Diseases in the Elderly

Age-Related Changes and Pathophysiology

Nages Nagaratnam
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Preface

The elderly have been categorised as young old between the ages of 65 and 74 years, old old between 75 and 84 years and oldest old those above 85 years and over. Current demographic data predicts an increase in the elderly population worldwide. The oldest old group is said to be a rapidly growing segment of the population and is expected to grow nearly 4 % per annum in Australia. In the United States the oldest old is projected to double from 4.3 to 9.6 million by 2030. This trend has resulted in the alarming increase in prevalence of disease, patients with multiple pathologies and the alarming rise of care-demanding conditions such as dementia. As age advances there are innumerable problems confronting the elderly. The perception that all old people require care over extended periods of their lives is at variance with known facts. The majority of old people remain independent for the remaining years of their life. Several studies have highlighted the divergent attitudes between the health professionals towards elderly people, and many tend to discriminate against people because they are old. This has often compromised the quality of care older people receive.

Epidemiological data emphasise the value of studies which compel the need to broaden and disseminate knowledge about age-related problems especially in the very old. Understanding the ageing process and its consequences is of prime importance in identifying the health-care challenges posed by the growing elderly population. A proper understanding of the changes relating to ageing and their significance is necessary to develop appropriate corrective/remedial strategies. *Diseases in the elderly: Age-related Changes and Pathophysiology* provides a comprehensive overview of the two important issues relating to disease in elderly. The book has a strong focus on age-related changes and the pathophysiology of the disease in the elderly. Adequate knowledge of the structural and physiological changes that occur with ageing and the underlying pathophysiology of diseases in the elderly is a prerequisite for the proper understanding and forms a rational basis for the diagnosis and treatment of disease in the elderly. Apart from providing intense information on a given subject, it also provides means for self assessment which is composed of multiple-choice questions, short answer questions and extended matching questions. The questions have been largely based on the text. Since readers' time is often restricted, this book provides a bulleted box with key points at the end of each section.

The book contains 19 chapters which are arranged by organ system and structured to cover the specific areas. Many sections follow a common pattern with

headings and subheadings. The text offers the primary care physician, junior hospital doctors, medical undergraduates and specialist nurses and others working in aged-care settings a systematic approach to geriatric medicine. The intent is to provide information where interest demands, extending the 'aims and scope' of the book to anatomy and physiology and beyond. We strive to be concise and thorough in our approach to the stipulated areas.

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Contents

Cardiovascular Disease and Related Disorders in the Elderly

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1.1 Anatomical and Physiological Changes with Ageing

Tissue integrity and competency of systolic and diastolic function normally depends on the extracellular collagen concentration [1]. With ageing, there is an abnormal increase in the extracellular fibrillar collagen which contributes to myocardial stiffness [1] and decrease in compliance [2]. Normal early diastolic function is compromised and diastolic pressures increase leading to left ventricular diastolic dysfunction [3]. Animal studies and cultured cardiac fibroblasts have indicated that myocardial fibrosis is associated with chronic mineralocorticoid excesses relative to sodium intake and excretion [4]. Aldosterone plays a crucial role in the development of cardiac fibrosis [5].

Although there is a loss of myocytes with advancing age, the left ventricular wall thickens with age in both men and women due to increase in size of remaining cardiac myocytes [6], but there is no increase in the left ventricular mass [7]. As age advances, about 35 % of myocytes are lost [8]. The left ventricular (LV) diastolic filling rate decreases to a 50 % of the peak rate by the age of 80 [9]. The LV end-diastolic volume does not reduce with age due to the forceful contractility of the left atrium and this enhanced atrial contribution to ventricular filling is associated with left atrial hypertrophy. Resting left ventricular systolic function (ejection fraction and/or stroke volume) is not altered by ageing nor is the resting cardiac output [10]. The maximum heart rate decreases during exercise with age [10–12]. Furthermore, significant changes occur in cardiovascular function in ageing healthy adults during exercise [12]. There is resetting of the baroreceptor reflex in the elderly.

