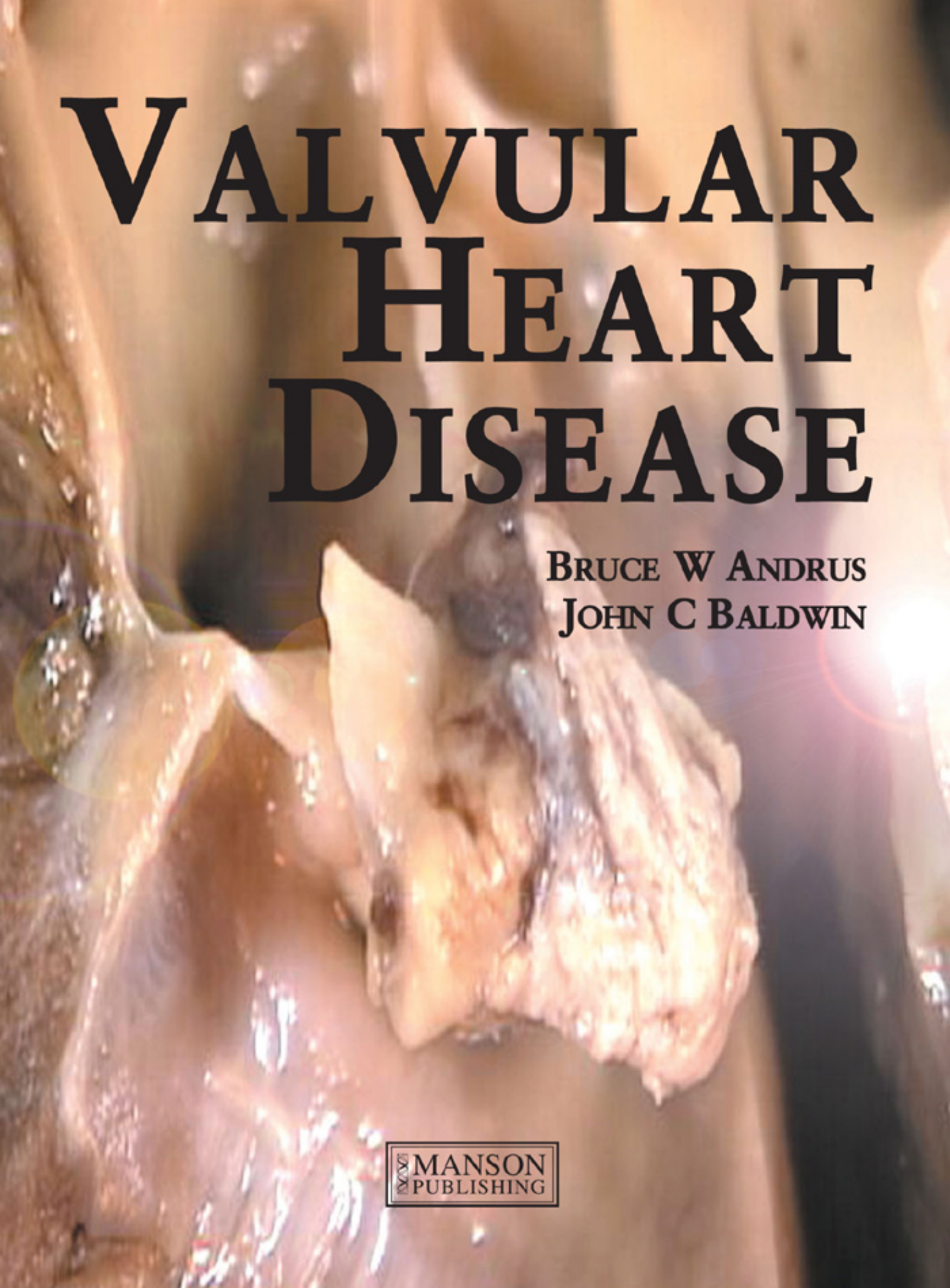
VALVULAR
HEART
DISEASE
BRUCE W ANDRUS
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MANSON
PUBLISHING

Valvular Heart Disease

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Preface

The study of valvular heart disease has progressed rapidly over the past two decades. The understanding of etiology and natural history, the precision of noninvasive assessment, and the surgical and interventional management of valve disease have all improved dramatically. Coupled with an appreciation of physiologic principles, thoughtful interviews and physical exam, current technology allows clinicians to characterize valve lesions fully. In addition, evolving techniques in interventional cardiology and cardiac surgery, guided by quantitative outcome analysis, have reduced the morbidity and mortality of these procedures. Throughout this handbook, we have endeavored to incorporate these developments.

Since the clinician's work generally begins with a patient's complaint, we have devoted most of the first chapter to the evaluation of symptoms commonly voiced by those with valvular heart disease. The second chapter focuses on the evaluation of murmurs, an important topic, since their recognition is critical to diagnosing asymptomatic valvular heart disease before irreversible myocardial damage occurs. The middle chapters provide a structured summary of the current understanding of the etiology, pathophysiology, natural history, clinical presentation, laboratory features, and medical and surgical treatment of valve disease. Single valve lesions are followed by mixed valve disease and an additional chapter on multiple valve disease. The final chapters address special topics in valvular heart disease which are not covered in a valve-by-valve approach. These include infective endocarditis, drug-related valvulopathy, pregnancy, special concerns in the elderly, valve prostheses, and improvement efforts in valvular heart disease.

