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Preface

We are delighted to present the second edition of *Understanding Pathophysiology*. The aim of this new edition was to revise and update the first edition to meet the ever-changing landscape of pathophysiology for health professional students. We recognise that students need the latest evidence about diseases and disorders and that these disorders and diseases need to have high relevance to students’ clinical practice. Therefore we have drawn together a team of clinical and scientific experts in the different body systems as contributors. The synergy between the scientific and the clinical experts has created a unique perspective, one that we believe enhances the content of the textbook.

In addition, we have expanded the life-span approach to normal structure and function of body systems chapters. We live in an ageing society and more healthcare is being delivered to this segment of the population. This new section will enhance students’ understanding of ageing and its application to pathophysiological alterations. We also have a new feature, Research in Focus, which highlights areas of scientific research translation, or potential translation, to clinical practice. Finally, we have bolstered the number of case studies for each chapter with the inclusion of an ageing-focused case study. This is to support academics and educators in the development of learning opportunities and to augment student learning.

As in the first edition, local clinical terminology and current health statistics are integrated to identify and examine the conditions with the highest incidence, prevalence and relevance in our communities.

Organisation of content

The textbook is organised into six parts, which group areas of common pathophysiological concepts.

Part 1 (Chapters 1–5) provides the necessary background knowledge of health science principles and processes relevant to pathophysiology. This includes an exploration of what constitutes pathophysiology, and how the disease process manifests in clinical signs and symptoms. It also encompasses relevant information about the population-level measures of disease, such as incidence, prevalence and mortality rates, to allow students to successfully interpret these in subsequent chapters. Chapter 1 provides an overview of the essentials of anatomy, physiology, chemistry and physics that are relevant to the study of pathophysiology. Chapter 2 is devoted to homeostasis — arguably one of the most important themes underlying all aspects of health, since disease results when homeostasis cannot be maintained. Chapter 3 explores the normal structure and function of the cell, and Chapter 4 deals with alterations to cellular biology. Finally in this part, Chapter 5 examines genes and how genetic information controls events within the cell.

Parts 2–5 provide an in-depth examination of body systems, and are grouped into areas of common and key concepts. Each part has chapters on normal anatomy and physiology, as well as pathophysiology. Although this textbook focuses on pathophysiology, we have included chapters on anatomy and physiology because an understanding of normal body processes is vital for an understanding of pathophysiology. Part 2 (Chapters 6–11) encompasses the nervous and endocrine systems, which undertake overall control and coordination of the body systems. Part 3 (Chapters 12–21) covers the different features relating to immunity, haematology, the integumentary system (skin) and the musculoskeletal system. Part 4 (Chapters 22–30) focuses on major body systems that provide the constituents essential for life: the cardiovascular and lymphatic systems, the pulmonary system, the digestive system and the urinary system. Part 5 (Chapters 31 and 32) explores the reproductive systems.

Finally, Part 6 (Chapters 33–40), examines those diseases and disorders that have greatest significance in the current health environment in Australia and New Zealand. The main emphasis is on issues that are more encompassing than the body system diseases covered in Parts 2–5. Many of the concepts discussed in Part 6 are advanced, drawing on the knowledge that has been laid down earlier in the book. Chapter 34 looks at the impact of our modern lifestyle and the types of diseases that are strongly related to stress. Chapter 35 considers two conditions whose incidence has increased tremendously in recent years: obesity and diabetes mellitus. Chapter 36 examines themes relating to a variety of cancers, the current state of cancers in Australia and New Zealand and current screening and prevention programs. Chapter 37 discusses the role of genes and the environment in disease pathogenesis — a hot topic given that so many conditions seen in developed countries are described as preventable. Chapter 38 explores the biological bases of mental illnesses, which remain poorly understood and yet are prevalent in our community. Chapters 39 and 40 examine the health of the Indigenous populations in Australia and New Zealand, respectively. We investigate the overall health of the Indigenous populations, often comparing it to the non-Indigenous population.
The Australian and New Zealand context

While many say that pathophysiology is similar the world over, this is not the case. Australia and New Zealand both have disease and disorder profiles that are different from other countries. For instance, both countries have very high rates of asthma; Australia has the world’s highest rates of melanoma and the Indigenous populations have poor health outcomes, especially in comparison to other first world peoples. Therefore, the diseases and disorders relevant to the Australian and New Zealand landscape are given precedence in this text. The pathophysiology of these diseases and disorders is explained in detail with an epidemiological focus relevant to the particular country.

Concept maps: a unique feature of the text

We have populated the text heavily with concept maps, which are easily identified by their bright orange background. Concept maps are a useful learning tool as they link concepts and processes in a visually stimulating way — our students often comment that using such maps helps the information to fall into place.

The concepts within each map are boxed and may be an anatomical abnormality, a physiological process, a risk factor or an alteration of homeostasis. The different concepts are then linked by lines and arrows, and in many cases descriptive joining words are included to provide a crucial link demonstrating how the concepts relate to each other. We have included both simple and complex concept maps: simple maps are to be read from top to bottom, while to read the more complex maps start at the top and follow each loop around back to the starting point to complete a process.

Acknowledgments

A textbook this size is constructed with a team of people. As such, we would like to formally acknowledge our colleagues whose expertise was sought in the refinement of this new edition and who have been part of the process of creating this text. We are particularly indebted to the many clinicians and academics who provided expert knowledge from their specialty domains. We thank them for their contribution and the time they gave to the contributors.

Of course, we also are indebted to the Australian Elsevier team, which has provided the guidance and support needed in the construction of a new edition. We would particularly like to thank Melinda McEvoy, Vicky Spichopoulos, Anitha Rajarathnam and Tamsin Curtis for assisting us in the completion of this edition. A special mention must also go to Amanda Simons and Vicky Spichopoulos, our wonderful Developmental Editors who were part of the journey.

And finally, we would like to thank our families who provided support and love during the writing of this textbook. They are at the coal face and often don’t see us for extended periods of time when we are in writing and editorial modes, but they are always there for us and this is greatly appreciated.

Judy Craft
Christopher Gordon
Alterations of cardiovascular function across the life span

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Introduction
Cardiovascular diseases are conditions and diseases that affect the heart and vasculature (blood vessels). There are variations in the definition of cardiovascular diseases, with some classifications including heart disease, vascular disease, stroke and circulatory disease. The most common forms of cardiovascular diseases are hypertension, coronary heart disease, heart failure and cerebrovascular disease. Cerebrovascular disease arises from pathological processes in blood vessels of the brain, with stroke being the most frequent manifestation of cerebrovascular disease. Although stroke is classified as a cardiovascular disease, it is discussed in Chapter 9 to consider the effects on the brain.

In Western countries, cardiovascular disease is an epidemic and major health problem. Approximately 18% of Australians (3.5 million people) are reported to have a long-term cardiovascular condition, with the prevalence of disease increasing with age (see Figure 23-1). In addition, cardiovascular disease remains a contributor to mortality, accounting for 34% and 40% of all deaths in Australia and New Zealand, respectively. In more recent years, there has been a reduction in the mortality rate attributable to cardiovascular disease due to improvements in cardiovascular disease management and a lowering of some risk factors (such as smoking). Unfortunately, these reductions are somewhat offset by the increased prevalence of cardiovascular disease in the elderly, combined with increasing rates of obesity and diabetes mellitus in the population (see Chapter 35). In addition, most people are afflicted with more than one cardiovascular condition and many have multiple cardiovascular risk factors. Furthermore, in both Australia and New Zealand cardiovascular disease is more prevalent in the Indigenous population than in the non-Indigenous population.1

It is vital that you have a comprehensive understanding of the pathophysiology of cardiovascular conditions, due to the high prevalence of cardiovascular disease in the community. Nurses are more actively involved than they have been previously in the management of cardiovascular conditions such as hypertension and heart failure, and your comprehension of the pathophysiology will aid your ability to care for individuals with cardiovascular conditions.