The beta-adrenergic responsiveness decreases with age limiting the maximum achievable heart rate (HR) [2]. Due to the reduced maximal heart rate and the limit to increase contractility in response to beta-adrenergic blockade in the elderly, the exercise cardiac output may be reduced and the heart partially compensates for this by exercise-induced dilatation of the left ventricle [13]. Both at rest and on exercise, the incidence of cardiac arrhythmias increases with age [14]. Numerous alterations

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occur in the heart and vessels as a result of deregulation of molecular longevity pathways resulting in compromised function [15]. About 80 % of old people have aortic valvular sclerosis and moderate to severe aortic incompetence is present in 16 % [16]. Mitral annular calcification increases with advancing age [17]. The blood supply of the tissues and cardiovascular function is influenced by structural changes to the peripheral vessels with ageing [13]. Some researchers had advocated cautious interpretation of these age-associated changes in cardiac performance since they may be age-related diseases rather than primarily the ageing process [17]. It is likely that cardiovascular ageing involves mechanisms which are the result of a variety of insults such as oxidative stress, inflammation, non-enzymatic glycation and changes in the cardiovascular genes [18].

Normal ageing is associated with both physiological and structural changes in the arterial vasculature which have functional implications. There is increase in the size of the lumen and increased wall thickness with stiffening mainly involving the arteries [19]. With age, arterial calcification together with changes in the elastin collagen balance leads to generalised thickening of the conduit arteries [20]. The stiffening of the vasculature results in an age-related shift of the velocity of the reflected pulse wave from diastole to late systole [20]. This leads to increased systolic workload for the heart, decreased coronary perfusion and transmission of higher pressures to the end organs [21]. The stiffening leads to left ventricular hypertrophy, renal impairment and cerebrovascular disease [21]. With age, the walls of the peripheral vessels become thicker and stiffer [22]. Likewise, the walls of the veins become thicker due to increase in the connective tissue and calcium deposits [22]. Table 1.1 summarises the anatomical and physiological changes with ageing.

Box 1.1. Key Points. Cardiovascular Changes with Ageing

- Increase in extracellular fibrillar collagen [1].
- Loss of myocytes and increase in size of remaining myocytes [6, 8].
- Fibrous tissue of the skeleton of the heart becomes sclerotic and calcifies ([4, 5] and Table 1.1).
- Left ventricular wall thickens, left atrium hypertrophies, valves calcify [17, 21].
- Fibrous tissue in the conducting system increases (see Table 1.1).
- Beta-adrenergic responsiveness decreases [2].
- Large artery walls thicken [22].

1.2 Heart Failure

Introduction

Heart failure is a progressive disorder, acute or insidious in onset, due to ventricular dysfunction resulting from a decline in pump failure [26]. In the population all over the world, heart failure is most prevalent in the 75 years and over age group [27]. Heart failure is the major cause of disability in the elderly and increasing age itself is a risk factor in its development. The incidence of congestive heart failure among

Table 1.1 Anatomical and physiological cardiac changes with ageing

Anatomical	Physiological	Results
Myocardium		
Cardiac myocytes increase in size	Afterload increased, early diastolic filling impaired	Reduced up to 50 % by 80 years
changes in collagen and left ventricular thickness	Increased atrial contractility	Hypertrophy of atrium
	End-diastolic volume increased at rest	
Fibrous skeleton – sclerotic, calcifies		Mitral annular calcification and aortic valve calcifies
Amyloid deposition	Systolic and diastolic dysfunction	Arrhythmias, conduction defects, restrictive myocardial changes
Pacemaker		
Increased elastic and collagen tissue in conducting system	Beta-adrenergic responses to the heart decreased	Maximal HR is limited
		Decreased contractility of myocardium, cardiac output decreased
	Duration of contractility lessened, spill over of catecholamines responses to beta-adrenergic receptor stimulation	Further reduction of contractility of myocardium
Valves		
Collagen tissues – sclerotic + calcification of cardiac skeleton aortic and mitral annulus – nodular thickenings at closure lines of valves and summit of intraventricular septum. Valves calcify and/or become myxomatous	Aortic sclerosis mitral insufficiency AV conduction abnormalities	Aortic sclerosis, mitral incompetence, AV node, AV bundle, bifurcation, proximal L and R BB may be affected
Arterial system		
Intimal hyperplasia and thickening	Decrease in compliance	Increased stiffness
Increased peripheral vascular resistance	Increase in blood pressure	Systolic and diastolic hypertension
Elastic content decreases	Increase in systolic pressure	Systolic hypertension
Endothelial dysfunction	Structural changes	Reduced endothelium-dependent vasodilatation

