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STRUCTURAL HEART DISEASE (RJ SIEGEL AND NC WUNDERLICH, SECTION EDITORS)

Tricuspid and Pulmonic Valve Pathology

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Abstract
Purpose of Review This review describes the normal structure and pathologic changes that affect the right-sided cardiac valves and chambers.
Recent Findings The anatomy and pathology described have been known for many years. Knowledge of these findings has gained relevance. The pattern of endocarditis is changing. New diagnostic techniques have allowed better characterization of lesions responsible for cardiac dysfunction. Novel, less invasive interventions have made recognition of abnormalities more clinically relevant.
Summary There are many different pathologic entities that can affect the right-sided cardiac valves. These are discussed in this review.

Keywords Tricuspid valve · Pulmonic valve · Carcinoid valve disease · Regurgitation · Stenosis · Intravenous drug use · Endocarditis · Congenital heart disease

Introduction

Right-sided valvular heart disease, that is, pathology affecting the tricuspid and/or pulmonic valves, is less common than disease affecting the left-sided heart valves. However, there are certain situations in which right-sided valvular disease is more prevalent. The etiology of right-sided valvular dysfunction may be primary or secondary, congenital or acquired, or iatrogenic or natural. Congenital malformations, such as Ebstein anomaly, tricuspid/pulmonic atresia, and valvular dysplasia, may result in stenosis or regurgitation. The presence of such anomalies, corrected or uncorrected, also increases the risk of developing right-sided infective endocarditis, as does the presence of foreign material, such as pacemakers, and intravenous drug use. Metastatic tumors of the gastrointestinal tract may cause carcinoid syndrome, selectively affecting the valves of the right side of the heart. Other causes of valvular disease, such as post-inflammatory (rheumatic) valvular disease, drug-induced valve disease, and radiation-induced injury, while more likely to affect the left side of the heart, may concomitantly occur with right-sided involvement.

This article is part of the Topical Collection on *Structural Heart Disease*

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Normal Anatomy

Tricuspid Valve

The right atrium and ventricle are separated by a fibrous annulus attached to which is the tricuspid valve, that, as its name implies, usually has three leaflets: anterior, septal, and posterior. The three leaflets are not always well demarcated, so the valve may appear to have four or even five somewhat separate portions. The leaflets are anchored by a variable number of relatively thin chordae tendineae to papillary muscles. The largest and most constant papillary muscle is the anterior papillary muscle that sends chordae to the anterior and posterior leaflets. There is usually a small posterior papillary muscle that has chordae to the posterior and septal leaflets. One or more small septal papillary muscles send chordae to the septal and anterior leaflets. A fourth group of more prominent papillary muscles (sometimes called the papillary muscle of Lancisi or papillary muscle of Luschka) [1] is present near

the commissure of the anterior and septal leaflets. The mitral valve has two distinct papillary muscles to which all chordae attach. This is not the case with the tricuspid valve, whose chordae attach to a variable number of papillary muscles and the interventricular septum. This difference helps distinguish a morphologic right ventricle from a morphologic left ventricle, an important distinction in evaluating congenital malformations of the heart. The chordae of the tricuspid valve are generally thinner than those of the mitral valve, perhaps because the right-sided valve is exposed to lower pressure than the mitral valve [2]. Histologically, the leaflets of the tricuspid valve are composed of three layers—the atrialis, spongiosa, and fibrosa. As its name implies, the atrialis is the superficial layer on the atrial side of the valve. It is lined by endothelial cells and contains numerous elastin fibers, thus giving the valve elasticity. The other superficial layer, lining the ventricular side of the valve, is the fibrosa. Its outer surface is also lined by endothelial cells. The fibrosa consists of dense fibrous tissue that mechanically supports the leaflets. In between the atrialis and fibrosa is the spongiosa, consisting of loose collagen, proteoglycans, and mesenchymal cells. The spongiosa acts as the "shock absorber" of the valve.

