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# Aortic Valve Disease from Etiology to Bedside

Shahab Shahrzad and Samira Taban  
*Shiraz University of Medical Science,  
Cardiology Department, Cardiology Research Center,  
Iran*

## 1. Introduction

Aortic valve is located in the outflow tract of left ventricle (LV), the systemic ventricle, and it should provide LV with an open tract during systolic period in order to have a perfect tissue perfusion with the least energy consumed by LV, and a closed tract during diastole to prevent blood regurgitation from systemic circulation to LV in diastole to avoid acute and late consequences of LV volume overloading.

Aortic valve diseases are mostly asymptomatic for a long period of time. This may culminate in irreversible LV damage before diagnosis.

Nowadays aortic valve replacement (AVR) for aortic stenosis is the most frequent cause of cardiac valvular surgery, because most of the mitral valve procedures are performed percutaneously.

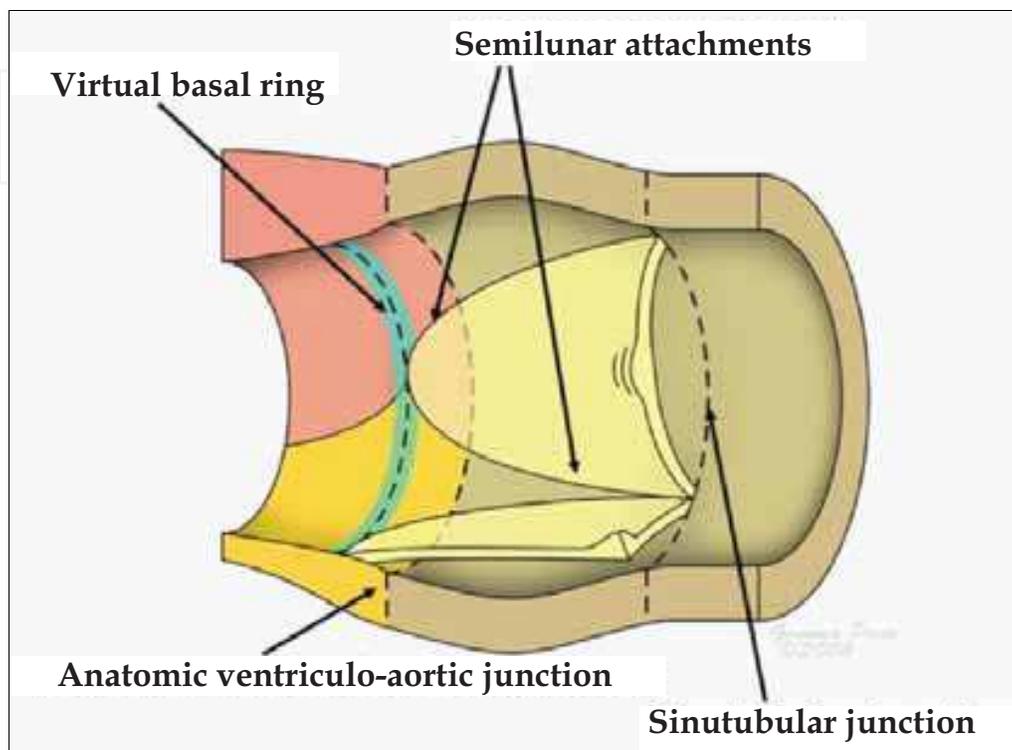
### 1.1 Aortic root anatomy

Aorta is mainly composed of two parts: abdominal and thoracic, before it bifurcates to two common iliac arteries. The thoracic aorta is divided to three parts. The first one is ascending aorta which extends from aortic root to the arch of aorta and has no branches. The arch is the second part which has three main branches: Brachiocephalic artery, Left common carotid artery and left subclavian artery. After the last branch the descending aorta begins which extends inferiorly and passes through diaphragm where it turns to the abdominal aorta.

Left ventricle connects to ascending aorta via aortic root which provides the supporting structures for the leaflets of the aortic valve and the heart (Anderson 2000), and forms the bridge between the left ventricle and the ascending aorta. There is still no consensus as how best to describe the components of the root (Antunes 2005). The root itself, surrounding and supporting the leaflets, has length in that it extends from the basal attachments of the leaflets within the left ventricle to the ascending aorta (Anderson 2007). The very proximal part of aorta after leaflets is somehow dilated and is named sinus of valsalva. Its function is to support the leaflets and also right and left coronary arteries arise from this part of aorta. The tubular portion of ascending aorta is just after sinus of valsalva and the junction of this two parts is named sinotubular junction. (Figure 1, 2). The aortic valve itself is composed of three leaflets which attach to the aortic root like a crown (Figure 3). This crown like structure is essential for the function of the valve and in some congenital disorders of the valve such as bicuspid aortic valve restoration of this structure will result in better valvular function (Pretre et al., 2006). The aortic ring is the part that these leaflets attach to. These leaflets

attachment vary in the way that some of them attach to the muscular part of LV and some of them to the fibrinous part of the ring (Anderson 2000)

In conclusion the left ventricular blood goes to left ventricular outflow tract which ends in aortic root which is composed of aortic valve, aortic ring, sinus of valsalva and the sinotubular junction.



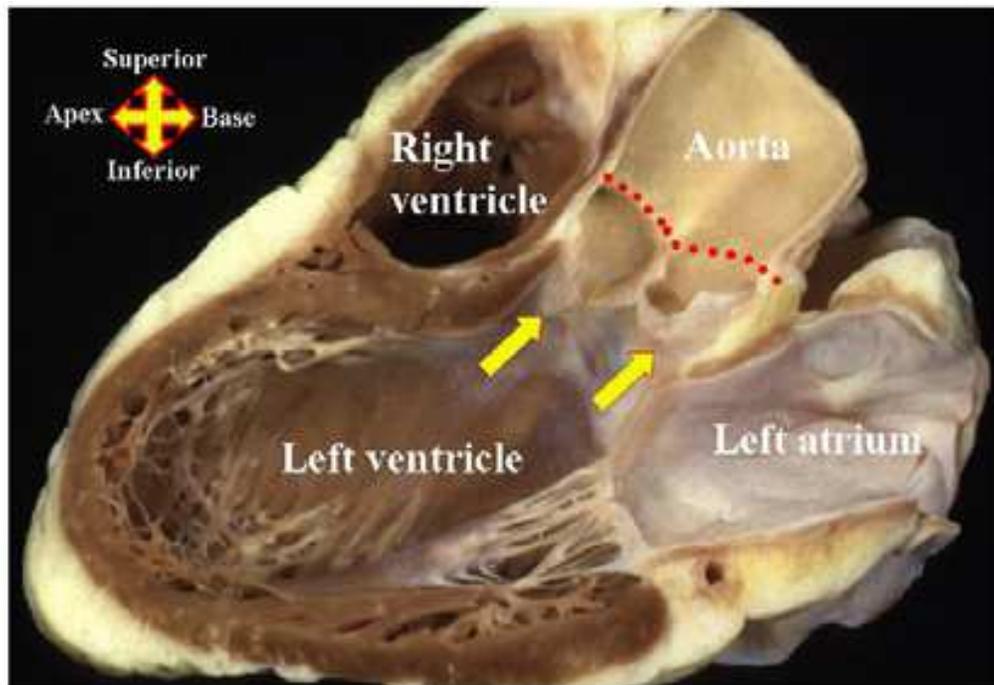
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Fig. 1. The anatomy of Aortic Root