Information sources: Aalami et al. [2]; Burlew [3]; Olivetti et al. [4]; Lakata [15, 21, 22]; Esler et al. [23]; Taddei et al. [24]; Stamato et al. [25]

community-dwelling elderly is 7–8 % after the age of 75 [28]. Its prevalence is likely to increase over the next few decades with the increase in world population, and in the over 65 years. The elderly are inclined to developing chronic heart failure as a result of age-related changes in the cardiovascular system and high prevalence of coronary heart disease and hypertension [29].

Age-related cardiovascular changes

With ageing, there is abnormal increase in the extracellular fibrillar collagen giving rise to increased myocardial stiffness adversely affecting myocardial elasticity leading to systolic and diastolic dysfunction [30]. Age-related changes in the cardiovascular system and function may lower the threshold at which cardiac disease becomes evident [31]. Many changes occur in the cardiovascular system such as decreased heart rate, reduced cardiac output and systolic hypertension. Due to age-related changes in the sarcoplasmic reticulum, myocardial relaxation is slowed [32]. There is increased thickness of the muscle wall of both ventricles due to the increased myocyte size [33]. The heart rate is unchanged at rest and early diastolic filling is reduced; however, an enhanced atrial contraction helps to maintain ventricular filling at a normal volume. With exercise, there is an age-related reduction in heart rate [34, 35], but the cardiac output is maintained during exercise by an augmentation of stroke volume brought about by cardiac dilatation at end diastole and end systole. However, many studies concluded that the cardiac output decreases with advancing age [36]. There is a decreased responsiveness to beta-adrenergic modulation [31], and beta-adrenergic stimulation enhances the strength of contraction but decreases its duration thus permitting relaxation and proper filling. Decreased conservation of sodium and changes in the baroreceptor reflex function may bring about postprandial and orthostatic hypotension in some individuals [32]. The maximum exercise level (VO_2 max) decreases with age, and this is largely due to decrease in the skeletal muscle mass [37]. In addition to these, there are changes in hepatic and renal function with advancing age.

Pathophysiology of chronic heart failure

In heart failure, the ventricular dysfunction results in an inability of the ventricles either to eject or to fill [38]. Thus, there are two types of heart failure, one as a result of the systolic dysfunction resulting in systolic heart failure with ejection fraction less than 40 % and the other diastolic dysfunction resulting in diastolic heart failure with normal ejection fraction. The term diastolic heart failure is now largely replaced by the more favoured term, heart failure with preserved ejection fraction (HF-PEF). In many patients, both systolic and diastolic dysfunction coexist.

The ventricular end-diastolic pressure increases as a result of both systolic and diastolic dysfunction, thereby enhances the force of contraction and consequently the stroke volume [39]. With progression of systolic and diastolic dysfunction, the ability of this mechanism is enfeebled and the stroke volume can decline considerably resulting in reduction of the cardiac output [26]. Diastolic heart failure is the result of altered ventricular relaxation and abnormal ventricular filling.

Several compensatory neurohormonal mechanisms are activated with the reduction in the cardiac output [40]. Although these compensatory mechanisms provide benefit for the heart in normal physiological situations, they can intensify the progression of chronic heart failure [39, 40]. The neurohormonal mechanisms include increase in sympathetic activity, the renin-angiotensin-aldosterone system [28, 37], the antidiuretic hormone-vasopressin system and atrial natriuretic peptide [39, 40]. The eventual result of these responses is arterial and venous constriction [39].

Angiotensin II is a strong vasoconstrictor of renal and systemic circulation leading to release of aldosterone which causes retention of sodium and water and increased loss of potassium [40]. The natriuretic peptides (atrial, brain and C-type) exert a wide range of effects on the heart, kidneys and the central nervous system [40].

