Cardiomyopathies
• the term cardiomyopathy (literally, heart muscle disease) has been historically applied to any cardiac dysfunction resulting from a myocardial abnormality
Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure-related disability.”
• cardiomyopathies manifest as failure of myocardial performance; this can be mechanical (e.g., diastolic or systolic dysfunction) leading to CHF, or can culminate in life-threatening arrhythmias.

• **Primary** cardiomyopathies can be genetic or acquired diseases of myocardium,

• **Secondary** cardiomyopathies have myocardial involvement as a component of a systemic or multiorgan disorder.
• A major advance in our understanding of cardiomyopathies stems from the frequent identification of underlying genetic causes, including mutations in myocardial proteins involved in contraction, cell-cell contacts, and the cytoskeleton, lead to abnormal contraction or relaxation, or to dysregulated ion transport across cell membranes.
• Although chronic myocardial dysfunction secondary to ischemia, valvular abnormalities, or hypertension can cause significant ventricular dysfunction, these conditions should not be denoted as cardiomyopathies.
three pathologic patterns:
1. Dilated cardiomyopathy (including arrhythmogenic right ventricular cardiomyopathy)
2. Hypertrophic cardiomyopathy
3. Restrictive cardiomyopathy

Dilated cardiomyopathy is most common (90% of cases), and restrictive cardiomyopathy is the least frequent.
Figure 12-29 The three major morphologic patterns of cardiomyopathy. Dilated cardiomyopathy leads primarily to systolic dysfunction, whereas restrictive and hypertrophic cardiomyopathies result in diastolic dysfunction. Note the changes in atrial and/or ventricular wall thickness. Ao, Aorta; LA, left atrium; LV, left ventricle.
Dilated Cardiomyopathy

• Dilated cardiomyopathy (DCM) is characterized morphologically and functionally by progressive cardiac dilation and contractile (systolic) dysfunction, usually with concomitant hypertrophy.
• Pathogenesis:
familial (genetic)
acquired
• Genetic Influences:
DCM is familial in at least 30% to 50% of cases, in which it is caused by mutations in a diverse group of more than 20 genes encoding proteins involved in the cytoskeleton, sarcolemma, and nuclear envelope.

**autosomal dominant** inheritance is the predominant pattern; X-linked, autosomal recessive, and mitochondrial inheritance are less common.
- Acquired:
  - Myocarditis: viral
  - Alcohol: **direct** toxic effect on the myocardium. Moreover, chronic alcoholism may be associated with **thiamine deficiency**, which can lead to beriberi heart disease
  - Other toxins: myocardial injury caused by certain chemotherapeutic (doxorubicin), targeted cancer therapeutics (e.g., tyrosine kinase inhibitors) and Cobalt (heavy metal)
  - Childbirth (peripartum cardiomyopathy): can occur late in pregnancy or up to months postpartum. The mechanism underlying this entity is poorly understood (hypertension, volume overload, nutritional deficiency, prolactin, microvascular angiogenic imbalance)
  - Iron overload
  - Supraphysiologic stress: Excess catecholamines (pheochromocytomas, hyperthyroidism, takotsubo cardiomyopathy/ psychological stress) leading to direct myocyte toxicity due to calcium overload or to focal vasoconstriction
• MORPHOLOGY:
the heart is usually enlarged, heavy (often weighing two to three times normal), and flabby, due to dilation of all chambers. Mural thrombi are common and may be a source of thromboemboli.
• The histologic abnormalities in DCM are nonspecific and usually do not point to a specific etiology.

• Most muscle cells are hypertrophied with enlarged nuclei, but some are attenuated, stretched, and irregular. Interstitial and endocardial fibrosis of variable degree is present, and small subendocardial scars may replace individual cells or groups of cells, probably reflecting healing of previous ischemic necrosis of myocytes caused by hypertrophy-induced imbalance between perfusion and demand.