## 2. Aortic stenosis

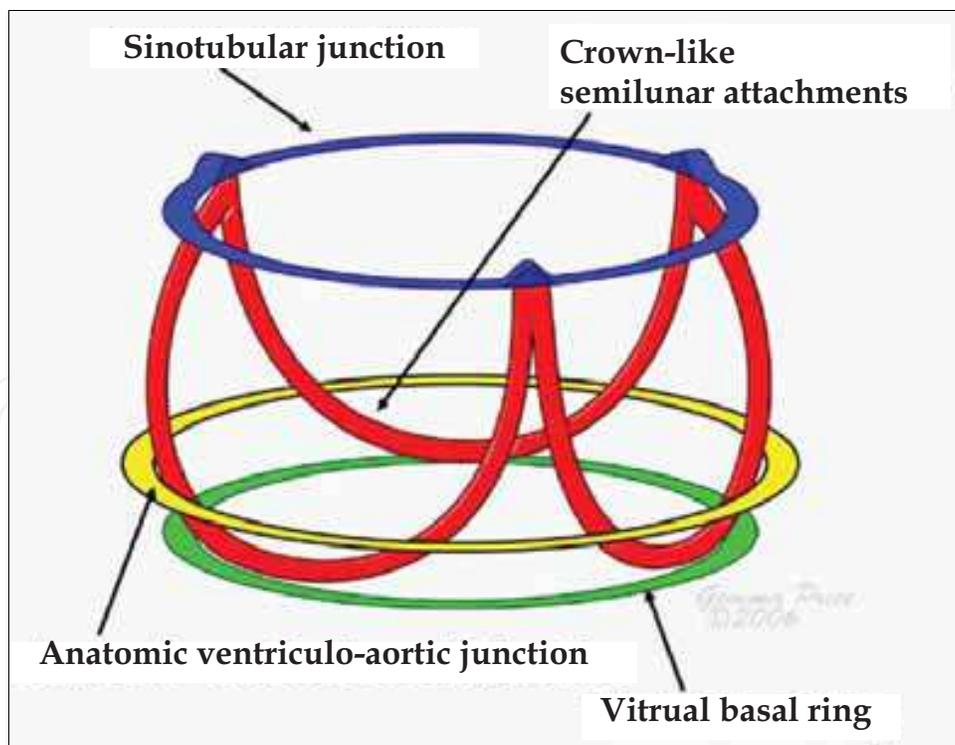
### 2.1 Definition

Aortic stenosis (AS) means obstruction in left ventricular outflow tract (LVOT). It can be easily divided to three categories: subvalvular AS, valvular AS and supra valvular AS. Valvular AS is the most common cause of LVOT obstruction. Sub valvular AS comprises hypertrophic obstructive cardiomyopathy and sub aortic web. These two entities are almost always congenital but may show themselves later in the life. Supra valvular aortic stenosis is mainly part of complex congenital anomalies such as William syndrome that is associated with hypercalcemia. Valvular aortic stenosis is the mainstay of this article. It's a slowly progressive disease which progresses over time and causes a gradually aggravating LVOT obstruction. In an adult the average aortic valve area is about  $4\text{cm}^2$  and the normal aortic valve area should be at least  $2\text{cm}^2$ . Areas less than that are defines as aortic stenosis. There are some other definition criteria by echocardiography or cardiac catheterization. Aortic flow peak gradient more than  $20\text{ mmHg}$  in echocardiography (Baumgartner 2009) (Bonow 2006 ACC AHA guidelines) or in left side catheterization is also defined as AS. But the best definition is always the surface area of the valve because these gradients can be influenced



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Fig. 2. The anatomy of Aortic Root



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Fig. 3. The anatomy of Aortic Root

by the cardiac output of the patient. In a normal man with anemia the cardiac output is increased to compensate for the decreased oxygen carrying capacity of the blood. This can cause increase in flow velocity across the valve and the overestimation of the gradient and a false diagnosis of an AS or overestimation of the AS severity. On the other hand in a patient with severe AS and advanced LV dysfunction the left ventricle do not have enough power to pump the blood across the valve and the trans-valvular jet velocity and gradient will be falsely low. This can have therapeutic importance because if these kind of patients are not diagnosed as AS their only option is medical therapy with limited outcome but with the proper diagnosis and alleviation of LVOT obstruction LV function will restore although partially (Bonow 2006 ACC AHA guidelines).

## **2.2 Etiology**

AS is the most common valvular heart disease in human (Kurtz 2010). Most cases of adult aortic stenosis are caused by calcification of normal tricuspid or bicuspid aortic valve (Bonow 2006 ACC AHA guidelines). These are most commonly seen in elderly and those older than 65. The third most common cause of AS is rheumatic heart disease which is highly associated with mitral valve disease as well. There are couple of other etiologies for AS which are all rare, they include homozygous familial hypercholesterolemia, congenital heart disease (other than bicuspid aortic valve such as unicuspid aortic valve), radiation induced aortic stenosis.