Pulmonic Valve

The pulmonic valve, like the aortic valve, is a semilunar valve, normally with three cusps or leaflets. Each leaflet has a small fibrous nodule in the center of the leaflet near the free edge, called the corpus arantii, or nodule of Arantius. The leaflets of the normal pulmonic valve are thinner than those of the aortic valve, again, likely due to lower pressures on the right side of the heart. The pulmonic valve may have small holes, or fenestrations, above the line of closure; these are generally clinically insignificant. The pulmonic valve is separated from the tricuspid valve by a body of myocardium called the infundibulum. This represents another feature that distinguishes a morphologic right ventricle from a morphologic left ventricle, in which there is fibrous continuity between the aortic and mitral valves. Histologically, the pulmonic valve cusps are similar to those of the aortic valve, composed of three layers of connective tissue with outer surfaces lined by endothelial cells. On the ventricular side is the ventricularis—the elastic layer. On the arterial side is the fibrosa—the dense fibrous supportive layer. In between, like all other valves, is the spongiosa—the "shock absorber" of the valve.

Pathology of the right-sided valves may result in functional stenosis or regurgitation. However, in many cases, functional valve disease is not related to primary valvular pathology. Increased right-sided pressure, usually from heart failure or connective tissue disease (e.g., scleroderma), is a leading cause "functional" valvular disease in which the valves themselves may appear normal or show mild myxomatous degeneration [3]. The most common causes of right-sided stenosis and regurgitation are listed in Table 1.

Congenital Malformations

Congenital malformations of the right-sided valves are uncommon, and usually associated with other malformations. The tricuspid valve may be absent completely—tricuspid atresia. The most common isolated malformation is Ebstein anomaly, in which most of the valve tissue is displaced below the valve annulus. Only the anterior leaflet is in its normal position. There is excessive, or redundant, leaflet tissue. The redundancy is less conspicuous if the leaflets are plastered against the myocardium of the right ventricle, as is often the case. The abnormal structure of the valve may cause it to leak, or less frequently, become stenotic. The abnormal portion of the right ventricular wall above the downwardly displaced valve is said to be "atrialized". Histologically, this tissue is often scarred, possibly the reason for dysrhythmias present in about half of the affected patients [4].

Tricuspid insufficiency may be due to dysplasia of the valve, an irregular thickening of the leaflet tissue by myxoid connective tissue (Fig. 1). There may be insufficiency in a structurally normal valve related to morphologic changes in the shape and size of the right-sided heart chambers. Isolated tricuspid stenosis is rare and usually acquired. Congenital stenosis of the tricuspid valve is most often seen as one manifestation of complex congenital heart disease.

Congenital malformations of the pulmonic valve usually occur with other malformations, as in tetralogy of Fallot. There may be no orifice—pulmonic atresia—or no leaflets—congenital absence of the pulmonic valve [5].

Congenital pulmonic stenosis may be an isolated anomaly, but more often, it is associated with other abnormalities [6]. The valve appears cone- or dome-shaped due to fusion of the commissures. Like the aortic valve, the pulmonic valve may be bicuspid or quadricuspid but these abnormalities are usually not functionally significant [7].

Table 1 Causes of tricuspid or pulmonic valve dysfunction

Post-inflammatory scarring (e.g., rheumatic disease)
Infective endocarditis
Heart failure
Drug/radiation induced endocardial disease
Carcinoid heart disease
Endomyocardial fibrosis
Rheumatoid/connective tissue disease
Right ventricular myocardial disease Pulmonary hypertension
Congenital valvular malformations (e.g., dysplasia, Ebstein anomaly)

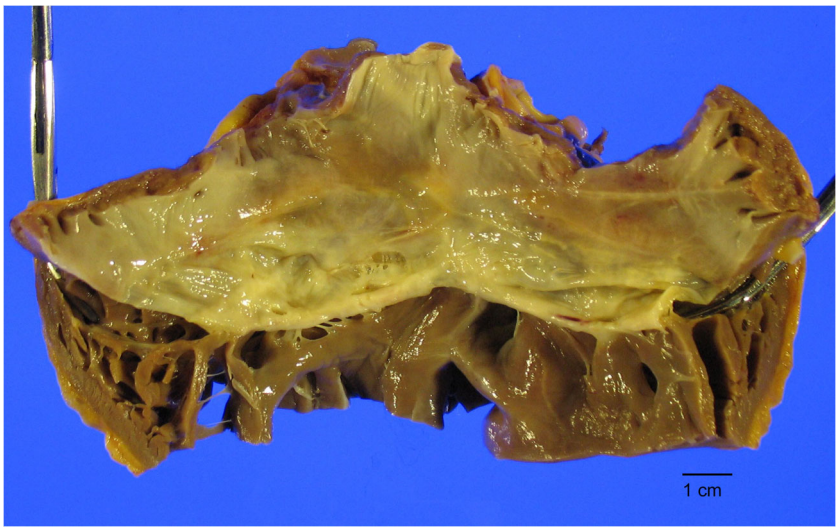

Fig. 1 Tricuspid valve dysplasia in an adult. This congenitally dysplastic "tricuspid" valve has only two abnormally and irregularly thick leaflets with short or absent chordae tendineae. The valve was functionally regurgitant