Alterations of blood flow and pressure
Pathophysiological alterations to arteries and veins include hypertension, atherosclerosis and peripheral vascular disease, and all of these conditions can lead to other cardiovascular diseases. The damage to the arteries in particular can lead to coronary heart disease, cerebrovascular disease or heart failure — the top three causes of death due to cardiovascular disease in Australia and New Zealand.1 This section details the formation of arterial and venous alterations, which will aid your understanding of the primary cardiovascular diseases. We start with the most common cardiovascular condition worldwide, hypertension.

Hypertension
Hypertension, or high blood pressure, is consistent elevation of systemic arterial blood pressure. It considerably increases the individual's risk of developing coronary heart disease, heart failure and strokes. It is the most prevalent cardiovascular condition and is estimated to afflict about one billion people worldwide — just over one-quarter of the world’s adult population.1 Approximately 3.7 million Australians over the age of 25 years (30% of adults) have high blood pressure or are on medication to treat high blood pressure.1 Unfortunately, evidence suggests that a large number of adults and children have undiagnosed hypertension.14 The prevalence of hypertension increases in the elderly and in Aboriginal and Torres Strait Islander peoples and Maori and Pacific Islander peoples compared to the non-Indigenous population.13

The diagnosis of hypertension is based on repeated blood pressure (BP) measurements at different times, when systolic blood pressure is equal to or greater than 140 mmHg or diastolic pressure is 90 mmHg or greater (see Table 23-1).7 Normal blood pressure is associated with the lowest cardiovascular risk, whereas those who fall in the ‘high–normal’ range are at risk for developing hypertension unless they institute lifestyle modifications.7 All categories of hypertension are associated with an
Factors associated with primary hypertension

A specific cause for primary hypertension has not been identified, but a combination of genetic and environmental factors is thought to be responsible for its development. Genetic predisposition to hypertension is thought to be polygenic; that is, there is more than one gene involved (see Chapter 37). A range of environmental factors are associated with primary hypertension — see the box ‘Risk factors for primary hypertension.’ You may notice that many of these factors are also risk factors for other cardiovascular disorders; this is a recurring feature of cardiovascular disease.

Although populations with a high dietary sodium intake have long been shown to have an increased incidence of hypertension, studies indicate that low dietary potassium, calcium and magnesium intakes are also risk factors, because, without their intake, sodium is retained in the blood, rather than being excreted in the urine. The nicotine in cigarette smoke is a potent vasoconstrictor that can elevate both systolic and diastolic blood pressure acutely. The incidence of hypertension is higher among heavy drinkers of alcohol (more than three drinks per day) than among non-drinkers, but moderate drinkers (two to four drinks per week) appear to have lower blood pressures, as well as lower cardiovascular mortality. Obesity is recognised as an important risk factor for hypertension and is discussed in Chapter 35.

### Risk factors for primary hypertension

- Family history
- Advancing age
- Cigarette smoking
- Obesity
- Heavy alcohol consumption
- Sex (males > females before age 55 years; females > males after 55 years)
- High dietary sodium intake
- Low dietary intake of potassium, calcium, magnesium
- Glucose intolerance

**Primary hypertension**

Primary hypertension is the result of an extremely complicated interaction of genetics and environmental or lifestyle factors causing neural and hormonal effects. Multiple pathophysiological mechanisms mediate these effects, including the sympathetic nervous system, the renin-angiotensin-aldosterone system (see Chapter 28) and natriuretic peptides (peptides consist of small numbers of amino acids). The term natriuresis refers to the excretion of large amounts of sodium in the urine, which in an otherwise healthy individual would be accompanied by loss of water in the urine, and hence a decrease in the total blood volume. Inflammation, endothelial dysfunction and insulin resistance also contribute to both an increase in peripheral resistance and blood volume. Increased vascular volume is related to a decrease in renal excretion of sodium, often referred to as a shift in the pressure–natriuresis relationship (see Figure 23-2). This means that individuals with hypertension tend to excrete less sodium in their urine.¹

The sympathetic nervous system has been implicated in both the development and the maintenance of elevated blood pressure. Increased sympathetic nervous system activity causes increased heart rate and systemic vasoconstriction, thus raising blood pressure. Structural changes in blood vessels, called vascular remodelling, which result in permanent increases in peripheral resistance, are induced by sympathetic nervous system activity. In addition, renal sodium retention, insulin resistance, increased renin and angiotensin levels and procoagulant effects are all induced by the sympathetic nervous system (see Figure 23-3).¹

---

**Table 23-1 Classification of blood pressure levels in adults**

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<tr>
<td>High-normal</td>
<td>120–139</td>
<td>80–89</td>
</tr>
<tr>
<td>Grade 1 (mild)</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Grade 2 (moderate)</td>
<td>160–179</td>
<td>100–109</td>
</tr>
<tr>
<td>Grade 3 (severe)</td>
<td>≥180</td>
<td>≥110</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated systolic hypertension with widened pulse pressure</td>
<td>≥160</td>
<td>≤70</td>
</tr>
</tbody>
</table>

*When a patient’s systolic and diastolic blood pressure levels fall into different categories, the higher diagnostic category and recommended action/s apply.
Inflammatory injury, chronic inflammation contributes to vascular remodelling and smooth muscle contraction. Endothelial injury and dysfunction in primary hypertension are further characterised by a decreased production of vasodilators, such as nitric oxide, and increased production of vasoconstrictors, such as endothelin.

Finally, insulin resistance (see Chapter 35) is common in hypertension, even in individuals without clinical diabetes mellitus. Insulin resistance is associated with decreased endothelial release of nitric oxide and other vasodilators. It also affects renal function and causes the kidneys to retain sodium and water. Insulin resistance is associated with overactivity of the sympathetic nervous system and the renin-angiotensin-aldosterone system. The pathophysiology of primary hypertension is summarised in Figure 23-4.

**Secondary hypertension**

Secondary hypertension is caused by an underlying disease process or medication that raises peripheral vascular resistance or cardiac output. The condition is more prevalent in younger people (< 30 years of age) and those over 50 years of age. If the cause is identified and removed before permanent structural changes occur, blood pressure returns to normal. Examples include kidney disease due to the retention of sodium and water (see Chapter 30), adrenocortical hormonal imbalances such as primary hyperaldosteronism (see Chapter 11), and drugs (oral contraceptives, corticosteroids, antihistamines).

**Isolated systolic hypertension**

*Isolated systolic hypertension* is typically defined as a sustained systolic BP > 140 mmHg and diastolic BP below 90 mmHg. Isolated systolic hypertension accounts for a substantial proportion of hypertension in individuals older than 65 years of age and is strongly associated with cardiovascular and cerebrovascular events.

An increased pulse pressure (systolic minus diastolic pressure) indicates reduced vascular compliance of large arteries. Pulse pressure is always increased in isolated systolic hypertension and is related to either an increase in cardiac output (heart valve disease) or peripheral resistance (caused by atherosclerosis). Pharmacological management of isolated systolic hypertension is required because the systolic blood pressure is greater than 140 mmHg.