### **2.2.1 Calcific degenerative aortic stenosis (CDAS)**

This is the most common cause of aortic stenosis. This is also called senile degenerative aortic sclerosis and stenosis, but the pathophysiology of this disease is not an irreversible simple age related degenerative disorder. On the other hand Calcific AS is an active disease process characterized by lipid accumulation, inflammation, and calcification, with many similarities to atherosclerosis (Bonow 2006 ACC AHA guidelines)(Kurtz 2010). CDAS is started by accumulation of lipid particles and oxidized low density lipoprotein (LDL) in aortic leaflets just like precursors of atherosclerosis plaque. These particles and their oxidative products cause activation of local lymphocytes and macrophages and production of angiotensin II, which all ultimately convert leaflet fibroblasts to osteoblasts which are the cells that produce bony and calcific structure. These cells are responsible for calcium deposition in CDAS. These changes start from the base of the leaflet and extend to their tip but no leaflet and commissural fusion happens like the one seen in rheumatic heart disease. These changes resulted in emergence of therapeutic medical ideas for treatment of AS. The most important of them are STATINs which are lipid lowering agents. Unfortunately clinical trials have not showed any benefit in reversing CDAS by STATINs. Chan KL et al., (2010) studied this concept and their result was that Cholesterol lowering with rosuvastatin 40 mg did not reduce the progression of AS in patients with mild to moderate AS; thus, statins should not be used for the sole purpose of reducing the progression of AS. The main reason may be the advanced degenerated calcific nature of the disease. These changes are very similar to those that occurs in vascular atherosclerosis and actually they have similar risk factors, both are more prevalent in patients with diabetes mellitus, hypertension, hyperlipidemia and renal failure. CDAS is accelerated in patients with intrinsic aortic valve disease such as bicuspid aortic valve.

### 2.2.2 Bicuspid aortic valve

This is the most common congenital cause of AS and the most common cause of AS in neonates and the most common cause of CDAS in those younger than 60. Bicuspid aortic valve can be associated with severe aortic regurgitation but most commonly it is associated with AS before 60. Also it is associated with diseased aortic wall which can culminate in aortic aneurysm as well as aortic dissection (Roberts 1970). Most of the time replacement of aortic root is indicated during operation of the valve in bicuspid valve patients. Some have reported the repair of the valve and restoration of normal crown structure of the aorta as the surgical therapeutic modality for bicuspid aortic valve (Pretre et al., 2006)

### 2.2.3 Rheumatic AS

It is the third common cause of AS. Its prevalence is decreasing because of increasing proper management of streptococcal pharyngitis. It's almost always associated with some amount of aortic regurgitation and mitral stenosis. In fact rheumatic fever only involves aortic valve in one third of the patients. It most commonly involves tip of aortic leaflets with thickening, commissural fusion and finally calcification which causes doming of the valve in echocardiography. It is important to remember to evaluate the mitral valve in every patient with rheumatic AS (Bonow 2006 ACC AHA guidelines) (Kurtz 2010).

## 2.3 Pathophysiology of LV changes induced by AS

AS is the most common cause of LV outflow tract (LVOT) obstruction. It progresses slowly over the time, so the LV can compensate for the pathologic changes that it can cause. AS causes increases resistance in LVOT and the after load of the LV (which is the force that the LV contracts against). This results in increased wall stress of LV. Wall stress is equal to pressure of LV multiplied by radius of LV divided by wall thickness of LV:

$$\text{Wall stress} = \text{Pressure} \times \text{radius} / (2 \times \text{wall thickness})$$

Increased wall stress can cause ischemia and ultimately myocardial damage. LV increases its own thickness by hypertrophy to compensate the increase in wall stress. This can compensate for the increase in after load and LV ejection fraction (LVEF) remains in normal range. But if the amount of hypertrophy is less than enough the LVEF will decrease, this is called after load mismatch and can be corrected by alleviating the obstruction in LVOT. On the other hand in some patients the decrease LVEF is due to intrinsic myocardial damage. In these patients even aortic valve replacement cannot increase the LV function. Increased LV thickness and hypertrophy is not all physiologic and has some negative effects on the myocardium. First of all the hypertrophied myocardium has less coronary blood flow reserve (Marcus 1982) that exposes it to ischemia specially during exercise. Then is the fact that the hypertrophied myocardium is more sensitive to a constant level of ischemia compared to normal myocardium. The final problem is over hypertrophy which is almost exclusively seen in old women. This can cause even high LVEF but conversely is associated with high operative mortality (Bonow 2006 ACC AHA guidelines). In the majority of AS patients the final step is the time that LV hypertrophy cannot compensate for increased after load and LV dysfunction ensues. This is the step that the patient finally becomes symptomatic. That's why a patient with AS has a good prognosis till he or she is asymptomatic, and stays symptom free for a long time, but as soon as the symptoms emerge the prognosis of the disease worsens and progresses rapidly by LV failure.

## 2.4 Sign and symptoms

Unfortunately AS is asymptomatic for a long period of time. AS symptoms is mainly due to 3 physiologic phenomena: cardiac ischemia, elevated LV filling pressure, and decreased cardiac output (Kurtz 2010). The first symptom in most cases is dyspnea in exertion. The dyspnea progresses over time and the more the disease progresses the less will become the level of the activity that the patient can take without dyspnea. Finally the patient will have dyspnea at rest. All three mentioned phenomena's are responsible for dyspnea. The second common sign is chest pain which is again seen in specially on activity. The cause of the chest pain is multi-factorial. Half of them have coronary artery disease (CAD) which can cause the chest pain. In those without CAD the chest pain caused by increased demand because of LV hypertrophy and decreased aortic pressure because of the AS itself. Also as mentioned decreased coronary flow reserve can cause real ischemia in AS. Syncope specially during activity is the third common symptom and is caused because of low cardiac output, and decreased cerebral perfusion. Other causes of syncope are inappropriate vasodilatation because of abnormal myocardial receptor activation (reflex mediated syncope) and rarely arrhythmias. Sudden cardiac death usually happens in 1% of patients and occurs mostly in those with other symptoms and not as the first presentation. Peripheral embolization and heart failure are rarer symptoms of AS and are mostly seen in final stages of the disease. There is a very special symptom in AS patients that happens because of vascular dysplasia. AS patients can have angiodysplasia in their right colon. the exact reason of this vascular abnormality is not known but it can be due to increased shearing stress and platelet activation. This problem is associated with gastrointestinal bleeding and is relieved after AS is corrected. Although the patient may have no symptom, in physical examination we can find couple of symptoms that can relive the problem. The peripheral pulses and cardiac auscultation are the main targets in physical examination. The best pulse to evaluate is carotid pulse. It becomes narrow and the time to the peak pressure increases. this is called pulsus parvus et tardus. In cardiac auscultation a mid-systolic ejection murmur which is crescendo decrescendo can be heard in right second intercostals space which radiates to the right side of the neck. Also aortic ejection click can be heard in those patients whose valve is not heavily calcified. Heavy calcification of the valve can decrease the doming of the valve which is the main cause of the ejection click. The severity of the murmur although helpful in assessing the severity of AS, can be influenced by the level of cardiac output and be misleading.