Infective Endocarditis

Infective endocarditis (IE) is the incorporation and proliferation of microorganisms in the valvular endocardium. The organisms, acute inflammation, and thrombi coalesce to form vegetations on the valve cusps or leaflets. IE involving the right-sided valves is far less common than IE involving the left side. In the general population, right-sided IE represents about 5–10% of cases [8]. There are a number of risk factors for right-sided IE, the most common of which are intravenous (IV) drug use, congenital heart disease (whether corrected or uncorrected), and implanted foreign material, such as pacemakers [9•]. (Fig. 2 and Table 2) The tricuspid valve is much more likely to be involved than the pulmonic valve, but even vestigial valves, such as the valve of the inferior vena cava (Eustachian valve), may be affected [10]. In contrast to left-sided IE, in which viridans group *Streptococcus* is the most common agent, *Staphylococcus aureus* is the most common culprit organism causing right-sided IE [8].

Unlike the general population, in which right-sided IE is rare, IE affects the right side of the heart in almost half of cases involving IV drug users [11, 12]. Concomitant HIV infection augments the risk of IE about fourfold. While the tricuspid valve is the most common valve affected in IV drug users with IE, the pulmonic valve is rarely involved. Thus, left-sided IE remains more common than right-sided IE in this special population. Polymicrobial IE is also more common in IV drug users, as are infections of fungal etiology [13]. The habits of the user may influence the species of organism involved. For example, *Pseudomonas aeruginosa*, an organism readily found in sinks and drains, is more prevalent in users of pentazocine and tripelennamine, perhaps because the pills are

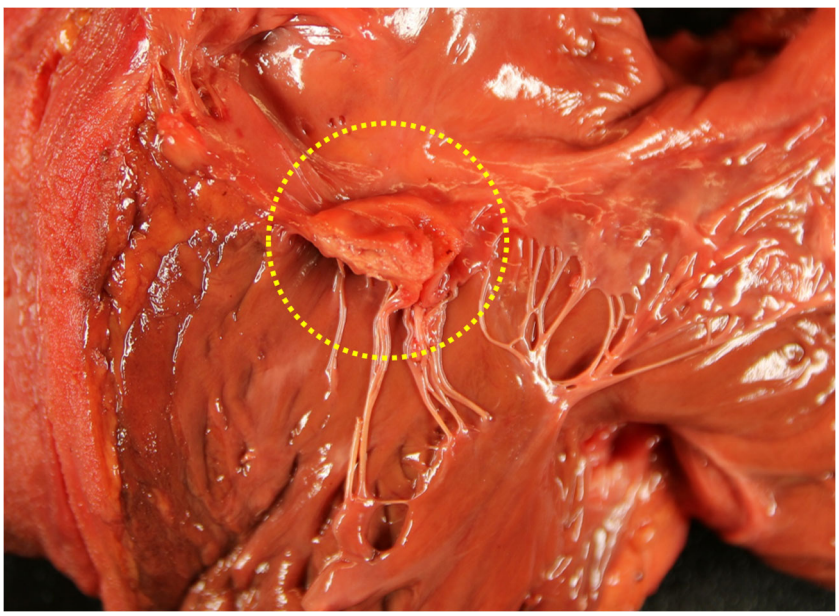

Fig. 2 Tricuspid valve infective endocarditis associated with pacemaker implantation. There is a vegetation on the posterior leaflet of the tricuspid valve (*yellow circle*) where a pacemaker lead previously coursed. The lead was removed due to the infection

Table 2 Risk factors predisposing to right-sided endocarditis

Portal of entry (e.g., IV drug use, venous catheter, hemodialysis)
Implanted foreign material (e.g., pacemaker)
Congenital heart disease
Invasive dental/medical procedure
Infection elsewhere in the body
History of infective endocarditis

crushed and dissolved in tap water prior to injection [12]. Similarly, brown heroin, which may be dissolved in lemon juice, has a higher association with candidal infection [14]. Polymicrobial infection by organisms of the normal oral flora (e.g., *Haemophilus parainfluenzae*, *Eikenella corrodens*, *Stretococcus milleri*, etc…) is also increased, perhaps owing to the habit of using saliva to clean used needles [15]. Frequency of injection may also augment the risk. IE has a higher prevalence in users of IV cocaine than IV heroin, possibly due to its shorter half-life and trend toward more frequent dosing [16].