**Complicated hypertension**

Cardiovascular complications of sustained hypertension include left ventricular hypertrophy, angina pectoris, heart failure, coronary heart disease, myocardial infarction and sudden death. Myocardial hypertrophy in response to hypertension is mediated by several neurohormonal substances, including catecholamines from the sympathetic nervous system (adrenaline and noradrenaline) and angiotensin II. In addition, the increased size of the heart muscle increases demand for oxygen delivery over time, contractility of the heart is impaired, and the individual is at increased risk for heart failure. Vascular complications include the formation, dissection and rupture of aneurysms (outpouchings in vessel walls) and atherosclerosis leading...
to vessel occlusion. Microalbuminuria (small amounts of protein in the urine) occurs in 10–25% of individuals with essential hypertension and is now recognised as an early sign of impending renal dysfunction and significantly increased risk for cardiovascular events. The pathological effects of sustained essential hypertension are summarised in Table 23-2.

### CLINICAL MANIFESTATIONS

The early stages of hypertension have no clinical manifestations other than elevated blood pressure. Most importantly, there are usually no signs and symptoms; thus, hypertension is often called a silent disease. Some hypertensive individuals never have signs, symptoms or complications, whereas others become very ill. Still other individuals have anatomical and physiological damage caused by past hypertensive disease, despite current blood pressures being within normal ranges.

The chance of developing primary hypertension increases with age. Although hypertension is usually thought to be an adult health problem, it is important to remember that hypertension does occur in children and is being diagnosed with increasing frequency. Usually, however, increased peripheral resistance and early hypertension develop in the second, third and fourth decades of life. If elevated blood pressure is not detected and treated, it becomes established and may begin to accelerate its effects on tissues when the individual is 30–50 years of age. This sets the stage for the complications of hypertension that begin to appear during the fourth, fifth and sixth decades of life.

Most clinical manifestations of hypertensive disease are caused by complications that damage organs and tissues outside the vascular system. Besides elevated blood pressure, the signs and symptoms therefore tend to be specific for the organs or tissues affected. Evidence of heart disease, renal insufficiency, central nervous system dysfunction, impaired vision, impaired mobility, vascular occlusion or oedema can all be caused by sustained hypertension.

### EVALUATION AND TREATMENT

A single elevated blood pressure reading does not indicate hypertension. Diagnosis requires the measurement of blood pressure on at least two separate occasions. The individual should be seated and relaxed, preferably in a quiet room prior to measurement, the arm supported at heart level and free of clothing that could impede blood flow. After 30 seconds, repeat the procedure on the same arm and average the readings if the systolic blood pressure difference is less than 10 mmHg and the diastolic blood pressure difference is less than 6 mmHg. In addition, the person should have a physical examination, with investigations such as 24-hour blood pressure monitoring in selected individuals, blood analysis (testing for sodium, potassium, chloride, bicarbonate, urea, creatinine, uric acid, haemoglobin, fasting glucose, total cholesterol, LDL cholesterol (see ‘Dyslipidaemia and atherosclerosis-promoting diet’ below), HDL cholesterol, triglycerides, liver function), urinalysis (testing for blood and protein) and an electrocardiogram. Individuals who have elevated blood pressure are assumed to have primary hypertension unless their history, physical examination or investigations indicates secondary hypertension.

Treatment of primary hypertension depends on its severity. Lifestyle modification is important for preventing
Orthostatic hypotension

Orthostatic hypotension, or postural hypotension, refers to a decrease in both systolic and diastolic arterial blood pressure on standing. Normally when an individual stands up, the gravitational changes on the circulation are compensated by mechanisms such as reflex arteriolar and venous constriction controlled by the baroreceptors and increased heart rate. Furthermore, mechanical factors such as the closure of valves in the venous system, pumping of the leg muscles and a decrease in intrathoracic pressure assist in increasing venous return in the heart. Collectively, these maintain blood pressure.

Orthostatic hypotension is often accompanied by dizziness, blurring or loss of vision and syncope (fainting) caused by insufficient vasomotor compensation and reduction of blood flow through the brain. This occurs because the normal or compensatory vasoconstrictor response to standing is absent so that there is blood pooling in the muscle vasculature, as well as in the splanchnic and renal beds.

**TABLE 23-3** Drug classifications used to treat hypertension and the variables they affect

<table>
<thead>
<tr>
<th>REDUCE STROKE VOLUME</th>
<th>REDUCE SYSTEMIC VASCULAR RESISTANCE</th>
<th>DECREASE HEART RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide diuretics</td>
<td>Combined α, β-adrenergic blockers</td>
<td>β-blockers</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>Carvedilol</td>
<td>Atenolol</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>Labetalol</td>
<td>Metoprolol</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>Angiotensin-converting enzyme (ACE) inhibitors</td>
<td>Captopril</td>
</tr>
<tr>
<td>Frusemide</td>
<td></td>
<td>Enalapril</td>
</tr>
<tr>
<td>Potassium-sparing diuretics</td>
<td>Angiotensin II receptor blockers</td>
<td>Irbesartan</td>
</tr>
<tr>
<td>Amiloride</td>
<td></td>
<td>Losartan</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Calcium channel blockers</td>
<td>Diltiazem</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme (ACE) inhibitors</td>
<td></td>
<td>Verapamil</td>
</tr>
<tr>
<td>Captopril</td>
<td>Angiotensin II receptor blockers</td>
<td>α-blockers</td>
</tr>
<tr>
<td>Enalapril</td>
<td></td>
<td>Prazosin</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>Calcium channel blockers</td>
<td>Clonidine</td>
</tr>
<tr>
<td>Irbesartan</td>
<td></td>
<td>Methyldopa</td>
</tr>
<tr>
<td>Losartan</td>
<td>Calcium channel blockers</td>
<td>Direct-acting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>vasoconstrictors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydralazine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minoxidil</td>
</tr>
</tbody>
</table>

α = alpha; β = beta.

**First choice**

ACE inhibitor (or angiotensin II receptor antagonist) or calcium channel blocker or low-dose thiazide diuretic (consider for people aged ≥ 65 years only)

**If target BP not reached**

ACE inhibitor (or angiotensin II receptor antagonist) + calcium channel blocker or ACE inhibitor (or angiotensin II receptor antagonist) + low-dose thiazide diuretic

**If target BP not reached**

Consider seeking specialist advice

**FIGURE 23-6**

Initiating drug treatment for newly diagnosed hypertension.

ACE = angiotensin-converting enzyme.
Orthostatic hypotension may be acute and temporary or chronic:

- **Acute orthostatic hypotension** is caused when the normal regulatory mechanisms are sluggish as a result of (1) altered body chemistry, (2) drug action (e.g. antihypertensives, antidepressants), (3) prolonged immobility caused by illness, (4) starvation, (5) physical exhaustion, (6) any condition that produces volume depletion (e.g. dehydration, diuresis, potassium or sodium depletion) or (7) venous pooling (e.g. pregnancy, extensive varicosities of the lower extremities). The elderly are particularly susceptible to this type of orthostatic hypotension.

- **Chronic orthostatic hypotension** may be (1) secondary to a specific disease or (2) idiopathic or primary. The diseases that cause secondary orthostatic hypotension are endocrine disorders (e.g. adrenal insufficiency, diabetes mellitus), metabolic disorders (e.g. porphyria) or diseases of the central or peripheral nervous systems (e.g. intracranial tumours, cerebral infarcts, Wernicke's encephalopathy, peripheral neuropathies). It is more prevalent in the aged population and may be attributable to an increase in mortality due to secondary effects of orthostatic hypotension, such as falls. In addition to cardiovascular symptoms, associated impotence and bowel and bladder dysfunction are common.