## 2.5 Evaluation of patients with AS

The evaluation begins with meticulous history taking and physical examination. The quality of pulses, second heart sound, systolic murmur and peripheral signs of heart failure are used for diagnosis and determining the severity and prognosis of the disease. Narrow pulse pressure and systolic murmur of grade III or more and signs of heart failure are usually associated with severe AS, although the severity of the murmur can be influenced by the level of the cardiac output (it increases with increased cardiac output like anemia). Symptoms of the patient are very important because even in the presence of normal LV function emergence of symptoms are strong indication for aortic valve replacement (Bonow 2006 ACC AHA guidelines)(Kurtz 2010). It is important to obtain specific history for dyspnea and exercise intolerance as the patient may ignore them because of the chronic nature of the disease. Electrocardiography (ECG) is the next tool to evaluate the patient, which shows LV hypertrophy, abnormal ST-T changes, arrhythmias, atrio-ventricular and

inter-ventricular conduction abnormalities. Inter-ventricular conduction delay specially left bundle branch block is mostly seen in advanced myocardial dysfunction. ECG is primarily important in diagnosing the associated cardiac problems such as ischemic heart disease, and all of the findings that can be seen in AS are neither specific nor sensitive. Echocardiography is the most commonly used and the most practical mean of diagnosing and evaluation the severity of AS and associated conditions. There are multiple echocardiographic modalities such as 2D imaging, Doppler mode and color Doppler mode for this purpose (Table 1). The aortic valve area can be measured by 2-D echocardiography via parasternal short axis view of the aorta. Also Doppler echocardiography can measure the valve area by continuity equation. This is based on the rule that the amount of blood that passes the LVOT is equal the blood that crosses the aortic valve.

$$\text{Aortic valve area} = \text{LVOT VTI} \times \text{LVOT AREA} / \text{Aortic valve VTI}$$

Where VTI is velocity time integral and can be calculated easily by Doppler echocardiography. The easiest and most commonly used method is assessing trans valvular flow velocity and gradient. AS then can be categorized to mild, moderate and severe. (Table 1) Other imaging tools such as CT scan and MRI are also useful. They can specially evaluate the ascending aorta that can be dilated and aneurismal in AS. Cardiac catheterization is almost always used when the previously mentioned modalities fail to accomplish the diagnosis or when there are conflicts between them.

Indicator	Aortic Stenosis		
	Mild	Moderate	Severe
Jet velocity (m per second)	Less than 3.0	3.0–4.0	Greater than 4.0
Mean gradient (mm Hg) <sup>a</sup>	Less than 25	25–40	Greater than 40
Valve area (cm <sup>2</sup> )	Greater than 1.5	1.0–1.5	Less than 1.0
Valve area index (cm <sup>2</sup> per m <sup>2</sup> )			Less than 0.6

Table 1. Assessment of AS severity by echocardiography (Source: American Heart Association, Inc.)

## 2.6 Medical management of patients with AS

AS does not have a medical treatment, but the medical follow up is very important before AVR to determine the perfect time of operation according to guideline and charts, and post AVR for proper anticoagulation and complication management. Periodic echocardiographic and clinical evaluation of the patients with AS is the main nonsurgical management of AS patients. This intervals are determined by the severity of AS and patients symptoms. Those with mild AS should be evaluated every 3-5 years, patients with moderate AS every 1-2 years and severe AS should be evaluated yearly. Also pregnant women and those who become symptomatic should have prompt evaluation (Bonow 2006 ACC AHA guidelines) (Kurtz 2010). Other major medical therapy targets associated risk factors such as hypertension, hyperlipidemia and diabetes mellitus. Endocarditis prophylaxis is no longer needed for AS patients because the risk of infection is low. Many investigators have tried to find a way to delay or even reverse the progression of AS. There are couple of reports that some drugs such as STATINs may have some effect in slowing the progression of AS, but most studies have failed to show any effect. Rosenhek et al., (2004) compared the effect of angiotensin converting enzyme inhibitors (ACEIs) with statins in reducing AS progression. According to their study ACEIs do not appear to slow AS progression. However, statins significantly

reduce the hemodynamic progression of both mild-to-moderate and severe AS, an effect that may not be related to cholesterol lowering. On the other hand Chan et al., (2010) reported that Cholesterol lowering with rosuvastatin 40 mg did not reduce the progression of AS in patients with mild to moderate AS.

## 2.7 Endovascular management of patients with AS

This method is mostly used during childhood according to specific guidelines and with specific methods. In adults this procedure has little value because of high risk of complication, procedure failure and high rates of recurrence on the contrary in childhood the valve is more pliable and the success rate of the procedure is high, so percutaneous aortic valvoplasty is the standard procedure for treatment of AS in childhood. Nevertheless percutaneous balloon valvoplasty can be performed in highly selected adult patients such as those with very high surgical risk and also as a bridge to AVR in those with decompensated condition. Although it cannot replace for standard AVR procedure (springing 1995)(Webb 2006). The other option is percutaneous valve replacement. Three different methods are available but all of them are associated with high mortality and morbidity and are not routinely performed.

- **Class I:** Conditions for which there is evidence for and/or general agreement that the procedure or treatment is beneficial, useful, and effective.
- **Class II:** Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/ efficacy of a procedure or treatment.
  - **Class IIa:** Weight of evidence/ opinion is in favour of usefulness/ efficacy.
  - **Class IIb:** Usefulness/ efficacy is less well established by evidence/ opinion.
- **Class III:** Conditions for which there is evidence and/or general agreement that the procedure/ treatment is not useful/ effective and in some cases may be harmful.

Table 2. Definition of multiple classes (Source: American Heart Association, Inc.)