Box 1.2. Key Points. Heart Failure in the Elderly

- With ageing, heart rate decreases, cardiac output reduces, systolic BP elevates.
- Decreased responsiveness to beta-adrenergic modulation [2, 31].
- Maximum exercise level (VO_2 max) decreases [37].
- Ventricular end-diastolic pressure increases following systolic and diastolic dysfunction [39].
- Several compensatory neurohormonal mechanisms are activated which can intensify the progression of chronic heart failure [40].
- Combined right and left ventricular failure most common.

1.3 Cardiac Arrhythmias in the Elderly

Introduction

Cardiac arrhythmias comprise any abnormality that hinders the initiation and/or progression of normal activation of the myocardium [41]. Cardiac arrhythmias are a large concern among the elderly, and they occur so frequently that they are often regarded as "normal" and inevitable part of the ageing process [42]. Not only are cardiac arrhythmias more frequent than in the younger age group, they are influenced by certain aspects of aetiology, pathophysiology, diagnoses and treatment [43].

Ageing and the conduction system

A number of characteristic morphological, histological and biochemical changes are associated with ageing of the heart [44]. Both the sinus and AV nodes decrease in size [45]. There is a reduction in the number of cells with increase in collagen fibres which is more evident in the SA node and less so in the AV node and the bundle of His [46]. There is a reduction in the number of myocytes of the conduction tissue with development of cardiac fibrosis [44]. The electrical characteristics of the conducting system also change with age together with cardiac calcium regulation [47]. There is a slow inward current caused by calcium and alterations in potassium conductance resulting in transmembrane electrical ageing changes [45]. The heart rate (HR) is generally not affected by ageing, but the responsiveness to stress and exercise especially is decreased limiting the maximum achievable heart rate. The atrial depolarisation results in the P wave. Normally, the cardiac impulse is physiologically delayed in the AV node thereby the ventricles are protected from being depolarised, during supraventricular tachycardia. With healthy ageing, the time of conduction through the AV node is increased and hence the P-R interval increases with age.

Pathophysiology

The conducting system consists of three parts, the sinoatrial (SA) node, the atrioventricular (AV) node and bundle of His, bundle branches and the Purkinje network. The conducting system is composed of specialised myocytes [48] which are capable of generating and conducting the cardiac impulse from the atria to the ventricular chambers [49]. The myocytes are connected to each other by intercalated discs and play an important role in the electrical conducting system [50]. The SA node initiates the conduction of the cardiac impulse [51]. There are no specialised conducting tracts between sinus node and AV node [52]. The bundle of His originates from the distal portion of the AV node [53] which consists of specialised cells surrounded by a fibrous collar [54] that penetrates the right fibrous trigone [48] and courses through the membranous septum and bifurcates into the right and left bundle branches. The left bundle branch in turn bifurcates into the left anterior and posterior fascicles [51], and the bundle branches end in the Purkinje system of both the ventricles. The Purkinje fibres are long strands of barrel-shaped cells called Purkinje myocytes.

The cardiac impulse originates in the SA node and activates both atria which depolarises spontaneously resulting in the P wave on the electrocardiogram (ECG). The impulse travels through the right atrium after some delay [55] to the AV node resulting in the P-R interval on the ECG. It is then conducted through the AV node to the bundle of His and bundle branches to the Purkinje system and activates both ventricles. The conducting system of the heart is innervated by both the sympathetic and parasympathetic nervous system. Sympathetic stimulation increases the automaticity and enhances conduction. The parasympathetic (vagal) stimulation decreases sinus node automaticity and slows atrioventricular conduction [50]. There is considerable variation in the resting heart rate among healthy asymptomatic population.