• Moreover, the severity of morphologic changes may not reflect either the degree of dysfunction or the patient’s prognosis.
Figure 12-32 Dilated cardiomyopathy. A, Four-chamber dilatation and hypertrophy are evident. There is a mural thrombus (arrow) at the apex of the left ventricle (on the right in this apical four-chamber view). The coronary arteries were patent. B, Histologic section demonstrating variable myocyte hypertrophy and interstitial fibrosis (collagen is highlighted as blue in this Masson trichrome stain).
Clinical Features:
- can occur at any age, but it most commonly affects individuals between the ages of 20 and 50.
- It presents with slowly progressive signs and symptoms of CHF including dyspnea.
- Secondary mitral regurgitation and abnormal cardiac rhythms are common, and embolism from intracardiac thrombi can occur
- Death usually results from progressive cardiac failure or arrhythmia, and can occur suddenly.
- The annual mortality is high (10% to 50%), some severely affected patients respond well to pharmacologic therapy.
• **Arrhythmogenic right ventricular cardiomyopathy:**
  - inherited disease (autosomal dominant) attributed to defective cell adhesion proteins in the desmosomes that link adjacent cardiac myocytes
  - Morphologically, the right ventricular wall is severely thinned due to loss of myocytes, accompanied by extensive fatty infiltration and fibrosis
  - causing right ventricular failure and rhythm disturbances (particularly ventricular tachycardia or fibrillation) with sudden death
  - **Naxos syndrome**: mutations in the gene encoding the desmosome-associated protein plakoglobin
Figure 12-33 Arrhythmogenic right ventricular cardiomyopathy. A, Gross photograph, showing dilation of the right ventricle and near-transmural replacement of the right ventricular free-wall by fat and fibrosis. The left ventricle has a virtually normal configuration in this case, but can also be involved by the disease process. B, Histologic section of the right ventricular free wall, demonstrating replacement of myocardium (red) by fibrosis (blue, arrow) and fat (Masson trichrome stain).
Hypertrophic Cardiomyopathy

• Hypertrophic cardiomyopathy (HCM) is a common (incidence, 1 in 500), clinically heterogeneous, genetic disorder characterized by myocardial hypertrophy, poorly compliant left ventricular myocardium leading to abnormal diastolic filling, and (in about one third of cases) intermittent ventricular outflow obstruction.

• It is the leading cause of left ventricular hypertrophy unexplained by other clinical or pathologic causes.

• The heart is thick-walled, heavy, and hypercontracting, in striking contrast to the flabby, hypocontracting heart of DCM.

• HCM causes primarily diastolic dysfunction; systolic function is usually preserved.
• Pathogenesis:
In most cases, the pattern of transmission is autosomal dominant. HCM is caused by mutations in any one of several genes that encode sarcomeric proteins. Mutations causing HCM are found most commonly in the gene encoding β-myosin heavy chain (β-MHC).
Although such sarcomeric alterations have been thought to be pathologic on the basis of abnormal cardiac contraction causing a secondary compensatory hypertrophy, newer evidence suggests that HCM may instead arise from defective energy transfer from its source of generation (mitochondria) to its site of use (sarcomeres).
• MORPHOLOGY:
The essential feature of HCM is **massive myocardial hypertrophy, usually without ventricular dilation.**

The classic pattern involves disproportionate thickening of the ventricular septum relative to the left ventricle free wall (with a ratio of septum to free wall greater than $3 : 1$), termed **asymmetric septal hypertrophy.** In about 10% of cases, the hypertrophy is concentric and symmetrical.

The normally round-to-ovoid left ventricular cavity may be compressed into a “banana-like” configuration by bulging of the ventricular septum into the lumen.