## 2.8 Surgical management of AS

Aortic valve repair for AS is almost never done because of high rate of failure therefore AVR is the standard management of AS. Although Pretre et al., (2006) reported repair of bicuspid aortic valve and restoration of normal anatomical crown like structure, AVR is still the procedure of choice for AS patients. The timing and indication of surgery is determined through specific guidelines (Figure 4 and Table 2). the most important issues in this manner are patients symptoms and LVEF. Symptomatic patients or those with LVEF less than 50% should undergo AVR. There are multiple kinds of prosthetic valve. Each kind has its own properties. Selection of the prosthetic valve is also done via the guidelines. Aortic root size is the other important issue that should be considered before operation. Aortic root size

should be exactly determined with CT scan or MR. Aortic root more than 4.5 cm specially in those with bicuspid aortic valve or marfan syndrome is an indication for aortic root replacement. This operation is called Bentall operation and involves a metallic prosthesis sewed in a Dacron artificial ascending aorta that is replaced for aortic root (Hiratzka 2010).

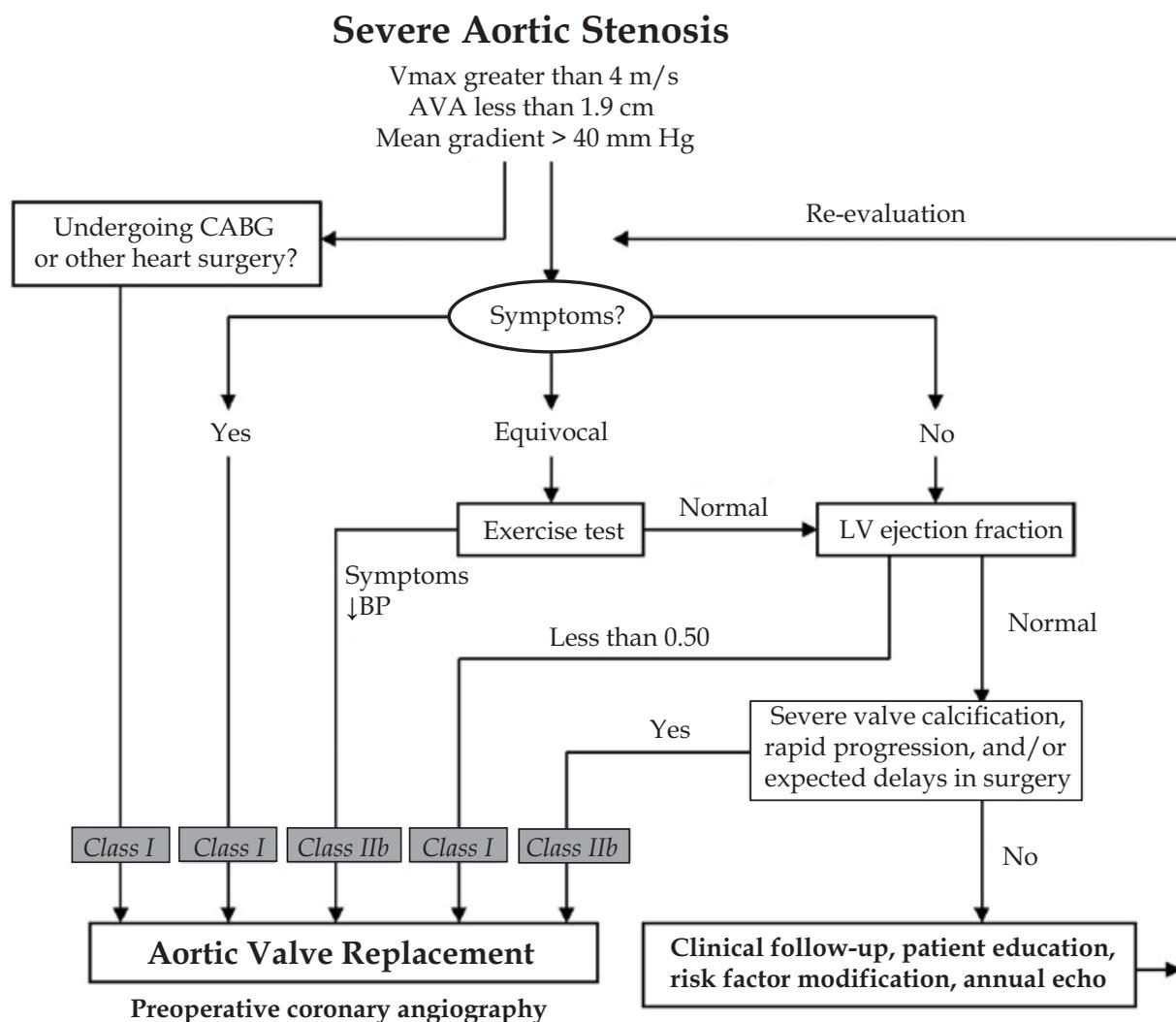


Fig. 4. Timing of operation in AS patients (Source: American Heart Association, Inc.)

### 2.9 Natural course of AS

Frank S et al (1973) studied the natural history of the patients with severe AS who did not undergo AVR. He showed that during a 10 year follow up 90% of the patients will die without surgical intervention. He also found that those with combination of symptoms such as dyspnea, Angina and syncope has the worst prognosis. Aortic stenosis has good prognosis when it's asymptomatic and its mortality rate is almost the same as those without AS. But as soon as it gets symptomatic the survival is only about 2-3 years without treatment. The mean survival is 5, 3, 2 years for angina, syncope and heart failure respectively (Kurtz 2010). With operation in perfect time the survival will remain good. After operation patients should be evaluated by history and physical examination yearly.

### 3. Aortic insufficiency

#### 3.1 Definition

Inability of aortic valve to withhold regurgitation of blood from aorta to LV in diastole is defined as aortic insufficiency (AI) or aortic regurgitation. It is not as prevalent as AS but it can be seen in at least 75% of patients with CDAS. The main difference of AS and AI is that AS imposes a systolic pressure overload to the LV, in contrast to AI that mainly increases the diastolic LV load. Thus LV dilatation during asymptomatic period is more prevalent in AI.