In the interest of evidence-based medical practice and consistent, rational application of limited resources, we have extensively cited clinical guidelines and recommendations from specialty societies on both sides of the Atlantic.

We expect the succinct and structured text, complemented by current guidelines and abundant images, will be a valuable reference for all involved in the care of patients with valvular heart disease including medical students, house officers/registrars, cardiac nurse specialists, generalist physicians, and cardiologists.

Bruce W. Andrus
John C. Baldwin

Glossary of Abbreviations

ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
AHA	American Heart Association
AI	aortic insufficiency (synonym for AR)
ALT	alanine aminotransferase
AMVL	anterior mitral valve leaflet
aPTT	activated partial thromboplastin time
AR	aortic regurgitation
ARB	angiotensin receptor blocker
AS	aortic stenosis
ASD	atrial septal defect
AST	aspartate aminotransferase
AV	atrioventricular
AVA	aortic valve area
AVR	aortic valve replacement
BSA	body surface area
CAD	coronary artery disease
CDC	Center for Disease Control
CE	Carpentier Edwards
CHF	congestive heart failure
CMR	cardiac magnetic resonance
CO	cardiac output
COPD	chronic obstructive pulmonary disease
CRT	cardiac resynchronization therapy
CT	computed tomography
CVP	central venous pressure
CXR	chest X-ray
DCCV	direct current cardioversion
DNA	deoxyribonucleic acid
EBCT	electron beam computed tomography
ECG	electrocardiogram
EF	ejection fraction
ESC	European Society of Cardiology
ERO	effective regurgitant orifice
ESD	end-systolic diameter
ESRD	end-stage renal disease
FC	functional class
FDA	Food and Drug Administration
FSV	forward stroke volume
GI	gastrointestinal
GU	genitourinary
HMG-CoA	hydroxymethylglutaryl coenzyme A
HOCM	hypertrophic obstructive cardiomyopathy
IE	infective endocarditis
INR	international normalized ratio
IVC	inferior vena cava
JVP	jugular venous pulsation
LA	left atrium
LV	left ventricle
LVEDP	left ventricular end-diastolic pressure
LVEDV	left ventricular end-diastolic volume
LVH	left ventricular hypertrophy
LVOT	left ventricular outflow tract
MAC	mitral annular calcification
MDCT	multidetector computed tomography
MR	mitral regurgitation
MRI	magnetic resonance imaging
MS	mitral stenosis
MSCT	multislice computed tomography
MV	mitral valve
MVA	mitral valve area
MVP	mitral valve prolapse
MVR	mitral valve replacement
OSA	obstructive sleep apnea
PA	pulmonary artery
PABV	percutaneous aortic balloon valvotomy
PAF	paroxysmal atrial fibrillation
PAP	pulmonary artery pressure
PASP	pulmonary artery systolic pressure
PAWP	pulmonary artery wedge pressure
PCI	percutaneous coronary intervention
PCWP	pulmonary capillary wedge pressure
PET	positron emission tomography
PHT	pulmonary hypertension
PMBV	percutaneous mitral balloon valvotomy
PMI	point of maximal intensity
PMVL	posterior mitral valve leaflet
PR	pulmonic regurgitation
PS	pulmonic stenosis
RA	right atrium
RCT	randomized clinical trial
RF	regurgitant fraction
RSV	regurgitant stroke volume
RT3D	real-time three dimensional
RV	right ventricle
RVEDP	right ventricular end-diastolic pressure
RVG	radionuclide ventriculogram
RVH	right ventricular hypertrophy
SEP	systolic ejection period
SVC	superior vena cava
SVR	systemic vascular resistance
TEE	transesophageal echocardiography
TIA	transient ischemic attack
TR	tricuspid regurgitation
TS	tricuspid stenosis
TSP	Toronto stentless prosthetic valve
TSV	total stroke volume
VHD	valvular heart disease
V_{regurg}	regurgitant volume
VSD	ventricular septal defect
WPW	Wolf–Parkinson–White (syndrome)

Chapter One

Approach to the Patient

General principles

The recognition of valvular heart disease can be challenging. The condition of the patient may range in severity from asymptomatic to severe distress. Moreover, the illness may not be readily attributable to the cardiovascular system. Infective endocarditis may mimic a rheumatologic or neurologic condition, while acute mitral regurgitation may be misinterpreted as a primary pulmonary disorder. Making a prompt and accurate diagnosis, while avoiding excessive laboratory investigation, may test the acumen of seasoned clinicians.

The successful approach to these patients depends upon an open-minded history and careful physical exam, an understanding of the pathophysiology and the cardinal features of each disorder, and the discipline to consider the differential diagnosis of each patient's chief complaint. Intelligent use of a rapidly growing diagnostic menu serves to confirm or exclude competing diagnoses.