Although no curative treatment is available for orthostatic hypotension, often it can be managed adequately with a combination of non-pharmacological
and pharmacological therapies. For both acute and chronic forms, hypotension resolves when the underlying disorder is corrected.

**FOCUS ON LEARNING**

1. Describe the major risk factors for hypertension.
2. Summarise the pathophysiology of primary hypertension.
3. Discuss the causes of orthostatic hypotension.

### Arteriosclerosis

**Arteriosclerosis** is a chronic disease of the arterial system characterised by abnormal thickening and hardening of the vessel walls. Smooth muscle cells and collagen fibres migrate into the tunica intima (internal layer of the arterial wall), causing it to stiffen and thicken, gradually narrowing the arterial lumen (see Figure 23-8). Changes in lipid, cholesterol and phospholipid metabolism within the tunica intima also contribute to arteriosclerosis. Although these changes may be part of normal ageing, pathophysiological conditions such as hypertension, insufficient perfusion (blood flow) of tissues or weakening and outpouching of arterial walls can be exacerbated by the changes to the arterial walls brought about by arteriosclerosis.

### Atherosclerosis

**Atherosclerosis** is the most common form of arteriosclerosis. It is characterised by soft deposits of intra-arterial fat and fibrin in the vessels walls that harden over time. Atherosclerosis is not a single disease entity but rather a pathological process that can affect vascular systems throughout the body, resulting in ischaemic syndromes that can vary widely in their severity and clinical manifestations. It is the leading cause of coronary heart and cerebrovascular disease. (Atherosclerosis of the coronary arteries is described later in this chapter, and atherosclerosis of the cerebral arteries leading to heart and cerebrovascular disease is described in Chapter 9.)

#### PATHOPHYSIOLOGY

Inflammation plays a fundamental role in mediating all of the steps in the initiation and progression of atherosclerosis formation. **Atherosclerosis** begins with injury to the endothelial cells that line the artery walls. Possible causes of endothelial injury include the common risk factors for atherosclerosis, such as smoking, hypertension, diabetes mellitus, increased levels of **low-density lipoprotein** (LDL) cholesterol and decreased levels of **high-density lipoprotein** (HDL) cholesterol. Other possible causes of endothelial injury include elevated C-reactive protein (CRP), increased serum fibrinogen, insulin resistance, oxidative stress, infection and periodontal disease. There is recent evidence that individuals with a defect in the production of precursor endothelial cells in the bone marrow are at greater risk for atherosclerotic disease because these precursor cells are not available to repair injured endothelium.

Injured endothelial cells become inflamed and cannot make normal amounts of antithrombic and vasodilating substances. When the endothelium is injured, it loses the ability both to prevent clotting and to vasodilate. This results in platelets aggregating when thromboxane A2 increases (refer to Chapter 6), and the release of serotonin and endothelin combines to cause vasoconstriction. This leads to a decrease in blood flow and, ultimately, ischaemia. At the same time, sympathetic nervous system activation causes vasoconstriction when noradrenaline is released. The enzyme ACE in the endothelium also converts angiotensin I to angiotensin II (Figure 23-9 summarises these events). Collectively, this leads to vasoconstriction and increased clotting.

The next step in the formation of atherosclerosis occurs when inflamed endothelial cells express adhesion molecules that bind monocytes and other inflammatory and immune cells. Monocytes adhere to the injured endothelium and release numerous inflammatory cytokines (e.g. tumour necrosis factor-alpha [TNF-α], interferons, interleukins and C-reactive protein) and enzymes that further injure the vessel wall. **Toxic oxygen radicals generated by the inflammatory process cause oxidation** (i.e. addition of oxygen) of LDL. Oxidised LDL is engulfed by macrophages, which then penetrate into the intima of the vessel. These lipid-laden macrophages are called **foam cells** and when they accumulate in significant amounts, they form a lesion called a **fatty streak** (see Figures 23-10 and 23-11). Even small-sized lesions can be found in the walls of arteries of most people, including young children. Once formed, fatty streaks produce more toxic oxygen radicals and cause immunological and inflammatory changes resulting in progressive damage to the vessel wall.

Macrophages also release growth factors that stimulate smooth muscle cell proliferation. Smooth muscle cells in the region of endothelial injury proliferate, produce collagen and migrate over the fatty streak forming a fibrous plaque (see Figure 23-11). The fibrous plaque may calcify, protrude into the vessel lumen and obstruct blood flow to distal tissues (especially during exercise), which may cause
nutrients include those found in fruits and vegetables and omega-3 polyunsaturated fatty acids.\textsuperscript{40,41}

Coronary heart disease, myocardial ischaemia and acute myocardial infarction form a pathophysiological continuum that impairs the pumping ability of the heart by depriving the heart muscle of blood-borne oxygen and nutrients.\textsuperscript{599} We now explore how coronary heart disease results in myocardial dysfunction and possible cardiac cell death.

**RESEARCH IN FOCUS**

**Inflammatory markers for cardiovascular risk**

It is well recognised that inflammation underlies the pathophysiology of atherosclerosis and transduces the effects of many known risk factors for the disease. Although controversial, biomarkers of inflammatory status, such as tumour necrosis factor-α, interferon-γ and C-reactive protein (CRP), have lent clinical credence to the connection between inflammation biology and human atherosclerosis. Statins effectively lower LDL and CRP levels in humans. Analyses of several large studies of statins in primary- and secondary- prevention populations suggest that some of their clinical benefit accrues from an anti-inflammatory action distinct from LDL lowering although that anti-inflammatory intervention can reduce cardiovascular events independent of lipoprotein effects still requires testing. Several are underway or in the planning stage. For example, the Cardiovascular Inflammation Reduction Trial (CIRT) will test whether treatment with weekly low dose methotrexate, a regimen used successfully in the management of rheumatoid arthritis, can reduce recurrent cardiovascular events. Meanwhile, biomarkers can be used to help treat people, with, or at risk of, atherosclerosis by improving prognostication, by assessing the need for and intensity of treatment, by individualising the use of specific treatments, and by helping to develop new therapeutics.

For example, including CRP with conventional risk factors improves risk prediction for atherosclerotic events, both in people with and without established disease. Moreover, evidence accumulated demonstrates that small increases in biomarkers of inflammatory (such as CRP) can predict future cardiovascular events in apparently healthy people.

**Myocardial ischaemia**

**PATHOPHYSIOLOGY**

The coronary arteries supply blood flow sufficient to meet the demands of the myocardium during normal levels of cardiac activity, as well as when the heart is working harder (such as during exercise). Oxygen is extracted from these vessels with maximal efficiency. If demand increases, healthy coronary arteries dilate to increase the flow of oxygenated blood to the myocardium. Various pathological mechanisms can interfere with blood flow through the coronary arteries, giving rise to **myocardial ischaemia**. Narrowing of a major coronary artery by more than 50% impairs blood flow enough to interfere with cellular metabolism (see Figure 23-13).