#### 3.2 Etiology

It can be divided into problems of the valve itself and those that are due to aortic root dilatation (Bonow 2006 ACC AHA guidelines). Diseases that involve the aortic valve itself cause AI by disturbing the normal motion or normal coaptation of the leaflets. These include, congenital abnormalities of the aortic valve (most notably bicuspid valves), calcific degeneration, rheumatic disease, infective endocarditis, systemic hypertension, myxomatous degeneration. Anorectic drugs radiation and trauma are rare valvular causes of AI. Nowadays aortic root diseases are responsible for at least 50% of cases of aortic insufficiency (AI). It can be caused by systemic disorders such as hypertension or Marfan syndrome or can be idiopathic. One interesting cause of AI is consumption of anorectic medications which can cause AI by damaging the valve itself. Most causes of AI cause a chronic disease that can be asymptomatic for even decades but some etiologies can cause acute severe AI that can be even fatal if left untreated. They include infective endocarditis, trauma and aortic dissection. Moaref et al. (2009) reported a case of acute aortic regurgitation due to acquired aorto-ventricular tunnel as a complication of infective endocarditis.

#### 3.3 Pathophysiology of acute AI

In acute severe AR, the sudden large regurgitant volume is imposed on a left ventricle of normal size that has not had time to accommodate the volume overload. With an abrupt increase in end-diastolic volume, the ventricle operates on the steep portion of a normal diastolic pressure-volume relationship, and LV end-diastolic and left atrial pressures may increase rapidly and dramatically. The Frank-Starling mechanism is used, but the inability of the ventricle to develop compensatory chamber dilatation acutely results in a decrease in forward stroke volume. Although tachycardia develops as a compensatory mechanism to maintain cardiac output, this is often insufficient. Hence, patients frequently present with pulmonary edema or cardiogenic shock. Acute AR creates especially marked hemodynamic changes in patients with pre-existing pressure overload hypertrophy, in whom the small, noncompliant LV cavity is set on an even steeper diastolic pressure-volume relationship and has reduced preload reserve. Examples of this latter situation include aortic dissection in patients with systemic hypertension, infective endocarditis in patients with pre-existing AS, and acute regurgitation after balloon valvotomy or surgical commissurotomy for congenital AS (Bonow 2006 ACC AHA guidelines).

#### 3.4 Pathophysiology of chronic AI

The left ventricle responds to the volume load of chronic AR with a series of compensatory mechanisms, including an increase in end-diastolic volume, an increase in chamber

compliance that accommodates the increased volume without an increase in filling pressures, and a combination of eccentric and concentric hypertrophy. The greater diastolic volume permits the ventricle to eject a large total stroke volume to maintain forward stroke volume in the normal range. This is accomplished through rearrangement of myocardial fibers with the addition of new sarcomeres and development of eccentric LV hypertrophy (Grossman 1975). As a result, preload at the sarcomere level remains normal or near normal, and the ventricle retains its preload reserve. The enhanced total stroke volume is achieved through normal performance of each contractile unit along the enlarged circumference (Ross 1972). Thus, LV ejection performance is normal, and ejection phase indexes such as ejection fraction and fractional shortening remain in the normal range. However, the enlarged chamber size, with the associated increase in systolic wall stress, also results in an increase in LV afterload and is a stimulus for further hypertrophy (Grossman 1975). Thus, AR represents a condition of combined volume overload and pressure overload. As the disease progresses, recruitment of preload reserve and compensatory hypertrophy permit the ventricle to maintain normal ejection performance despite the elevated afterload (Ricci 1982). The majority of patients remain asymptomatic throughout this compensated phase, which may last for decades. Vasodilator therapy has the potential to reduce the hemodynamic burden in such patients. For purposes of the subsequent discussion, patients with normal LV systolic function will be defined as those with normal LV ejection fraction at rest. It is recognized that other indices of LV function may not be “normal” in chronic severe AR and that the hemodynamic abnormalities noted above may be considerable. It is also recognized that the transition to LV systolic dysfunction represents a continuum and that there is no single hemodynamic measurement that represents the absolute boundary between normal LV systolic function and LV systolic dysfunction. In a large subset of patients, the balance between afterload excess, preload reserve, and hypertrophy cannot be maintained indefinitely. Preload reserve may be exhausted, and/or the hypertrophic response may be inadequate, so that further increases in afterload result in a reduction in ejection fraction, first into the low normal range and then below normal. Impaired myocardial contractility may also contribute to this process. Patients often develop dyspnea at this point in the natural history. In addition, diminished coronary flow reserve in the hypertrophied myocardium may result in exertional angina. However, this transition may be much more insidious, and it is possible for patients to remain asymptomatic until severe LV dysfunction has developed. LV systolic dysfunction (defined as an ejection fraction below normal at rest) is initially a reversible phenomenon related predominantly to afterload excess, and full recovery of LV size and function is possible with AVR. With time, during which the ventricle develops progressive chamber enlargement and a more spherical geometry, depressed myocardial contractility predominates over excessive loading as the cause of progressive systolic dysfunction. This can progress to the extent that the full benefit of surgical correction of the regurgitant lesion, in terms of recovery of LV function and improved survival, can no longer be achieved AS (Bonow 2006 ACC AHA guidelines).

### 3.5 Signs and symptoms

Similar to AS, AI is also asymptomatic for a long time, and at the time of diagnosis many of them have dilated LVs with severe dysfunction. The first sign is almost always exercise intolerance, followed by chest pain sudden cardiac death, syncope and heart failure. Such as AS symptoms are most commonly seen during exercise, but exceptionally the chest pain can

be seen during sleep. The reason is the bradycardia during sleep. Bradycardia will increase the diastolic time during a cardiac cycle. The more the diastolic interval the more the regurgitant volume (because the regurgitation of the blood occurs in diastolic interval). The reason of angina is coronary artery disease in a fraction of patients but even in the absence of coronary artery disease angina can be seen. In these patients the reason of angina is decreased coronary flow reserve because of decreased driving pressure (low aortic diastolic pressure) and increased LV diastolic pressure (Nitenberg 1988). As in AS sudden cardiac death is more prevalent in symptomatic patients. In physical examination there are couples of signs that can help in diagnosis of AI and almost all of them are because of high stroke volume. Bounding pulse is the vigorous large pulses that can be palpated in severe AI and is because of high cardiac output and low diastolic pressure. Muller sign is the pulsation of uvula with each heart beat and is again because of high cardiac output. De Musset's sign is the bobbing motion of the head with the heart beat. Becker's sign is the pulsation of retinal vessels with beating heart. These peripheral signs are seen in chronic severe AI and are absent in acute AI, because they are the result of high stroke volume and cardiac output. In chronic AI the heart has the time to compensate and can pump the extra amount of blood that has been regurgitated to LV in diastole, but in acute severe AI the LV will fail suddenly and the stroke volume will remain the same or even decrease, so these signs would be absent. The cardiac auscultation of patients with AI will show a diastolic murmur that starts from early diastole in a decrescendo manner and regarding the severity of AI and its chronicity it will extend throughout the diastole. In acute severe AI the murmur will end soon in middle of diastole, but in chronic severe AI it will extend to the end of diastolic time.