History

As in nearly all of medicine, most clues to a diagnosis come from the history. This should not be compromised. Trying to save minutes at this stage may waste hours in fruitless investigation later.

PAST MEDICAL HISTORY

A patient's prior medical history importantly shapes his future risk of valvular heart disease. Examples of relevant past events and the cardiac valve lesions they are associated with include the following: a history of rheumatic fever (mitral stenosis, MS and aortic stenosis, AS); prior episodes of infective endocarditis (recurrent, IE); intravenous drug use (IE); use of anorectic medications (pulmonic stensosis, PS); carcinoid tumors (pulmonic stenosis, PS); long-term indwelling vascular devices, dental, genitourinary, or gastrointestinal procedures (IE); hypertension or hyperlipidemia (AS); chromosomal abnormalities such as Trisomy 21 (mitral valve prolapse, MVP, mitral regurgitation, MR, aortic regurgitation, AR); collagen vascular disease such as Marfan's syndrome (AS); end-stage renal disease (valvular calcification); syphilis (AR); congenital bicuspid aortic valve (AS); coronary artery disease (MR). Additionally, pulmonary hypertension leads to tricuspid regurgitation (TR) even in anatomically normal tricuspid valves, and radiation therapy may predispose to TR (Waller *et al*., 1995a). Fabry's disease and Whipple's disease may result in tricuspid stenosis (TS). Methysergide may increase the risk of TS (Waller *et al*., 1995b). Finally, a history of past valve surgery increases the risk of future valve problems by way of prosthetic valve endocarditis or structural failure.

FAMILY HISTORY

Although genetics undoubtedly plays a role in valvular heart disease, it usually does not participate in a simple Mendelian manner. An exception to this is myxomatous valve disease, which may be transmitted as an autosomal dominant trait. For most valve lesions, a positive family history only modestly increases the risk of disease. It is worth recording, nonetheless. In so doing, the clinician may identify a family with a previously unrecognized genetic mutation and allow early diagnosis of relatives.

SOCIAL HISTORY

The social history may provide valuable information about predisposing illnesses or habits mentioned above. For example, a childhood spent in a nonindustrialized region of the world greatly increases the risk of rheumatic valve disease. A history of unprotected sex or intravenous drug abuse raises the possibility of syphilitic aortitis or infective endocarditis.

Chief complaint and present illness

The time course for valvular heart disease varies widely, ranging from minutes in the case of a ruptured papillary muscle, to decades in calcified aortic stenosis. Regardless of the tempo, however, there are some symptoms which are repeatedly encountered in patients with valvular heart disease (VHD). These symptoms are discussed in the following section.

Dyspnea

This is the most common presenting complaint in valvular heart disease. Unfortunately, it is also very nonspecific, occurring in nearly any disturbance of cardiopulmonary function. Features which are somewhat more specific for left heart failure include orthopnea and paroxysmal nocturnal dypsnea. In valvular heart disease, these symptoms result from increased left atrial pressure > increased pulmonary venous pressure > increased pulmonary capillary pressure > interstitial edema > impaired pulmonary compliance and stimulation of juxtacapillary receptors. In its most extreme form, pulmonary edema, the alveoli are flooded with a plasma transudate (**1**).

In cases of mild pulmonary venous hypertension, dyspnea may not be the most prominent complaint. Rather, the patient may complain of a persistent cough and be mistakenly diagnosed with reactive airway disease or a persistent viral infection.

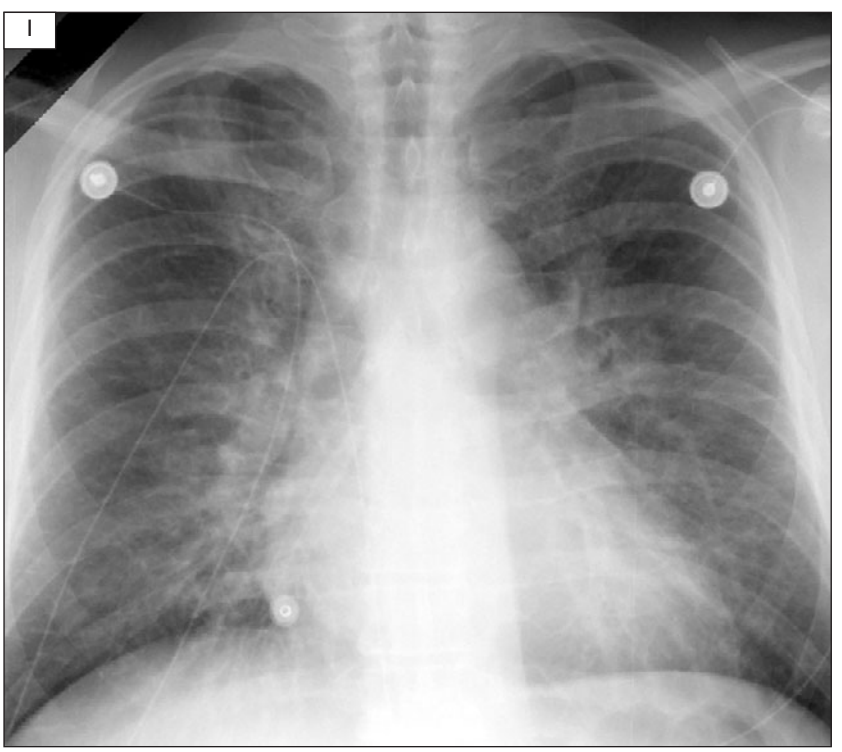
In addition, the plasma moistened alveoli represent an environment predisposed to infection. As a result, recurrent and difficult to treat respiratory infections may be the principal manifestation of disease.