There is an increase risk and severity of arrhythmias with increasing age [47]. The common conditions affecting the conducting system by altering impulse formation or impulse propagation or both are age-related degeneration, myocardial infarction, procedural complications of drug toxicity [56]. The dysregulation of intracellular calcium probably plays an important role in producing electrical instability [47]. The reason for the increased incidence of atrial and ventricular ectopic beats is unclear. This increase may be related in part to increase in atrial size in the occurrence for the atrial arrhythmias and the increase in ventricular beats to the age-associated increase in the left ventricular mass and catecholamine levels [57]. Two different fundamental disturbances, namely, alterations in impulse formation (automaticity) or alterations of impulse propagation, can result in bradyarrhythmias and tachyarrhythmias [57]. Focal or nonfocal mechanisms may be involved [19], and an abnormal impulse initiation can result from either automaticity caused by normal or abnormal automatic mechanisms (focal mechanism) or by triggered activity [41, 58]. Nonfocal mechanisms are diverse forms of re-entry due to circus movement [58]. The bradyarrhythmias are the result of abnormalities of the intrinsic automatic behaviour or conduction which impair sinoatrial or the atrioventricular conduction causing partial or total conduction

block [57]. The tachyarrhythmias may arise from altered automaticity (occurring in ordinary atrial or ventricular myocardium) or triggered activity (due to early or delayed afterdepolarisations) [41, 57, 58] and re-entry [58]. Most clinically significant tachyarrhythmias are probably due to re-entry.

Box 1.3. Key Points. Cardiac Arrhythmias in the Elderly

- Reduction of myocytes of the conduction tissues with development of cardiac fibrosis [44, 46].
- Electrical characteristics of the conducting system change [47].
- Alterations in impulse formation (automaticity) and impulse propagation [50].
- Common conditions affecting the conducting system are age-related degeneration, myocardial infarction and procedural complications and drug toxicity [56].
- Supraventricular ectopics may be related to age-related atrial size and increase in ventricular beats to age-related increase in left ventricular mass and catecholamines [57].
- Tachyarrhythmias may rise from altered automaticity or triggered activity and re-entry [41, 8].
- Bradyarrhythmias result from abnormalities of intrinsic automatic behaviour or conduction [57].

1.4 Infective Endocarditis in the Elderly

Introduction

Infective endocarditis can be defined as an infection of the endocardium which may affect the valves and involve the myocardium. The incidence of infective endocarditis (IE) is increasing in older patients. This is due to an increase in the life expectancy and general ageing of the population, longer survival of patients with congenital and valvular disease of the heart, the use of intravenous catheters and prosthetic devices [59], proliferation of invasive procedures [60] and higher prevalence of hospital-acquired bacteraemia [61, 62]. More than 50 % of the cases with IE occur in persons over the age of 60 with high-risk profile.

Pathophysiology and pathogenesis

It is customary to categorise IE into acute and subacute forms based largely on the severity of the disease and its course [63]. There is often no clear distinction between the typical acute IE which is usually abrupt in onset and rapidly progressive affecting even normal hearts and the subacute IE which usually begins insidiously and progresses over weeks to months [64] and where the heart has some underlying pathology. This subdivision however still has clinical value.

The development of infective endocarditis giving rise to vegetations occurs in areas of increased turbulence and eddy currents (on the atrial side of the atrioventricular valves and on the ventricular surface of the semilunar valves) or in lower pressure side of the defect in non-valvular congenital defects [63]. For example, atrial septal defect or in the case of mechanical prosthesis, the vegetations occur usually along the margin of the sewing ring causing a ring abscess and sometimes paravalvular perforation [63]. *Streptococci* adhere to the cardiac valves with pre-existing endothelial lesions [65], whereas Staphylococcus aureus not only settle on the damaged endothelium but also invade intact endothelium [65, 66]. These interactions are mediated by several surface adhesins [65]. The inflamed endothelia produce cytokines, integrins and tissue factor which in turn draw monocytes, platelets and integrins, and the bacteria attaching to these structures become embedded and protected from host defences [66]. The vegetations in acute IE tend to be larger and more often involve the normal valves and may cause perforation of the valve leaflet and sometimes erode into the underlying myocardium to produce paravalvular abscesses [63]. In a study of 44 elderly patients with IE, the mitral valve was affected in 45 %, aortic in 32 % and both in 5 % [67].