### 3.6 Evaluation of patients with AI

The evaluation begins with seeking the history of any disease that can be associated with AI and also looking for subtle symptoms of AI such as nocturnal chest pain and heart failure. It is very important to be able to diagnose AI in physical examination because AI will remain silent for many years and finally it will be emerged as an irreversible LV dysfunction when the therapy will have little effect. There are great amount of signs in the physical examination of a patient with AI such as Muller sign, Becker sign. They can be used for diagnosis and determining the severity of the problem. ECG showed eccentric LV hypertrophy with atrioventricular and interventricular (specially in LV dysfunction) conduction abnormalities. These ECG findings are neither specific nor sensitive. CXR shows huge cardiomegally with aortic dilatation. In patients with AS the ascending aorta will be dilated but in AI the entire aorta is dilated. Also in AS the rate of aortic valve calcification is higher, which can be seen in CXR. Echocardiography is again the most frequent way of diagnosing and evaluating AI which is done via its divers modalities (Table 2). All of the patients with AI should undergo serial echocardiography with specific intervals in order to prevent the irreversible LV damage (Figure 5). As soon as the time the symptoms begin or the LV dilates or the LV dysfunction starts surgical treatment is indicated. CT scan and MRI are also used in this matter specially when evaluation of the aorta itself is also needed. They can precisely measure the size of the aortic root and ascending aorta. These sizes are extremely important when the surgery is planned, because the ascending aorta may be replaced as well. Cardiac catheterization is reserved for those cases which need further evaluation after previously mentioned modalities.

	Aortic Regurgitation		
	Mild	Moderate	Severe
<b>Qualitative</b>			
Angiographic grade	1+	2+	3-4+
Color Doppler jet width	Central jet, width less than 25% of LVOT	Greater than mild but no signs of severe AR	Central jet, width greater than 65% LVOT
Doppler vena contracta width (cm)	Less than 0.3	0.3-0.6	Greater than 0.6
<b>Quantitative (cath or echo)</b>			
Regurgitant volume (ml per beat)	Less than 30	30-59	Greater than or equal to 60
Regurgitant fraction (%)	Less than 30	30-49	Greater than or equal to 50
Regurgitant orifice area (cm <sup>2</sup> )	Less than 0.10	0.10-0.29	Greater than or equal to 0.30
<b>Additional essential criteria:</b>			
Left ventricular size			Increased

Table 3. Echocardiographic evaluation of AI severity (Source: American Heart Association, Inc.)

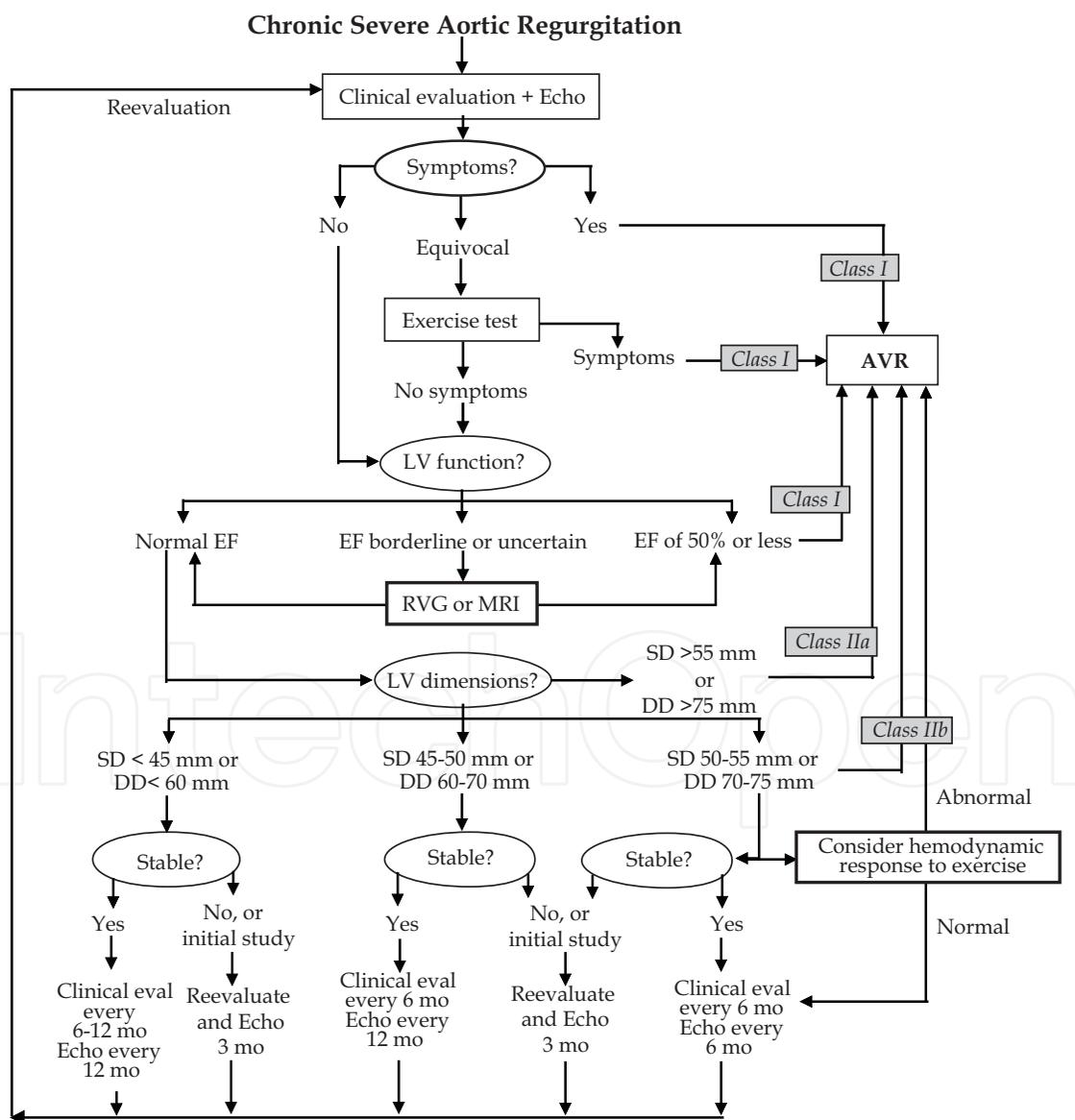


Fig. 5. Management of patients with severe AI (Source: American Heart Association, Inc.)