Palpitations

The sensation of a rapid or unusually vigorous heart beat may signal the development of atrial or ventricular arrhythmias. Atrial fibrillation is a common sequela of both MS and MR. Ventricular arrhythmias are much more ominous and may arise from concentric hypertrophy arising from an excess pressure load (**2**) or eccentric hypertrophy arising from an excessive volume load.

Angina

While more common as the presentation of coronary disease, angina may be the initial manifestation of valvular heart disease. This often occurs in severe AS when the dramatically elevated myocardial oxygen demand of severe concentric left ventricular hypertrophy (LVH) cannot be supplied by even normal coronary arteries.



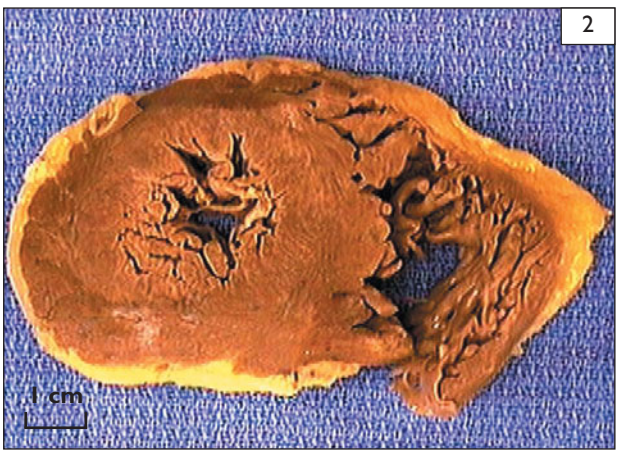
1 Chest X-ray to demonstrate many of the characteristic findings in pulmonary edema, including perihilar haze, vascular blurring, bronchial cuffing, Kerley B lines, and mild cardiomegaly. (Courtesy of Bill Black, MD.)

Syncope
A sudden loss of consciousness may be the presenting complaint in valvular heart disease. Most commonly, it arises from a sudden decrease in cardiac output resulting from a ventricular arrhythmia. However, in patients with AS, their inability to increase cardiac output in the face of exercise-induced peripheral dilation may lead to syncope as well. Pathophysiologically, this occurs when the 'mismatch' of static cardiac output and falling systemic vascular resistance results in decreasing blood pressure. If mean arterial pressure drops below a critical level of cerebral perfusion pressure, the ascending reticular activation system of the brain will cease to function and syncope will result.

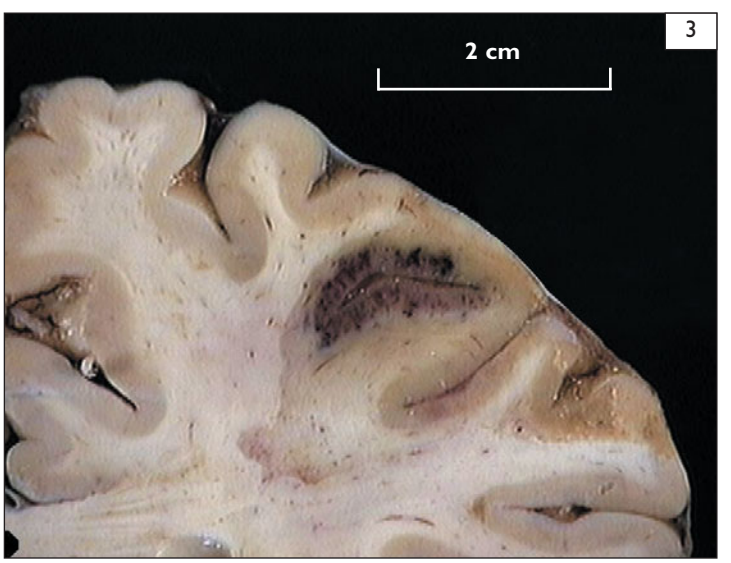
Weight gain, edema, and abdominal discomfort
These symptoms often occur together as manifestations of right heart failure. As systemic venous pressure rises, plasma extravasates into the dependent soft tissue resulting in rapid weight gain. In ambulatory patients, this is first seen in the ankles and legs. In hospitalized patients, excess extravascular fluid is first detected as pitting edema overlying the sacrum. Concomitantly, the elevated systemic venous pressure extends to the hepatic veins, which swells the liver and stretches the capsule causing right upper quadrant discomfort and anorexia. The lining of the gut often becomes edematous as well, resulting in impaired absorption or oral medications including diuretics.