The left ventricular outflow tract often exhibits a fibrous endocardial plaque associated with thickening of the anterior mitral leaflet.
• The most important histologic features of HCM myocardium are:
  (1) massive myocyte hypertrophy, with transverse myocyte diameters frequently greater than 40 μm (normal, approximately 15 μm)
(2) haphazard disarray of bundles of myocytes, individual myocytes, and contractile elements in sarcomeres within cells (termed myofiber disarray)
(3) interstitial and replacement fibrosis
Figure 12-34 Hypertrophic cardiomyopathy with asymmetric septal hypertrophy. **A,** The septal muscle bulges into the left ventricular outflow tract, and the left atrium is enlarged. The anterior mitral leaflet has been reflected away from the septum to reveal a fibrous endocardial plaque (arrow) (see text). **B,** Histologic appearance demonstrating myocyte disarray, extreme hypertrophy, and exaggerated myocyte branching, as well as the characteristic interstitial fibrosis (collagen is blue in this Masson trichrome stain).
Clinical Features:
- exertional dyspnea (reduced stroke)
- harsh systolic ejection murmur
- Anginal pain (focal myocardial ischemia)
- atrial fibrillation
- mural thrombus formation leading to embolization
- intractable cardiac failure
- ventricular arrhythmias
- sudden death

**HCM is one of the most common causes of sudden, otherwise unexplained death in young athletes.**

The natural history of HCM is highly variable. Most patients can be helped by pharmacologic intervention (e.g., β-adrenergic blockade) to decrease heart rate and contractility.
Figure 12-31 Causes and consequences of dilated and hypertrophic cardiomyopathy. Some dilated cardiomyopathies and virtually all hypertrophic cardiomyopathies are genetic in origin. The genetic causes of dilated cardiomyopathy involve mutations in any of a wide range of genes. They encode proteins predominantly of the cytoskeleton, but also the sarcomere, mitochondria, and nuclear envelope. In contrast, all of the mutated genes that cause hypertrophic cardiomyopathy encode proteins of the sarcomere. Although these two forms of cardiomyopathy differ greatly in subcellular basis and morphologic phenotypes, they share a common set of clinical complications. LV, left ventricle.
Restrictive Cardiomyopathy

- Restrictive cardiomyopathy is characterized by a primary decrease in ventricular compliance, resulting in impaired ventricular filling during diastole, the contractile (systolic) function of the left ventricle is usually unaffected.

- Restrictive cardiomyopathy can be idiopathic or associated with distinct diseases or processes that affect the myocardium, principally radiation fibrosis, amyloidosis, sarcoidosis, metastatic tumors, or the deposition of metabolites that accumulate due to inborn errors of metabolism.
Morphology:

• The ventricles are of approximately normal size or slightly enlarged, the cavities are not dilated, and the myocardium is firm and noncompliant.

• Biatrial dilation is commonly observed.

• Microscopically, there may be only patchy or diffuse interstitial fibrosis
<table>
<thead>
<tr>
<th>Functional Pattern</th>
<th>Left Ventricular Ejection Fraction*</th>
<th>Mechanisms of Heart Failure</th>
<th>Causes of Phenotype</th>
<th>Indirect Myocardial Dysfunction (Mimicking Cardiomyopathy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilated</td>
<td>&lt;40%</td>
<td>Impairment of contractility (systolic dysfunction)</td>
<td>Genetic; alcohol; peripartum; myocarditis; hemochromatosis; chronic anemia; doxorubicin (Adriamycin) toxicity; sarcoidosis; idiopathic</td>
<td>Ischemic heart disease; valvular heart disease; hypertensive heart disease; congenital heart disease</td>
</tr>
<tr>
<td>Hypertrophic</td>
<td>50% to 80%</td>
<td>Impairment of compliance (diastolic dysfunction)</td>
<td>Genetic; Friedreich ataxia; storage diseases; infants of diabetic mother</td>
<td>Hypertensive heart disease; aortic stenosis</td>
</tr>
<tr>
<td>Restrictive</td>
<td>45% to 90%</td>
<td>Impairment of compliance (diastolic dysfunction)</td>
<td>Amyloidosis; radiation-induced fibrosis; idiopathic</td>
<td>Pericardial constriction</td>
</tr>
</tbody>
</table>

*Normal, approximately 50% to 65%.
Myocarditis

• Myocarditis is a diverse group of pathologic entities in which infectious microorganisms and/or a primary inflammatory process cause myocardial injury.
• Pathogenesis:

**viral** infections are the most common cause of myocarditis. **Coxsackie viruses** A and B and other enteroviruses probably account for most of the cases. Other less common etiologic agents include cytomegalovirus, HIV, and influenza viruses can potentially cause myocardial injury either as a direct cytopathic effect, or by eliciting a destructive immune response.
• **Nonviral** agents are also important causes of infectious myocarditis, particularly the protozoan Trypanosoma cruzi, the agent of Chagas disease. Trichinosis (Trichinella spiralis) is the most common helminthic disease associated with myocarditis.