Myocardial ischaemia develops if blood flow or oxygen content of coronary blood is insufficient to meet the metabolic demands of myocardial cells. Imbalances between coronary blood supply and myocardial demand can result from a number of conditions. The most common cause of decreased coronary blood flow and myocardial ischaemia is the formation of atherosclerotic plaques in the coronary circulation. As the plaque increases in size, it may partially occlude the vessel, thus limiting coronary flow and causing ischaemia (see Figure 23-14). This is common when metabolic demand increases, such as during exercise. Some plaques are ‘unstable’, meaning they are prone to ulceration or rupture. When this occurs, underlying tissues of the vessel wall are

---

**FIGURE 23-13**

Ischaemic events that may lead to heart failure or sudden death.
impairs the delivery of the cells and biochemicals for the immune and inflammatory responses. This same sluggish circulation makes infection following reparative surgery a significant risk. Varicose veins and chronic venous insufficiency may be associated with DVT in up to 15% of affected individuals because of changes in collateral flow and shared risk factors; therefore, anyone with new-onset varicose veins should be evaluated for the possibility of underlying DVT.

Treatment of varicose veins and chronic venous insufficiency begins conservatively and excellent wound-healing results have followed non-invasive treatments such as leg elevation, compression stockings and physical exercise.

**FOCUS ON LEARNING**

1. List the major risk factors for DVT.
2. Describe chronic venous insufficiency and the clinical presentation.

---

**TABLE 23-8 Maternal conditions and environmental exposures and the associated congenital heart defects**

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>CONGENITAL HEART DEFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td></td>
</tr>
<tr>
<td>Intrauterine</td>
<td>Patent ductus arteriosus, pulmonary stenosis, coarctation of aorta</td>
</tr>
<tr>
<td>Systemic viral</td>
<td>Patent ductus arteriosus, pulmonary stenosis, coarctation of aorta</td>
</tr>
<tr>
<td>Rubella</td>
<td>Patent ductus arteriosus, pulmonary stenosis, coarctation of aorta</td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Ventricular septal defect, cardiomegaly, transposition of the great vessels</td>
</tr>
<tr>
<td>Phenylketonuria (PKU)</td>
<td>Coarctation of aorta, patent ductus arteriosus</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>Tetralogy of Fallot, atrial septal defect, ventricular septal defect</td>
</tr>
<tr>
<td>Peripheral conditions</td>
<td></td>
</tr>
<tr>
<td>Prematurity</td>
<td>Patent ductus arteriosus, ventricular septal defect</td>
</tr>
</tbody>
</table>

---

**Paediatrics and alterations of cardiac function**

**Congenital heart disease**

Congenital heart disease (present at birth) accounts for approximately one-third of all congenital defects and is the major cause of death in the first year of life other than prematurity. The incidence varies according to the particular defect; however, the overall rate is about 75 per 10,000 births (inclusive of live births and still births with at least 20 weeks of gestational age). Several environmental and genetic risk factors are associated with the incidence of different types of congenital heart disease. Among the environmental factors are:

- maternal conditions, such as intrauterine viral infections (especially rubella), diabetes mellitus, phenylketonuria, alcoholism, hypercalcaemia, drugs (e.g. phenytoin) and complications of increased age
- antepartal bleeding
- prematurity (see Table 23-8).

Genetic factors also have been implicated in the incidence of congenital heart disease, although the mechanism of causation is often unknown. The incidence of congenital heart disease is three to four times higher in siblings of affected children and chromosomal defects account for about 6% of all cases of congenital heart disease. However, the cause of most defects is multifactorial.

Congenital heart defects can be described with respect to three principal areas:

1. **Anatomical defects** include valvular abnormalities; abnormal openings in the septa, including persistence of the foramen ovale; continued patency of the ductus arteriosus; and malformation or abnormal placement of the great vessels.

2. **Haemodynamic alterations** caused by these anatomical defects consist of (a) increases or decreases of blood flow through the pulmonary or systemic circulatory systems and (b) the mixing...
of pulmonary and systemic blood through an abnormal communication that permits flow between the two circulatory systems. The movement of blood between the normally separate pulmonary and systemic circulations is termed a shunt. Movement from the pulmonary to the systemic circulation (i.e. from the right side of the heart to the left side of the heart) is called a right-to-left shunt. Movement from the systemic to the pulmonary circulation (from the left heart to the right heart) is a left-to-right shunt. Shunt direction depends on relative pressures and resistances of the heart and surrounding vessels.

The status of tissue oxygenation is gauged by the presence or absence of cyanosis. Cyanosis is a bluish discolouration of the skin indicating that the tissues are not receiving normal amounts of oxygen, a condition known as hypoxia. Hypoxia may result from any disorder that prevents oxygen from reaching the body's cells. Ischaemia, for example, is hypoxia from lack of blood flow. Some congenital heart defects that cause hypoxia and therefore cyanosis involve a right-to-left shunt, which directs blood flow away from the lungs (see Figure 23-30). These defects are commonly called cyanotic defects. Congenital defects that do not cause cyanosis, or acyanotic defects, may involve a left-to-right shunt, which directs blood towards the lungs, or no shunt at all.

One way to categorise congenital heart defects is according to (a) whether they cause cyanosis, (b) whether they increase or decrease blood flow into the pulmonary circulation and (c) whether they obstruct blood flow from the ventricles. In the following sections we examine the most common defects (rates >10%).

**Defects with increased pulmonary blood flow**

**Ventricular septal defect**

**PATHOPHYSIOLOGY**

A ventricular septal defect (VSD) is an opening of the septal wall between the ventricles (see Figure 23-31A). VSDs are the most common type of congenital heart defect and are classified by location, either high in the septal wall of the ventricle underneath the aortic valve or low in the septal wall. They can also be located in the inlet or outlet portion of the ventricle. VSDs shunt blood from left to right. Depending on the size and location, VSDs can spontaneously close, most often within the first 2 years of life.

**CLINICAL MANIFESTATIONS**

Depending on the size, location and degree of pulmonary vascular resistance, children may have no symptoms or they may have clinical effects from...
excessive pulmonary blood flow. Clinically, children with large left-to-right shunts present with poor growth (failure to thrive) and tachypnoea (rapid breathing). If the degree of shunting is significant and not corrected, the child is at risk for developing pulmonary hypertension. Children with VSD are also at increased risk of developing endocarditis.

**Atrial septal defect**

**PATHOPHYSIOLOGY**

An atrial septal defect (ASD) is an opening in the septal wall between the two atria (see Figure 23-31B). This opening allows blood to shunt from the higher pressure left atrium to the lower pressure right atrium.

**CLINICAL MANIFESTATIONS**

Children with an ASD are usually asymptomatic. Infants with a large ASD may, in rare cases, develop pulmonary overcirculation and slow growth. Some older children and adults will experience shortness of breath with activity as the right ventricle becomes less compliant with age. Pulmonary hypertension and stroke are associated rare complications. A systolic ejection murmur and a widely split second heart sound are the expected findings on physical examination.

**EVALUATION AND TREATMENT**

Diagnosis is confirmed by echocardiography. Cardiac catheterisation may be needed to calculate the degree of left-to-right shunting. Depending on the size of the VSD and the degree of symptoms, management may be minimal. Small VSDs may close completely or become small enough that surgical closure is not required. If the infant has severe heart failure or failure to thrive that is unmanageable with medical therapy, early surgical repair is performed.

**Patent ductus arteriosus**

**PATHOPHYSIOLOGY**

Patent ductus arteriosus is failure of the fetal ductus arteriosus (the artery connecting the aorta and pulmonary artery) to close within the first weeks of life (see Figure 23-32). The continued patency of this vessel allows blood to flow from the higher pressure aorta to the lower pressure pulmonary artery, causing a left-to-right shunt.