Carcinoid Heart Disease

Carcinoid tumors are neuroendocrine neoplasms that can originate in almost any organ. These tumors secrete serotonin and/or serotonin metabolites causing *carcinoid syndrome*: flushing, diarrhea, and bronchospasm [17•]. These circulating substances are metabolized by the liver. Accordingly, carcinoid heart disease does not occur associated with a primary midgut carcinoid unless the tumor has metastasized to the liver. In addition, these serotonin-like chemicals are metabolized in the lung so involvement of the left side of the heart does not occur, unless there is an intrapulmonary shunt (i.e., A-V malformation), an intracardiac shunt (i.e., patent foramen ovale), or a cardiac metastasis. If the carcinoid tumor occurs in an organ that drains directly into the inferior vena cava, such as the ovary, there can be cardiac involvement without liver metastasis [18].

The characteristic lesion of carcinoid valvular disease is a coating of the valve and chordal surfaces with dense, collagenous tissue, smooth muscle cells, and myofibroblasts, devoid of elastic fibers, most pronounced on the ventricular surface of the tricuspid valve, and arterial surface of the pulmonic valve [19] (Fig. 3). The mural endocardium may also be involved [20]. The fibrous tissue deposition not only thickens the leaflets but also constricts the annulus. Usually, there is tricuspid regurgitation, with or without stenosis, and pulmonic stenosis, with or without some element of insufficiency. The presence of pulmonary stenosis increases right ventricular pressure and makes the tricuspid insufficiency worse.

Valvulopathy associated with the appetite suppressants fenfluramine and phentermine affecting left-sided valves is histologically similar to that of carcinoid valve disease. These drugs exert a serotonergic activity on human tissues further supporting the primary role of serotonin and/or its metabolites, in the development of valvular disease.

Rheumatic (Post-inflammatory) Valve Disease

The pulmonic and tricuspid valves may be involved in rheumatic heart disease, but not without the involvement of the left-sided valves. On both sides, the pathology is the same, fibrous thickening of the valve leaflets with fusion of commissures, and in the case of the tricuspid valve, thickening, shortening, and fusion of the chordae tendineae. Histologically, the valve tissue shows diffuse effacement of its normal three-layer architecture, variable amounts of chronic inflammation, and neovascularization. Combinations of regurgitation and stenosis occur in both valves. Non-rheumatic inflammatory conditions, such as infective endocarditis, produce similar post-inflammatory changes. Whereas rheumatic valve disease tends to be diffuse, healed infective endocarditis is generally a more focal process.

Iatrogenic/Traumatic Injury

Pacemaker and defibrillator leads are passed across the tricuspid valve during implantation. It is surprising that pacemaker leads go through the tricuspid valve orifice and sometimes the tricuspid valve leaflets, yet seldom cause valvular dysfunction. Over time, the leads get encapsulated in dense fibrous scar tissue that makes their removal problematic [21]. The leads may become infected, but this occurs less than 1% of the time [22].

Catheters of various sorts are also passed across the tricuspid and pulmonic valves that can potentially cause traumatic injury. Often, the injury is clinically insignificant, however. In patients who have had a heart transplant, tricuspid regurgitation is common and is related to the number of endomyocardial biopsies performed to monitor for rejection [23]. Fragments of valve tissue and chordae can be seen in the biopsy specimens. Most patients affected can be managed medically, but some patients require surgical repair of the tricuspid valve.