Constitutional symptoms
In especially challenging cases, the presenting symptoms may be nonspecific, limited to malaise due to diminished cardiac output, fever, and weight loss.

Embolic phenomena
A dreaded manifestation of valvular heart disease is stroke or peripheral embolism due to ejection of an atrial clot. This most often occurs in atrial fibrillation associated with MR and MS (3).



2 Pathologic specimen of a heart from a female with both severe atherosclerotic coronary artery disease and severe calcific aortic stenosis. (Courtesy of Tom Farrell, MD.)



3 Pathologic specimen with a right frontal cerebral infarct that occurred in the context of nonbacterial thrombotic endocarditis, and probably represents an embolic phenomenon. (Courtesy of Tom Farrell, MD.)

Physical exam

General appearance

Much valuable information is gathered from the initial appearance of the patient, even from the distance of the patient's doorway. Important signs include the toxic appearance of acute infection, the muscle wasting of cardiac cachexia, the distressed facial expression, wet cough, accessory muscle use, upright posture, and diaphoresis of pulmonary edema, and the cool skin characteristic of hypoperfusion.

Vital signs

Tachycardia often represents an attempt to maintain a normal cardiac output or normal blood pressure in the face of a drop in stroke volume or systemic vascular resistance. Alternatively, it may result from hypoxemia or circulating mediators of inflammation. An increased pulse pressure suggests aortic insufficiency, severe hypotension suggests circulatory collapse, and severe hypertension often accompanies acute congestive heart failure.

Skin and mucosa

Cyanosis of the lips (central cyanosis) suggests inadequate oxygenation, while cyanosis of the digits (peripheral cyanosis) suggests impaired perfusion. Cold sweat implies hypoperfusion with severe sympathetic activation, while warm diaphoretic skin usually implies systemic infection. Other skin findings may suggest left-sided infective endocarditis. These include tender subcutaneous nodules in the pulp of the digits (Osler nodes), painless red macular lesions of the palms and soles (Janeway lesions), conjunctive petechia, and linear subungal hematomas (splinter hemorrhages) (**4**).

Central venous pulsations

Jugular venous pulsation and mean central venous pressure (CVP) are often abnormal in valvular heart disease. In most cases, right heart failure is secondary to left-sided valve disease causing left heart failure. However, in some instances, right heart failure may arise from right-sided valve lesions. In severe TR, giant c-v waves and a pulsatile liver are usually present. Less direct clues to the level of right atrial pressure include the presence of pedal edema in an ambulatory patient, sacral edema or anasarca in a hospitalized patient, tender hepatomegaly, eccymoses (from hepatic synthetic dysfunction), hepatojugular reflux, and ascites.

Arterial pulse

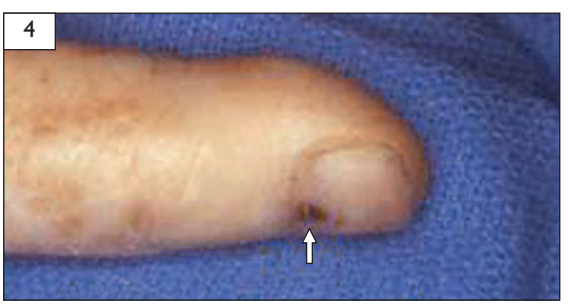
The volume, contour, and ausculatory findings of peripheral pulses can also provide important clues to the presence of valvular heart disease. These findings will be discussed in subsequent chapters in association with specific valvular abnormalities.

Precordial palpation

A right ventricular lift with thrill may betray pulmonic stenosis hidden below. A left ventricle dilated from chronic aortic regurgitation may shift the apical impulse laterally and expand the diameter beyond 3 cm (Eilen *et al.*, 1983). Left ventricular hypertrophy caused by AS may produce an apical impulse sustained throughout systolic ejection. Coupled with a left parasternal retraction, this may yield a rocking motion of the precordium (Braunwald and Perloff, 2001).

Cardiac auscultation

The ausculatory findings will be highlighted as each valvular abnormality is described in subsequent chapters. However, some general comments are appropriate in this section. Throughout the 19th and much of the 20th century, clinicians had to rely on the clinical skills of history taking and physical exam to make diagnoses and form judgements about prognosis. Acumen in these skills separated the master clinicians from the pedestrian practitioners. Perhaps more than any other, there developed a great



4 Splinter hemorrhage (arrow) from a patient who died from complications of infective endocarditis. Note the linear subungal discoloration. (Courtesy of Nora Ratcliff, MD.)

library of clinical findings in cardiac ausculatation, both extra heart sounds and murmurs. (Hanna and Silverman, 2002). Chapter 2 will focus entirely on cardiac murmurs since they are so often the first indication of significant valvular heart disease. Much attention has been focused on the apparent loss of these skills within the profession in an era of relatively easy, but expensive, access to 'high tech' tools (Schneiderman, 2001). However, ausculatation is a technical skill like any other and improves with repetition (Barrett *et al*., 2004). Therefore, students and physicians-in-training reading this text should not lose heart, but rather, should apply themselves diligently to acquire these valuable bedside skills. Listening to patients before and after echocardiographic findings are known is particularly helpful.