**CLINICAL MANIFESTATIONS**

Infants may be asymptomatic or show signs of pulmonary overcirculation, such as dyspnoea, fatigue and poor feeding. There is a characteristic machinery-like murmur. Children are at risk for bacterial endocarditis and, rarely, may develop pulmonary hypertension in later life from chronic excessive pulmonary blood flow.

**EVALUATION AND TREATMENT**

Diagnosis is confirmed by echocardiography. Administration of indomethacin (a prostaglandin inhibitor) has proved successful in closing a patent ductus arteriosus in premature infants and some newborns. Surgical division of the patent ductus arteriosus needs to be performed when pharmacological therapies are unsuccessful. Closure with an occlusion device during cardiac catheterisation is performed for mostly older children. Both surgical and nonsurgical procedures can be considered low risk.
Defects with decreased pulmonary blood flow

Tetralogy of Fallot

PATHOPHYSIOLOGY

The classic form of tetralogy of Fallot includes four defects: (1) VSD, (2) pulmonary stenosis, (3) overriding aorta and (4) right ventricular hypertrophy (see Figure 23-33). The pathophysiology varies widely, depending not only on the degree of pulmonary stenosis but also on the pulmonary and systemic vascular resistance to flow. If total resistance to pulmonary flow is higher than systemic resistance, the shunt is from right to left. If systemic resistance is higher than pulmonary resistance, the shunt is from left to right. Pulmonary stenosis decreases blood flow to the lungs and, consequently, the amount of oxygenated blood that returns to the left heart. Physiological compensation to chronic hypoxia includes production of more red blood cells, development of collateral bronchial vessels and enlargement of the nail beds (clubbing).

CLINICAL MANIFESTATIONS

Some infants may be acutely cyanotic at birth. In others, progression of hypoxia and cyanosis may be more gradual over the first year of life as the pulmonary stenosis worsens. Chronic cyanosis may cause clubbing of the fingers, poor growth and squatting. Without being instructed to do so, these children squat in compensation — the squatting position traps blood in the legs and allows for greater oxygenation of blood in the central organs. Children with unrepaired tetralogy of Fallot are at risk for emboli, cerebrovascular disease, brain abscess, seizures and loss of consciousness or sudden death.

EVALUATION AND TREATMENT

Diagnosis is confirmed with echocardiography. Elective surgical repair is usually performed in the first year of life. Indications for earlier repair include increasing cyanosis or the development of hypercyanotic spells. Complete repair involves closure of the VSD, resection of the stenosis and enlargement of the right ventricular outflow tract.

Alterations of the heart wall

Disorders of the pericardium

As you will recall, the pericardium is the outer layer of the heart, having approximately 10–30 mL of pericardial fluid to lubricate and protect the heart from infection and inflammation. Inflammation of the pericardium, known as pericarditis, is usually a response to other cardiac conditions, such as acute myocardial infarction or diseases of the thorax. The most common symptom arising from pericarditis is pain. Pericardial disease is often a localised manifestation of another disorder, such as infection
metabolic acidosis may occur if renal shutdown is severe. The gastrointestinal system is sensitive to ischaemic and inflammatory injury; clinical manifestations of bowel involvement are haemorrhage, ileus (impaired gut motility), malabsorption, diarrhoea or constipation, vomiting, anorexia and abdominal pain.

The signs and symptoms of cardiac failure in the hypermetabolic, hyperdynamic phase of the syndrome are similar to those of septic shock: tachycardia, bounding pulse, increased cardiac output, decreased peripheral vascular resistance and hypotension. In the terminal stages, hypodynamic circulation with bradycardia, profound hypotension and ventricular arrhythmias may develop. Ischaemia and inflammation are responsible for the central nervous system manifestations, which include apprehension, confusion, disorientation, restlessness, agitation, headache, decreased cognitive ability and memory, and decreased level of consciousness. When ischaemia is severe, seizures and coma can occur.

EVALUATION AND TREATMENT
Because presently there is no specific therapy for multiple organ dysfunction syndrome, early detection is extremely important so that supportive measures can be initiated immediately. Frequent assessment of the clinical status of individuals at known risk is essential. Once organ failure develops, monitoring of laboratory values and haemodynamic parameters can also be used to assess the degree of impairment. Therapeutic management consists of prevention and support.

FOCUS ON LEARNING
1. Discuss important causes of septic shock.
2. Describe how systemic inflammatory response syndrome arises.
3. Explain why correction of the underlying problem is important for all kinds of shock.
4. Describe why inflammation and clotting are triggered when the vascular endothelium is injured.
5. Describe the mechanisms that result in decreased oxygen delivery to the tissues in multiple organ dysfunction syndrome.

chapter SUMMARY

Alterations of blood flow and pressure
- Hypertension is the elevation of systemic arterial blood pressure resulting from increases in cardiac output or total peripheral resistance, or both.
- Hypertension can be primary, without a known cause, or secondary, caused by an underlying disease.
- The risk factors for hypertension include a family history; being male; advancing age; obesity; high sodium intake; diabetes mellitus; cigarette smoking; and heavy alcohol consumption.
- The exact cause of primary hypertension is unknown, although several hypotheses have been proposed, including overactivity of the sympathetic nervous system; overactivity of the renin-angiotensin-aldosterone system; sodium and water retention by the kidneys; hormonal inhibition of sodium-potassium transport across cell walls; and complex interactions involving insulin resistance, inflammation and endothelial function.
- Clinical manifestations of hypertension result from damage of organs and tissues outside the vascular system. These include heart disease, renal disease, central nervous system problems and musculoskeletal dysfunction.

- Hypertension is managed with both pharmacological and non-pharmacological methods.
- Systemic hypertension in children differs from adults in aetiology and presentation.
- Orthostatic hypotension is a drop in blood pressure that occurs on standing. The compensatory vasoconstriction response to standing is replaced by a marked vasodilation and blood pooling in the muscle vasculature.
- Orthostatic hypotension may be acute or chronic. The acute form is caused by a delay in the normal regulatory mechanisms. The chronic forms are secondary to a specific disease or are idiopathic in nature.
- The clinical manifestations of orthostatic hypotension include fainting and may involve cardiovascular symptoms, as well as impotence and bowel and bladder dysfunction.
- Arteriosclerosis is a thickening and hardening of the arteries, involving the intimal layer and leading to hypertension. It seems to be a part of the normal ageing process, but it is a disease state when it occurs to the point of symptom development.
- Arteriosclerosis raises the systolic pressure by decreasing arterial distensibility and lumen diameter.
• Atherosclerosis is a form of arteriosclerosis and is the leading contributor to coronary heart disease and cerebrovascular disease.
• Atherosclerosis is an inflammatory disease that begins with endothelial injury (smoking, hypertension, diabetes mellitus [insulin resistance], dyslipidaemia) and progresses through several stages to become a fibrotic plaque.
• Once a plaque has formed, it can rupture, resulting in clot formation and instability and vasoconstriction, leading to obstruction of the lumen and inadequate oxygen delivery to tissues.
• Coronary heart disease is almost always the result of atherosclerosis that gradually narrows the coronary arteries or that ruptures and causes sudden thrombus formation and myocardial ischaemia and even infarction. Many risk factors contribute to the onset and escalation of coronary heart disease, including dyslipidaemia, smoking, hypertension, diabetes mellitus (insulin resistance), advancing age, obesity, sedentary lifestyle, psychosocial factors and heavy consumption of alcohol.
• The three risk factors most predictive of coronary heart disease are hypercholesterolaemia, cigarette smoking and hypertension.
• Coronary heart disease is most commonly the result of atherosclerosis to the coronary arteries and the resultant decrease in myocardial blood supply.
• Angina pectoris is chest pain caused by myocardial ischaemia.
• Therapeutic interventions for coronary heart disease include the use of vasodilators and medications to reduce cardiac workload (e.g. β-blockers), as well as surgical procedures.
• Atherosclerotic plaque progression can be gradual, but sudden coronary obstruction due to thrombus formation causes the acute coronary syndromes. These include unstable angina and myocardial infarction.
• Unstable angina results in reversible myocardial ischaemia.
• Myocardial infarction is caused by prolonged, unrelieved ischaemia that interrupts blood supply to the myocardium. After about 20 minutes of myocardial ischaemia, irreversible hypoxic injury causes cellular death and tissue necrosis.
• Myocardial infarction is clinically classified as non-ST elevation myocardial infarction (non STEMI) and ST elevation myocardial infarction (STEMI), based on ECG findings that suggest the extent of the myocardial damage (subendocardial versus transmural).
• An increase in plasma enzyme levels is used to diagnose the occurrence of myocardial infarction and indicate its severity. Elevations of the creatine kinase-myocardial band (CK-MB), troponins and lactic dehydrogenase (LDH) are most predictive of a myocardial infarction.
• Treatment of a myocardial infarction includes revascularisation (thrombolitics or percutaneous coronary intervention), antithrombotics, ACE inhibitors and β-blockers. Pain relief and fluid management are also key components of care. Arrhythmias and cardiac failure are the most common complications of acute myocardial infarction.