### 3.7 Medical treatment of AI

There is a great controversy in this field. Some believe that amlodipine can postpone the time of surgery or preserve the LV function during a 6 months period of time. Most specialists believe that there is no proper medical therapy for AI except in those with high operative mortality and those with advanced LV dysfunction as a part of heart failure management. In these patients specially vasodilators are indicated. Meticulous medical follow up is needed before and after AVR as in aortic stenosis. In those with advanced LV dysfunction and high risk for surgery medical treatment with the same medications as other heart failure patients is started. The exception are those drugs that decrease the heart rate because they can prolong the diastolic time and as the result the regurgitant volume.

### 3.8 Endovascular therapy of AI

There has been a great advance in this field in recent years, and developing techniques of percutaneous AVR are developing which is done in selected patients. But more advances in this field is needed and its not performed routinely because of high failure rate.

### 3.9 Surgical therapy of AI

This is the mainstay of management of AI and the timing of operation is determined through specific guidelines (Figure 5). This timing is performed specially with determining the size of the LV as well as its function. The other important issue is the symptoms of the patient. Operation is indicated when the patient becomes symptomatic. Aortic valve repair is reserved for specific situation such as myxomatous valve disease, traumatic or infective cases. It is not performed in most of the patients because of its failure rate. AVR is the most common procedure used with or without root replacement (Bentall procedure). Root replacement is indicated in those patients that have dilated or dissected root. Selection of the valve can be done via specific guidelines. After AVR the dilatation and dysfunction of the LV will be reversed if the operation is performed on the proper time. Short-term and long-term improvement in left ventricular systolic function after operation is related significantly to the early reduction in left ventricular dilatation arising from correction of left ventricular volume overload. Moreover, late improvement in ejection fraction occurs commonly in patients with an early increase in ejection fraction after valve replacement but is unlikely to occur in patients with no change in ejection fraction during the first 6 months after operation (Bonow 2006 ACC AHA guidelines)(Bonow 1983)(Bonow 1988)(Bonow 1984).

### 3.10 Natural course of AI

As in AS the patients with AI have a good prognosis until they are asymptomatic (Tornos 1995). Also the LV function and the size of the LV are important prognostic factors. Decreased LV contractility and dilated LV are predictors of poor prognosis, so small LV sizes and normal ejection fraction show good long term and post operative survivals. But in patients who become symptomatic the prognosis worsens rapidly and the expected survival is about 2 to 4 years in these patients if surgical intervention is not performed. But even in these patients if the AVR is performed in the proper time the survival and prognosis is excellent. Bonow et al.,(1988) reported that in asymptomatic patients with normal left ventricular function, death is rare, and less than 4% per year require aortic valve replacement because symptoms or left ventricular dysfunction develop. When aortic valve replacement is delayed until symptoms or left ventricular dysfunction develop, postoperative survival is excellent, and left ventricular size and function improve postoperatively. Hence,

"prophylactic" aortic valve replacement to preserve left ventricular function should not be performed in asymptomatic patients with severe aortic regurgitation and normal left ventricular function.

#### 4. Aortic valve prosthesis

They can be mainly classified into two types: Metallic (Figure 6) and Bioprosthetic (Figure 7).



Fig. 6. Metallic valve



Fig. 7. Bioprosthetic valve

Metallic valves are made of different compound such as titanium and have different types. They would not degenerate over time but their disadvantage is that blood can clot on their surface and cause their dysfunction or systemic embolization. Valve dysfunction can be fatal if severe, by causing cardiac dysfunction. These dysfunctions are managed either surgically or medically depending on their severity and the size of the clot. To prevent these complications AVR patients should receive oral anticoagulation for their life time in order to prevent clot formation on the valve. Precise monitoring is needed for the patients who use these medications because overdosing may cause abnormal and occasionally fatal bleedings.

Under dosing can culminate in clot formation and the aforementioned complications. The most prevalent drug is warfarin which prevents clot formation by inhibiting activation of clotting factors in the liver. The medical follow up of the patients receiving warfarin is by serial checking of International Normalization Ratio (INR) and Prothrombin Time (PT). The optimal INR is about 2.5 in most AVR patients (Butchart 1991)(Cannegieter 1994).

Bioprosthetic valves on the other hand degenerate over time and even may need reoperation, but they do not need constant anticoagulation to prevent clot formation. So the risks associated with anticoagulation such as bleeding is less than metallic valves.

The selection of specific valve is then determined in every patients considering these properties. In a young man who is going to have the valve for many years replacing the valve with a bioprosthetic will expose him to the risk of reoperation because of valve degeneration, so the metallic valve is preferred. On the other hand in an old lady who is high risk for bleeding the bioprosthetic is preferred.

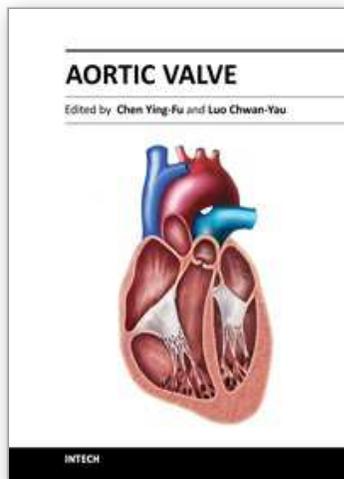
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## **Aortic Valve**

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Much has evolved in the field of aortic valve disease because of the increase in knowledge in the last decade, especially in the area of its management. This book "Aortic Valve" is comprised of 18 chapters covering basic science, general consideration of aortic valve disease, infective endocarditis, aortic sclerosis and aortic stenosis, bioprosthetic valve, transcatheter aortic valve implantation and a special section on congenital anomalies of the aortic valve. We hope this book will be particularly useful to cardiologists and cardiovascular surgeons and trainees. We also believe that this book will be a valuable resource for radiologists, pathologists, cardiovascular anesthesiologists, and other healthcare professionals who have a special interest in treating patients with aortic valve disease. We are certain that information in this book will help to provide virtually most new areas of aortic valve disease that will be employed in the current era.

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University Campus STeP Ri  
Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166  
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### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

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