Parasitic diseases, including toxoplasmosis, and bacterial infections such as Lyme disease and diphtheria.
There are also noninfectious causes of myocarditis. Broadly speaking they are either immunologically mediated (hypersensitivity myocarditis) or idiopathic conditions with distinctive morphology (giant cell myocarditis) suspected to be of immunologic origin.
<table>
<thead>
<tr>
<th>Table 12-13 Major Causes of Myocarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections</strong></td>
</tr>
<tr>
<td>Viruses (e.g., coxsackievirus, ECHO, influenza, HIV, cytomegalovirus)</td>
</tr>
<tr>
<td>Chlamydiae (e.g., <em>Chlamydophyla psittaci</em>)</td>
</tr>
<tr>
<td>Rickettsiae (e.g., <em>Rickettsia typhi</em>, typhus fever)</td>
</tr>
<tr>
<td>Bacteria (e.g., <em>Corynebacterium diphtheriae</em>, <em>Neisseria meningococcus</em>, <em>Borrelia</em> (Lyme disease))</td>
</tr>
<tr>
<td>Fungi (e.g., <em>Candida</em>)</td>
</tr>
<tr>
<td>Protozoa (e.g., <em>Trypanosoma cruzi</em> [Chagas disease], toxoplasmosis)</td>
</tr>
<tr>
<td>Helminths (e.g., trichinosis)</td>
</tr>
<tr>
<td><strong>Immune-Mediated Reactions</strong></td>
</tr>
<tr>
<td>Postviral</td>
</tr>
<tr>
<td>Poststreptococcal (rheumatic fever)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Drug hypersensitivity (e.g., methyldopa, sulfonamides)</td>
</tr>
<tr>
<td>Transplant rejection</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
</tr>
<tr>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Giant cell myocarditis</td>
</tr>
</tbody>
</table>

HIV, Human immunodeficiency virus.
• MORPHOLOGY:
Grossly, the heart in myocarditis may appear normal or dilated.
In advanced stages the ventricular myocardium is flabby and often mottled by either pale foci or minute hemorrhagic lesions.
Mural thrombi may be present.
Active myocarditis is characterized by an interstitial inflammatory infiltrate associated with focal myocyte necrosis.

A diffuse, mononuclear, predominantly lymphocytic infiltrate is most common.

If the patient survives the acute phase of myocarditis, the inflammatory lesions either resolve, leaving no residual changes, or heal by progressive fibrosis.

Hypersensitivity myocarditis: high proportion of eosinophils

Giant-cell myocarditis: multinucleate giant cells, extensive necrosis
Figure 12-35 Myocarditis. A, Lymphocytic myocarditis, associated with myocyte injury. B, Hypersensitivity myocarditis, characterized by interstitial inflammatory infiltrate composed largely of eosinophils and mononuclear inflammatory cells, predominantly localized to perivascular and expanded interstitial spaces. C, Giant-cell myocarditis, with mononuclear inflammatory infiltrate containing lymphocytes and macrophages, extensive loss of muscle, and multinucleated giant cells (fused macrophages). D, The myocarditis of Chagas disease. A myofiber distended with trypanosomes (arrow) is present along with individual myofiber necrosis, and modest amounts of inflammation.
• Clinical Features:
- fatigue, dyspnea, palpitations, precordial discomfort, and fever.
- The clinical features of myocarditis can mimic those of acute MI,
- patients can develop dilated cardiomyopathy as a late complication of myocarditis.
- asymptomatic, and patients can expect a complete recovery without sequelae
- heart failure or arrhythmias, occasionally with sudden death.
Pericardial Disease

• Pericardial Effusion and Hemopericardium: Normally, the pericardial sac contains less than 50 mL of thin, clear, straw-colored fluid. Parietal pericardium may be distended by serous fluid (pericardial effusion), blood (hemopericardium), or pus (purulent pericarditis).
With long-standing cardiac enlargement or with slowly accumulating fluid, the pericardium has time to dilate. This permits a slowly accumulating pericardial effusion to become quite large without interfering with cardiac function. Thus, with chronic effusions of less than 500 mL in volume, the only clinical significance is a characteristic globular enlargement of the heart shadow on chest radiographs.