Chest exam

Intercostal retractions, accessory muscle use, inspiratory crackles, wheezing, and evidence of pleural effusions may all be important signs of valvular disease.

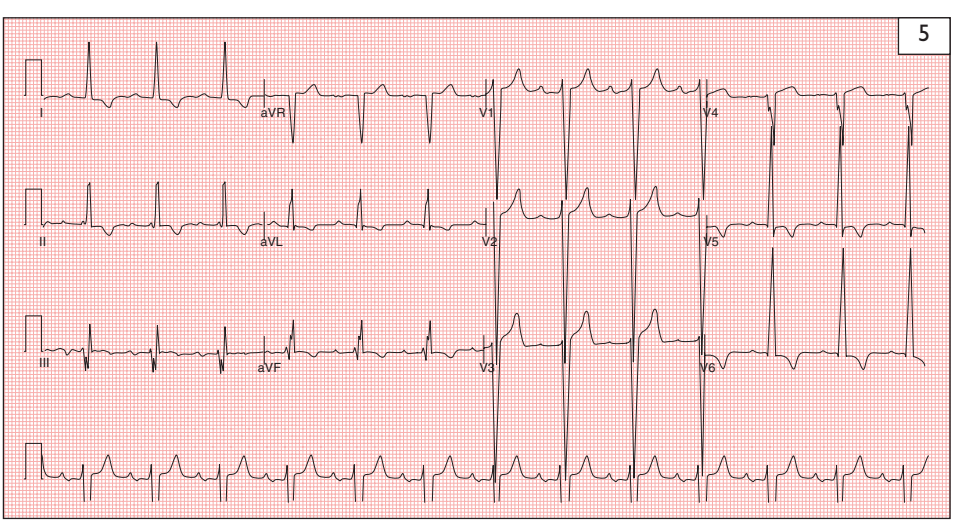
Laboratory investigations

Electrocardiography

As a result of its long history of use, there is an extensive literature of electrocardiographic findings in valvular disease. This experience, together with its low cost and accessibility, make it a valuable tool. Its principal value derives from its demonstration of chamber enlargement, ventricular hypertrophy, and associated arrhythmias (**5**). The characteristic findings associated with specific valve lesions will be discussed and displayed in subsequent chapters.

Chest radiography

Chest films may provide valuable clues regarding valvular heart disease. Pulmonary vascular congestion, chamber enlargement, valvular calcification, and type and position of prosthetic valve may all be ascertained with plain radiographs. Comparing changes over time is particularly helpful; hence obtaining previous studies can be very valuable.

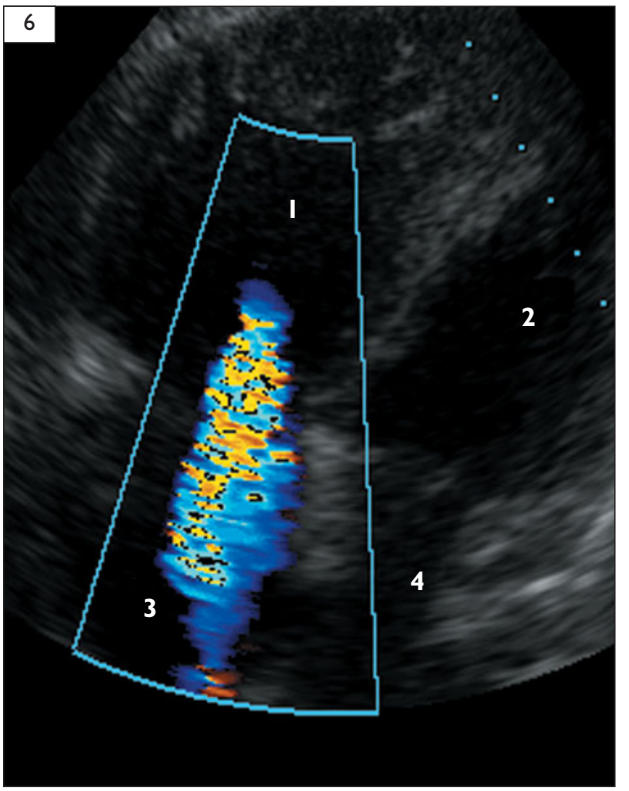


5 12-lead electrocardiogram demonstrating characteristic findings of left ventricular hypertrophy which often accompanies aortic stenosis. Note the increased voltage with repolarization changes and widened QRS duration. (Courtesy of Frances DeRook, MD.)