• An aneurysm is a localised dilation of a vessel wall, to which the aorta is particularly susceptible.
• A thrombus is a clot that remains attached to a vascular wall. Arteriosclerosis can generate thrombus formation through roughening of the intima that activates the coagulation cascade. Thrombus formation may be discrete or diffuse.
• An embolus is a mobile aggregate of a variety of substances that occludes the vasculature. Sources of emboli include clots, air, amniotic fluid, bacteria, fat and foreign matter. These emboli cause ischaemia and necrosis when a vessel is totally blocked.
• Emboli to the central organs cause tissue death in lungs, kidneys and mesentery.
• Deep venous thrombosis results from stasis of blood flow, endothelial damage or hypercoagulability. The most serious complication of deep venous thrombosis is pulmonary embolism.
• Varicosities are areas of veins in which blood has pooled, usually in the saphenous veins.
• Varicosities may be caused by damaged valves as a result of trauma to the valve or by chronic venous distension involving gravity and venous constriction.
• Chronic venous insufficiency is inadequate venous return over a long period of time that causes pathological ischaemic changes in the vasculature, skin and supporting tissues.
• Venous stasis ulcers follow the development of chronic venous insufficiency and probably develop as a result of the borderline metabolic state of the cells in the affected extremities.

Alterations of cardiac function

• Most congenital heart defects have begun to develop by the eighth week of gestation and some have associated causes, both environmental and genetic.
• Environmental risk factors associated with the incidence of congenital heart defects typically are maternal conditions. Maternal conditions include viral infections, diabetes, drug intake and advanced maternal age.
• Classification of congenital heart defects is based on whether they cause: (a) blood flow to the lungs to increase, decrease or remain normal; (b) cyanosis; and (c) obstruction to flow.
• Cyanosis, a bluish discolouration of the skin, indicates that the tissues are not receiving normal amounts of oxygenated blood. Cyanosis can be caused by defects that: (a) restrict blood flow into the pulmonary circulation; (b) overload the pulmonary circulation, causing pulmonary hypertension, pulmonary oedema and respiratory difficulty; or (c) cause large amounts of deoxygenated blood to shunt from the pulmonary circulation to the systemic circulation.
• Congenital defects that maintain or create direct communication between the pulmonary and systemic circulatory systems cause blood to shunt from one system to another, mixing oxygenated and deoxygenated blood and increasing blood volume and, occasionally, pressure on the receiving side of the shunt.
• The direction of shunting through an abnormal communication depends on differences in pressure and resistance between the two systems. Flow is always from an area of high pressure to an area of low pressure.

• Acyanotic congenital defects that increase pulmonary blood flow consist of abnormal openings (atrial septal defect, ventricular septal defect, patent ductus arteriosus or ativoventricular septal defect) that permit blood to shunt from left (systemic circulation) to right (pulmonary circulation). Cyanosis does not occur because the left-to-right shunt does not interfere with the flow of oxygenated blood through the systemic circulation.

• If the abnormal communication between the left and right circuits is large, volume and pressure overload in the pulmonary circulation lead to left heart failure.

• Initial treatment for congenital heart disease, depending on the defect, is aimed at controlling the level of congestive heart failure or cyanosis. Intervential procedures in the cardiac catheterisation laboratory and surgical palliation or repair are performed to restore circulation to as normal as possible.

**Alterations of the heart wall**

• Inflammation of the pericardium, or pericarditis, may result from several sources (infection, drug therapy, tumours). Pericarditis presents with symptoms that are physically troublesome, but in and of themselves they are not life-threatening.

• Fluid may collect within the pericardial sac (pericardial effusion). Cardiac function may be severely impaired if the accumulation of fluid occurs rapidly and involves a large volume.

• The cardiomyopathies are a diverse group of primary myocardial disorders that are usually the result of remodelling, neurohumoral responses and hypertension. The cardiomyopathies are categorised as dilated, hypertrophic and restrictive. The size of the cardiac muscle walls and chambers may increase or decrease depending on the type of cardiomyopathy, thereby altering contractile activity.

• The haemodynamic integrity of the cardiovascular system depends to a great extent on properly functioning cardiac valves. Congenital or acquired disorders that result in stenosis, incompetence or both can structurally alter the valves.

• Characteristic heart sounds, cardiac murmurs and systemic complaints assist in determining which valve is abnormal. If severely compromised function exists, a prosthetic heart valve may be surgically implanted to replace the faulty one.

• Mitral valve prolapse is a common finding, especially in young women. Although not grossly abnormal, the mitral valve leaflets do not position themselves properly during systole. Mitral valve prolapse may be a completely asymptomatic condition or can result in unpredictable symptoms. Afflicted valves are at greater risk for developing infective endocarditis.

• Rheumatic fever is an inflammatory disease that results from a delayed immune response to a streptococcal infection in genetically predisposed individuals. The disorder usually resolves without sequelae if treated early.

• Severe or untreated cases of rheumatic fever may progress to rheumatic heart disease, a potentially disabling cardiovascular disorder.

• Infective endocarditis is a general term for infection and inflammation of the endocardium, especially the cardiac valves. The most common cause of infective endocarditis is *Staphylococcus aureus*, followed by *Streptococcus viridans*. In the mildest cases, valvar function may be slightly impaired by vegetations that collect on the valve leaflets. If left unchecked, severe valve abnormalities, chronic bacteræmia and systemic emboli may occur as vegetations break off the valve surface and travel through the bloodstream. Antibiotic therapy can limit the extension of this disease.

**Alterations of cardiac conduction**

• Arrhythmias are disturbances of heart rhythm. Arrhythmias range in severity from occasional missed beats or rapid beats to disturbances that impair myocardial contractility and are life-threatening.

• Arrhythmias can occur because of an abnormal rate of impulse generation or the abnormal conduction of impulses.