In contrast, rapidly developing fluid collections of as little as 200 to 300 mL—e.g., due to hemopericardium caused by a ruptured MI or aortic dissection—can produce clinically devastating compression of the thin-walled atria and venae cavae, or the ventricles themselves; cardiac filling is thereby restricted, producing potentially fatal cardiac tamponade.
• Pericarditis:
Pericardial inflammation can occur secondary to a variety of cardiac, thoracic, or systemic disorders, metastases from remote neoplasms, or cardiac surgical procedures. **Primary** pericarditis is unusual and almost always of viral origin. Most evoke an *acute* pericarditis, but a few, such as tuberculosis and fungi, produce *chronic* reactions.
<table>
<thead>
<tr>
<th>Table 12-14 Causes of Pericarditis</th>
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</thead>
<tbody>
<tr>
<td><strong>Infectious Agents</strong></td>
</tr>
<tr>
<td>Viruses</td>
</tr>
<tr>
<td>Pyogenic bacteria</td>
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<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Fungi</td>
</tr>
<tr>
<td>Other parasites</td>
</tr>
<tr>
<td><strong>Presumably Immunologically Mediated</strong></td>
</tr>
<tr>
<td>Rheumatic fever</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Scleroderma</td>
</tr>
<tr>
<td>Postcardiotomy</td>
</tr>
<tr>
<td>Postmyocardial infarction (Dressler) syndrome</td>
</tr>
<tr>
<td>Drug hypersensitivity reaction</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Uremia</td>
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<tr>
<td>Following cardiac surgery</td>
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<tr>
<td>Neoplasia</td>
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<tr>
<td>Trauma</td>
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<tr>
<td>Radiation</td>
</tr>
</tbody>
</table>
• Acute Pericarditis:
  Serous pericarditis
  Fibrinous and serofibrinous pericarditis
  Purulent or suppurative pericarditis
  Hemorrhagic pericarditis
  Caseous pericarditis
• **Serous pericarditis** is characteristically produced by noninfectious inflammatory diseases, including rheumatic fever, SLE, and scleroderma, as well as tumors and uremia.

An infection in the tissues contiguous to the pericardium—for example, a bacterial pleuritis—may incite sufficient irritation of the parietal pericardial serosa to cause a sterile serous effusion that can progress to serofibrinous pericarditis and ultimately to a frank suppurative reaction. In some instances a well-defined viral infection elsewhere—upper respiratory tract infection, pneumonia, parotitis—antedates the pericarditis and serves as the primary focus of infection.

Tumors can cause a serous pericarditis by lymphatic invasion or direct contiguous extension into the pericardium. **Organization into fibrous adhesions rarely occurs.**
• **Fibrinous and serofibrinous pericarditis** are the most frequent types of pericarditis. Common causes include acute MI, postinfarction (Dressler) syndrome (an autoimmune response appearing days-weeks after an MI), uremia, chest radiation, rheumatic fever, SLE, trauma and cardiac surgery. Fibrin may be lysed with resolution of the exudate, or can become organized.
Purulent or suppurative pericarditis reflects an active infection caused by microbial invasion of the pericardial space; this can occur through:
- Direct extension from neighboring infections
- Seeding from the blood
- Lymphatic extension
- Direct introduction during cardiotomy
Complete resolution is infrequent, and organization by scarring is the usual outcome. The intense inflammatory response and the subsequent scarring frequently produce constrictive pericarditis.
Hemorrhagic pericarditis: it is most commonly caused by the spread of a malignant neoplasm to the pericardial space. It can also be found in bacterial infections, in persons with an underlying bleeding diathesis, in tuberculosis, and follows cardiac surgery.
Caseous pericarditis is, until proved otherwise, tuberculous in origin, it is a common antecedent of disabling, fibrocalcific, chronic constrictive pericarditis.
Chronic or Healed Pericarditis:
- adhesive pericarditis
- Adhesive mediastinopericarditis
- constrictive pericarditis
adhesive pericarditis:

In some cases organization merely produces plaque-like fibrous thickenings of the serosal membranes or thin, delicate adhesions. In other cases, fibrosis in the form of mesh-like stringy adhesions completely obliterates the pericardial sac. In most instances, this has no effect on cardiac function.
Adhesive mediastinopericarditis:
may follow infectious pericarditis, previous cardiac surgery, or mediastinal irradiation. The pericardial sac is obliterated, and adherence of the external aspect of the parietal layer to surrounding structures strains cardiac function. With each systolic contraction. The increased workload causes occasionally severe cardiac hypertrophy and dilation.
constrictive pericarditis:
the heart is encased in a dense, fibrous or fibrocalcific scar that limits diastolic expansion and cardiac output, features that mimic a restrictive cardiomyopathy.

A prior history of pericarditis may or may not be present.

Because of the dense enclosing scar, cardiac hypertrophy and dilation cannot occur.

Treatment consists of surgical resection of the shell of constricting fibrous tissue (pericardiectomy).
Tumors of the Heart

• **Primary tumors of the heart are rare; in contrast to metastatic tumors.**

• The most common primary cardiac tumors, in descending order of frequency (overall, including adults and children) are:

  1. myxomas
  2. fibromas
  3. lipomas
  4. papillary fibroelastomas
  5. rhabdomyomas,
  6. angiosarcomas.

The five most common tumors are all benign and collectively account for 80% to 90% of primary tumors of the heart.
Primary Cardiac Tumors

Myxomas:
- are the most common primary tumor of the adult heart.
- These are benign neoplasms.
- Although sporadic myxomas do not show consistent genetic alterations, familial syndromes associated with myxomas have activating mutations in the GNAS1 gene, encoding a subunit of G protein (Gsα) (in association with McCune-Albright syndrome) or null mutations in PRKAR1A, encoding a regulatory subunit of a cyclic-AMP dependent protein kinase (Carney complex).
- About 90% of myxomas arise in the atria, with a left-to-right ratio of approximately 4 : 1.
- The tumors are usually single.
Figure 12-38 Atrial myxoma. A, A large pedunculated lesion arises from the region of the fossa ovalis and extends into the mitral valve orifice. B, Abundant amorphous extracellular matrix contains scattered multinucleate myxoma cells (arrowheads) in various groupings, including abnormal vessel-like formations (arrow).
The major clinical manifestations are due to valvular “ball-valve” obstruction, embolization, or a syndrome of constitutional symptoms, such as fever and malaise.

Constitutional symptoms are probably due to the elaboration by some myxomas of the cytokine interleukin-6.

Surgical removal is usually curative.
Lipomas
- are localized, well-circumscribed, benign tumors composed of mature fat cells that can occur in the subendocardium, subepicardium, or myocardium.
- They may be asymptomatic, or produce ball-valve obstructions or arrhythmias.
- Lipomas are most often located in the left ventricle, right atrium, or atrial septum.
- In the atrial septum, nonneoplastic depositions of fat sometimes occur that are called “lipomatous hypertrophy.”
Papillary Fibroelastomas:
- usually incidental, sea-anemone-like lesions, most often identified at autopsy.
- benign neoplasms.
- are usually (>80%) located on valves
Rhabdomyomas:
- are the most frequent primary tumor of the pediatric heart.
- half of cardiac rhabdomyomas are due to sporadic mutations; the other 50% of cases are associated with tuberous sclerosis with mutations in the TSC1 or TSC2 tumor suppressor gene (hamartin and tuberin).
- Because rhabdomyomas often regress spontaneously, they may be considered as hamartomas rather than true neoplasms.
- They are usually multiple and involve the ventricles preferentially.
• Sarcoma. Cardiac angiosarcomas and other sarcomas are not clinically or morphologically distinctive from their counterparts in other locations