thrombosis, severe atheromatosis and aberrant aortic routes.

Patients with BA treated with TAVI had a similar mortality rate at 30-day and 1-year intervals due to stroke, but had a higher risk of moderate / severe paraprosthetic leak with conversion to surgery. A recent publication in 2020 detailed that the rate of events decreased significantly with the use of next-generation devices, but TAVI continued to show better procedural outcomes in the tricuspid aortic valve compared to BA, with a small number of patients with BA requiring surgical reoperation

TAVI is an alternative technique for treating severe aortic stenosis in high-risk patients who are not candidates for surgery and may be associated with a low complication rate.

In bicuspid aortic valve and severe aortic stenosis, the TAVI procedure had an acceptable result, similar to that of patients with tricuspid aortic valve.

Transesophageal echocardiography and computed tomography are reliable preprocedural measurement techniques for selecting the correct size of the valve prosthesis.

FINAL CONCLUSIONS

Bicuspid aortic valve can affect young patients becoming a risk factor in the population.

In our study, 50% had aortic stenosis, and bicuspid aortic was predominant in men (78.6% of cases).

Patients with aortic bicuspid, ascending aortic aneurysm and aortic regurgitation have a more pronounced loss of elastic fibers compared to patients with aortic bicuspid, ascending aortic aneurysm and aortic stenosis.

The bicuspid aortic valve presents early degenerations (fibrosis and calcifications) that underlie the aortic valve pathology.

Differentiation from tumor formations can enter the differential diagnosis of caseous calcifications on both the mitral valve and the aortic valve, not having a typical appearance.

Histological examination of samples collected from the excised aortic wall revealed interlamellar degeneration with mucoid replacement, as well as fragmentation and reduction of elastic fibers.

Immunohistochemical investigations showed that in areas with sclerotic tissue of the heart valves no myofibroblasts and macrophages were identified but were present in large numbers in areas with loose connective tissue.

The areas of the bicuspid aortic valve rich in fibrous connective tissue, hyalinized have calcification areas and collagen bands, these can be correlated with a reduction of vascularity and elastic fibers.

Patients with aortic bicuspid with ascending aortic aneurysm require long-term monitoring because the reductional plasty of the ascending aorta is effective in the short term, and redistribution occurs over time.

The echocardiographic examination was used preoperatively, intraoperatively and postoperatively, the information provided being useful in all case management, having high sensitivity and specificity.