Echocardiography

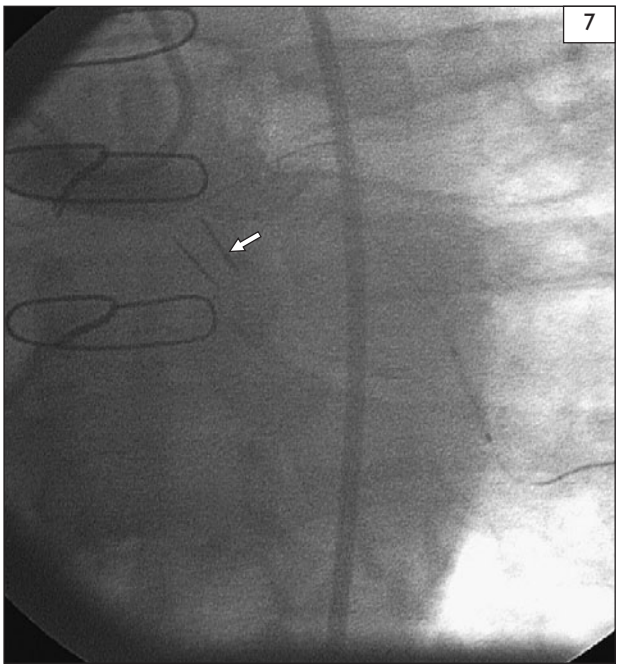
Echocardiography is the most valuable tool in valvular disease due to its portability, ease of use, safety, modest cost, steadily improving resolution, and ability to assess hemodynamics. Echocardiography began as a simple 'depth finder' which when plotted against time provided what is now known as 'M-mode'. Although this original mode provides tremendous temporal resolution useful for characterizing the rapid movements of intracardiac structures, it did not produce a familar image of the heart. There are now many additional ultrasound-based modalities which provide information about cardiac anatomy, cardiac function, and hemodynamics. These modalities include two dimensional (2D) or B-mode echocardiography in which sound waves are transmitted in a fan-like distribution, yielding a real time, wedge-shaped tomographic image of the heart. Doppler eachocardiography takes advantage of the change in pitch in sound waves which return after striking a moving object. As quantified by the Doppler shift equation, sound waves striking an approaching object will be compressed and become higher in frequency or pitch, while those striking a receding object will become rarified and assume a lower frequency. A commonly cited example of this is the change in pitch of a train whistle as it passes by. In echocardiography, the instrument estimates the velocity of flow in the heart and great vessels by bouncing ultrasound waves off red blood cells and measuring the change in frequency.

There are three subtypes of Doppler ultrasound. In continuous wave Doppler, all velocities along a continuous line through the heart are displayed as a spectrum over time. In pulse wave Doppler, a sample volume is placed on a 2D image and the spectral display of velocities represents the blood flow velocities in this region only. In color flow Doppler, the velocity of red blood cells across a 2D region is determined. The velocity of cells in each pixel of the image are color coded and this information is superimposed on a 2D or B-mode echocardiographic image (**6**). Tissue Doppler is yet another form of Doppler echocardiography which measures the velocity of anatomic structures rather than red blood cells; it currently has very limited application in valvular heart disease and won't be mentioned in this text. Echocardiographic assessments of valve area, pressure gradients, chamber size, and valve morphology will be central to evaluation of many conditions discussed in this book.

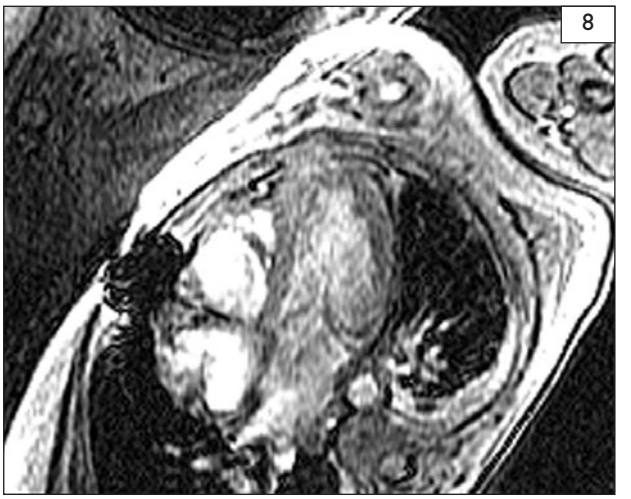


6 Apical 4-chamber echocardiographic view of a patient with tricuspid valve disease. The color flow Doppler imaging demonstrates the regurgitant flow through the tricuspid valve. 1: right ventricle; 2: left ventricle; 3: right atrium; 4: left atrium.

Because of their ubiquitous use, it is worthwhile to present some details of eachocardiographic hemodynamic assessment. Firstly, the pressure gradient across a valve or between two chambers can be estimated by taking advantage of the relationship between pressure (P) and velocity (v) as described in the Bernoulli equation. In cardiology, a modified (simplified) version of this equation is used, namely $P = 4v^2$. As an example, a velocity of 5 msec across the aortic valve translates to a peak instaneous pressure gradient of (4×5^2) or 100 mmHg (13.3 kPa).



7 Bileaflet mechanical prosthesis in the aortic position seen in profile during a percutaneous coronary intervention. Note the nearly parallel orientation of the two leaflets (arrow).