Radiation therapy applied to treat tumors of the chest is another iatrogenic cause of right-sided valve disease. Both the tricuspid and pulmonic valves may be affected. The result is diffuse leaflet fibrosis, with or without calcification. Unlike post-inflammatory/rheumatic disease, the fibrosis is not

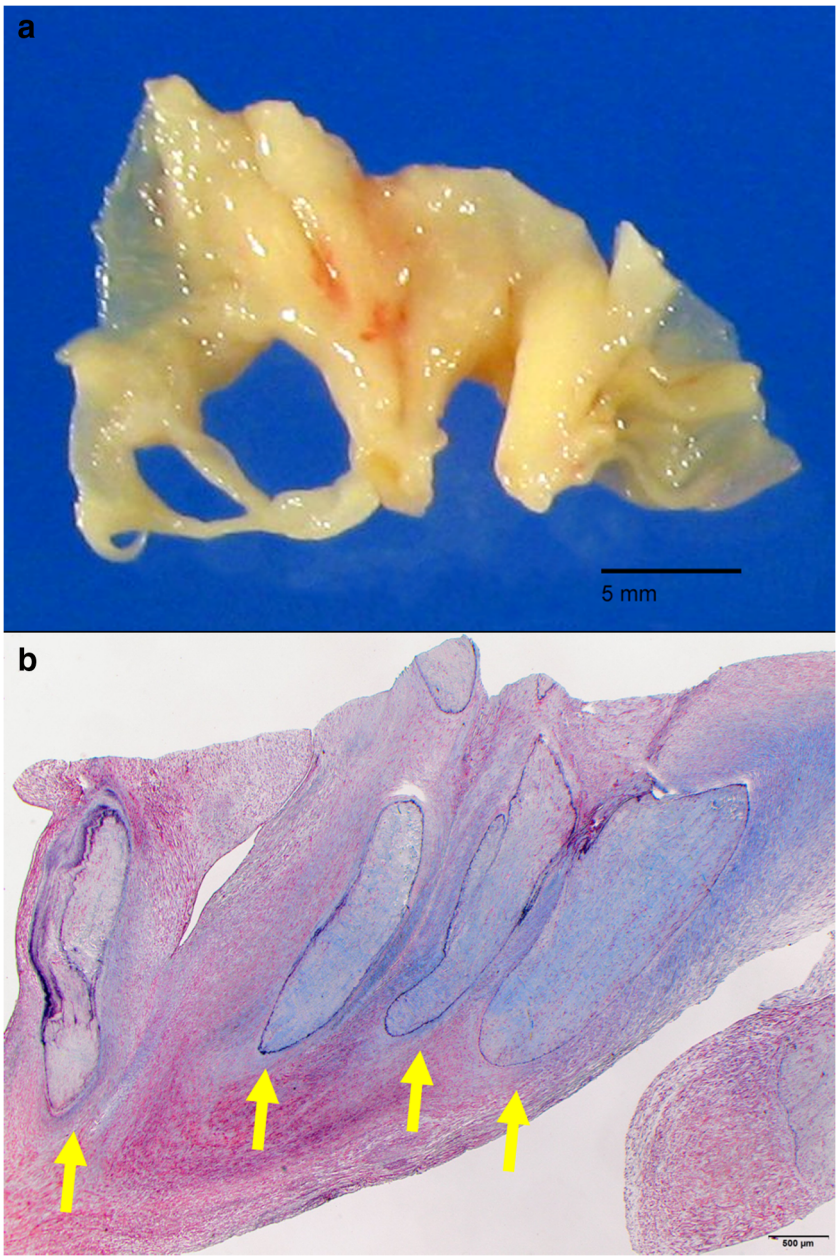

Fig. 3 Carcinoid valvular disease. **a** Gross photograph of the tricuspid valve with characteristic coating of the valve leaflet by dense connective tissue. **b** Microscopic examination shows the fibromuscular proliferation engulfing the chordae tendineae (*yellow arrows*). The trichrome/elastin stain demonstrates the plaque consists of smooth muscle (*red*) and collagen (*blue*) and is devoid of elastin fibers

associated with chronic inflammation and/or neovascularization [24]. In many cases, radiation-induced pathology of the tricuspid and pulmonic valves is clinically insignificant and without any hemodynamic consequences.

Conclusion

In this review, we have discussed the anatomy and pathology of the valves of the right side of the heart. Some lesions encountered may be limited to the valve leaflets, while others may affect the structures that support the leaflets, such as the chordae tendineae, papillary muscles, and underlying myocardium. Some disorders will result in valvular regurgitation, while others characteristically result in stenosis. Certain pathologic findings are nonspecific while others such are characteristic for specific disease states. Interpretation of novel imaging techniques and development of new interventions rely on an understanding of this anatomy and pathology.

Compliance with Ethical Standards

Conflict of Interest Gregory A. Fishbein and Michael C. Fishbein declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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