• Atrial fibrillation is the most common arrhythmia and is most prevalent in the elderly.

**Heart failure**

• Heart failure is an inability of the heart to supply the metabolism with adequate circulatory volume and pressure.

• Left heart failure (congestive heart failure) can be divided into systolic and diastolic heart failure.

• Systolic heart failure is caused by increased preload, decreased contractility or increased afterload.

• The most common causes of systolic heart failure are myocardial infarction, fluid overload, hypertension or valvular disease.

• In addition to the haemodynamic changes of systolic heart failure, there is a neuroendocrine response that tends to exacerbate and perpetuate the condition.

• The neuroendocrine mediators include the sympathetic nervous system and the renin-angiotensin-aldosterone system; thus, diuretics, β-blockers and ACE inhibitors are important components of the pharmacological therapy.

• Diastolic heart failure is a clinical syndrome characterised by the symptoms and signs of heart failure, a preserved ejection fraction and normal diastolic function.

• Diastolic dysfunction means that the left ventricular end-diastolic pressure is increased, even if volume and cardiac output are normal.

• Right heart failure is usually the result of chronic pulmonary hypertension caused by left heart failure or chronic hypoxic lung disease.

**Shock**

• Shock is a widespread impairment of cellular metabolism involving positive feedback loops that places the individual on a downward physiological spiral leading to the multiple organ dysfunction syndrome.

• Types of shock are cardiogenic, hypovolaemic, neurogenic, anaphylactic and septic. The multiple organ
dysfunction syndrome can develop from all types of shock.

- The final common pathway in all types of shock is impaired cellular metabolism — cells switch from aerobic to anaerobic metabolism. Energy stores drop and cellular mechanisms relative to membrane permeability, action potentials and lysosome release fail.
- Anaerobic metabolism results in activation of the inflammatory response, decreased circulatory volume and decreasing pH.
- Impaired cellular metabolism results in cellular inability to use glucose because of impaired glucose delivery or impaired glucose intake, resulting in a shift to glycogenolysis, gluconeogenesis and lipolysis for fuel generation.
- Glycogenolysis is effective for about 10 hours. Gluconeogenesis results in the use of proteins necessary for structure, function, repair and replication, which leads to more impaired cellular metabolism.
- Gluconeogenesis contributes to lactic acid, uric acid and ammonia build-up, interstitial oedema and impairment of the immune system, as well as general muscle weakness leading to decreased respiratory function and cardiac output.
- Cardiogenic shock is decreased cardiac output, tissue hypoxia and the presence of adequate intravascular volume.
- Hypovolaemic shock is caused by loss of blood or fluid in large amounts. The use of compensatory mechanisms may be vigorous, but tissue perfusion ultimately decreases and results in impaired cellular metabolism.
- Neurogenic shock results from massive vasodilation, causing a relative hypovolaemia, even though cardiac output may be high, and results in impaired cellular metabolism.
- Anaphylactic shock is caused by physiological recognition of a foreign substance. The inflammatory response is triggered and a massive vasodilation with fluid shift into the interstitium follows. The relative hypovolaemia leads to impaired cellular metabolism.
- Septic shock begins with impaired cellular metabolism caused by uncontrolled septicemia. The infecting agent triggers the inflammatory and immune responses. This inflammatory response is accompanied by widespread changes in tissue and cellular function.
- Multiple organ dysfunction syndrome is the progressive failure of two or more organ systems after a severe illness or injury. It can be triggered by chronic inflammation, necrotic tissue, severe trauma, burns, adult respiratory distress syndrome, acute pancreatitis and other severe injuries.
- Multiple organ dysfunction syndrome involves the stress response; changes in the vascular endothelium resulting in microvascular coagulation; release of complement, coagulation and kinin proteins; and numerous inflammatory processes. The consequences of all these mediators are an altered blood flow distribution, hypermetabolism, hypoxic injury and myocardial depression.
- Clinical manifestations of the multiple organ dysfunction syndrome include inflammation, tissue hypoxia and hyperpermeability. All organs can be affected, including the kidneys, lungs, liver, gastrointestinal tract and central nervous system.

**CASE STUDY**

**ADULT**

A 52-year-old man, Shannon, who is fit and lean because he trains for an Ironman triathlon, begins to complain of intermittent headaches, dizziness and for the most part, several epistaxis episodes. He visits his doctor for advice thinking perhaps he is overtraining. The following vital signs are recorded: temperature 36.1°C, pulse 106 beats per minute, ventilation rate 20 breaths per minute, blood pressure 168/98 mmHg. Shannon is 184 cm tall and weighs 81 kg.

He relates that he has a highly stressful job, is trying to train for an Ironman triathlon, married and is a father of two young children (ages 12 and 8 years). He says that it is difficult to eat right all of the time; however, he tries to follow a healthy, balanced diet to allow him the right energy intake for his exercise regime. Shannon considers himself to be an over-achiever, placing high demands on his outcomes. He further adds that his father died of a stroke at age 60 years and that his mother died at age 75 years from a heart attack. He has two brothers, both older, and they both have coronary heart disease. He also reveals that he used to smoke cigarettes (½ pack a day) and was overweight (>100 kg) until the age of 44 years when he started his ‘get-fit’ campaign. He has completed six Ironman distances races since the age of 44 years.

1. **What are the major complaints of this patient?**
2. **What is your diagnosis?**
3. **What key points on his physical examination led to this diagnosis?**
4. **What modifiable risk factors correlate with this cardiovascular disease?**
5. **What non-modifiable risk factors correlate with this cardiovascular disease?**
CASE STUDY

AGEING

A 70-year-old Caucasian woman, Betty, presented at the Emergency Department with sudden onset chest pain. She described the pain as a severe burning sensation that radiated across the chest to the shoulders, neck and jaw region. Betty also complained of nausea and epigastric discomfort. She was treated immediately with nitroglycerin and was placed on oxygen via nasal canula. This treatment provided partial relief, however the pain persisted.

Observations were taken and it was revealed that Betty was a pack-a-week cigarette smoker, suffered from hypertension and mild-to-moderate obesity. Cardiac catheterisation was scheduled and it was found that there was an 85% blockage of the right coronary artery. Betty then underwent a PTCA to open up the coronary artery blockage. She was then discharged and progressed well on an exercise program and tolerated physical activity.

1. What coronary risk factors are present for Betty?
2. Is the patient’s chest pain syndrome typical or atypical for women? Why or why not?
3. What is the common picture of a woman’s cardiac status when referred for coronary artery bypass graft (CABG) surgery?
4. Why can chest pain radiate to other body areas (e.g. neck, jaw, arm)?
5. What impact does cigarette smoking have on coronary heart disease?

REVIEW QUESTIONS

1. Describe the factors involved in the development of primary hypertension.
2. Outline the pathogenesis of atherosclerosis.
3. Discuss the risk factors associated with coronary heart disease.
4. Describe the pathophysiological events leading to myocardial ischaemia and infarction.
5. Differentiate between thrombus and embolism.
6. List the different types of congenital heart malformations and contrast defects that increase and decrease pulmonary blood flow.
7. Discuss the differences in disorders of the pericardium, myocardium and endocardium.
8. Differentiate between life-threatening and other arrhythmias.
9. Outline the differences between systolic and diastolic heart failure.
10. Provide brief descriptions of anaphylactic, cardiogenic, hypovolaemic, neurogenic and septic shock to highlight the pathophysiological differences.