8 Magnetic resonance image of a mitral valve seen during diastole in long axis. (Courtesy of J. Pearlman, MD, PhD, ME.)

Another commonly used physical principle used in echocardiography is the conservation of flow. This states the obvious fact that in a conduit with ends of different diameter, the flow of fluid through one end must match flow through the other end. Since flow equals the product of orifice area and flow velocity, this principle can be stated as $Area_1 \times Velocity_1 = Area_2 \times Velocity_2$. This is specifically used in the determination of aortic valve area where the first area is the outflow tract, the first velocity is that through the outflow tract, the second velocity is that through the stenotic aortic valve, and the second area is the one unknown which is determined by measuring the other three variables. A variation of this involves substituting velocity time integral (VTI), the distance traveled by a red blood cell during systole, for velocity. This generally yields more reproducible information.

Another hemodynamic measure important in valvular heart diseases is the rate of pressure equilibration between two chambers (e.g. pressure half-time, deceleration time). The chapters on specific valve lesions will make reference to these measurements.

Cardiac catheterization and contrast radiography

Although increasingly supplanted by echocardiography, direct measure of intracardiac pressures, ventriculography, aortography, and assessment of coronary vessels prior to valve surgery all continue to play a role in the evaluation of valvular heart disease. In addition, the opening angle of mechanical valve prostheses can be measured precisely in the catheterization laboratory (7). Finally, balloon valvotomy serves an important therapeutic role in mitral, and occasionally, aortic stenosis.

Magnetic resonance imaging/computed tomography

The complex and rapid movement of the heart has limited the application of these imaging techniques until recently. However, recent advances have made magnetic resonance imaging (MRI) and computed tomography (CT) practical, although expensive, means of imaging difficult patients (8).

Nuclear cardiology

Single photon emission computer tomography (SPECT) imaging with data pooled from many cardiac cycles (gating) can provide precise measurements of ejection fraction (EF) and chamber dimensions. However, it currently plays only a limited role in valvular heart disease (**9**).

Positron emission tomography

Positron emission tomography (PET) is an emerging imaging technique which allows improved resolution and more flexibility than SPECT, including the possibility of imaging metabolic substrates and neural transmitters. In light of its expense and dependency upon mostly cyclotron-produced isotopes, its role in valvular heart disease remains to be determined.

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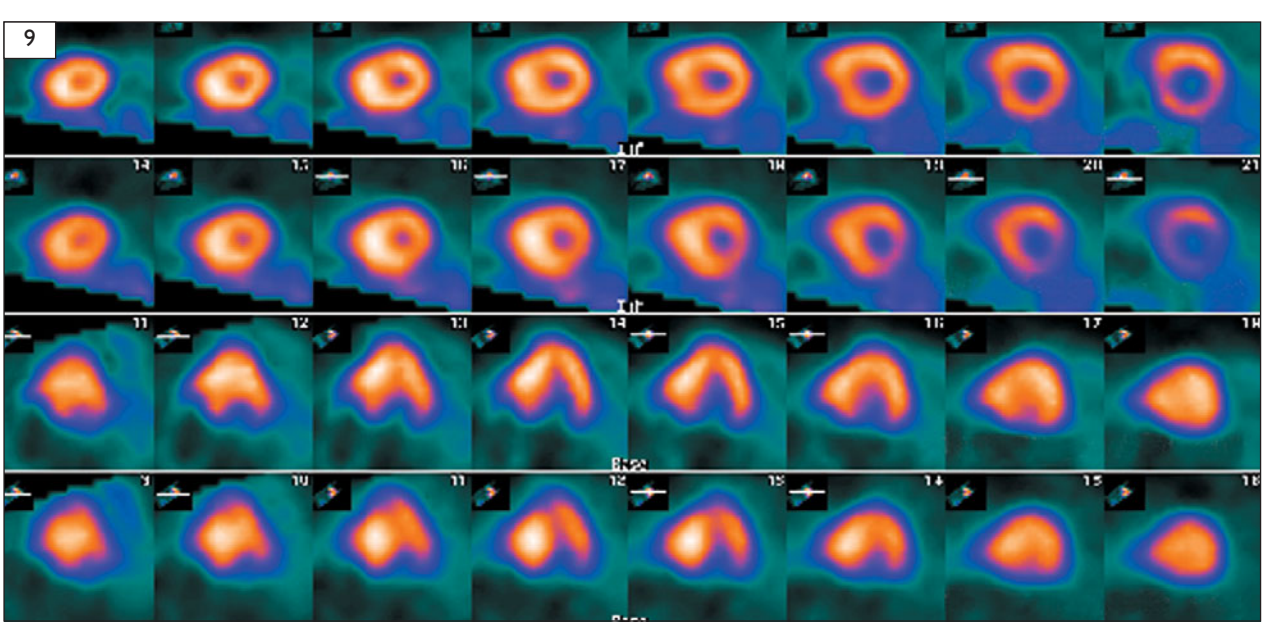

9 Short axis and horizontal long axis cardiac perfusion scintigraphic images demonstrating dramatic septal hypertrophy in a young female.