Streptococcus sp. is the most common cause and accounts for 25–75 % of endocarditis cases, *S. viridans* is less prevalent in older patients and *S. bovis*, a non-enterococcal group D streptococcus, is the causative organism in up to 25 %. In approximately 80 % of cases, the predominant organisms in the elderly population are *streptococci* and *staphylococci* [68]. *Staphylococcus aureus* has become the primary pathogen of endocarditis with the present-day use of intravascular devices [69, 70], and elderly diabetic patients are at increased risk of bacteraemia and IE [71]. Recently, many studies have shown a trend towards increasing incidence of *Staphylococcus aureus* IE [72, 73]. *Enterococci* can account for 25 % in the elderly and some studies have noted a high prevalence in the elderly [74]. Other commonly encountered organisms are the HACEK organisms (*Haemophilus parainfluenzae, Haemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella species* and *Kingella species*) [75].

The portal of entry and subsequent consequences of microbiology show specific features of IE in the elderly as compared with younger patients [76, 77]. Manipulations or procedures of oral cavity, genitourinary tract (prostatic and vesical disease) and gastrointestinal tract (colonic lesions) commonly produce transient bacteraemia involving streptococci and staphylococci.

Box 1.4. Key Points. Infective Endocarditis in the Elderly

- *Streptococcus* spp. is the most common cause in older patients [68].
- *Staphylococcus aureus* is increasing with present-day use of intravascular devices [72, 73].
- *Enterococci* accounts for 25 % in the elderly [74].
- Portal of entry – manipulations or procedures of oral cavity, genitourinary tract, gastrointestinal tract is commonly associated with *streptococci* or *staphylococci* bacteraemia [76, 77].

1.5 Coronary Artery Disease in the Elderly

Introduction
Coronary artery disease is characterised by the presence of atherosclerosis of the epicardial coronary arteries. Coronary artery disease (CAD) is the most common form of heart disease in the world today. Its prevalence increases with age affecting about two-third of men and women in the sixth decade and accounts for significant morbidity and mortality in the elderly. CAD accounted for 51 % of all cardiovascular deaths and half of them were from acute myocardial infarction [78].

Pathophysiology
Atherosclerosis is by far the commonest cause of coronary artery disease. Age is an important risk factor. Atherosclerosis is primarily typified by the formation of intimal plaques called *atheroma.* A chain of events leads to the formation of plaque. The endothelium has critical roles, preventing intravascular clotting and regulating vascular tone and endothelial permeability. Several theories have been proposed to explain the initial and subsequent growth of the atheromatous plaque. Many of the events are linked to at least initially to chronic injury of the endothelium [79]. The endothelial dysfunction may be triggered by factors such as sheer stress and turbulent flow [80], oxidative stress, hyperlipidaemia, hypertension, smoking among others [79, 81]. Insudation of the lipoproteins, mainly the low-density lipoprotein (LDL) into the intima undergoes modification and initiates monocyte migration to localise in the intima and promotes differentiation of monocytes into macrophages. The lipoproteins are taken up by the monocytes to become lipid-filled foam cells, the hall mark of atherosclerosis [82, 83]. Further plaque progression involves more macrophages and formation of a core of extracellular lipid and cholesterol within the plaque and expanding the plaque size. The endothelial cells, macrophages and smooth muscle cells (SMCs) release chemotactic growth factors which stimulate proliferation of SMC of intimal or medial origin. A fibrotic cap is formed separating the plaque from the lumen.

The macrophages also produce abundant tissue factor. It is believed that the main prothrombotic stimulus in the plaque is the tissue factor which activates coagulation [84, 85]. As the plaque evolves, denudation of the endothelium occurs followed by platelet deposition giving rise to the release of platelet-derived growth factor (PDGF) which further enhances the proliferation of SMC [86]. Thrombi are formed over the plaque as a result of (1) loss of endothelium, The thrombus could be superficial when it is formed on the plaque surface or deep when is formed within the plaque following plaque rupture. The fibrous cap of the plaque tears to expose the lipid core containing large amounts of cholesterol crystals, fragments of collagen and tissue factor, and thrombus forms rapidly within the plaque itself [87].

Injury (erosion/denudation) to the endothelium exposes the collagen allowing platelets to adhere to it. With continuing platelet-to-platelet adhesion, the platelet mass grows using the IIb/IIIa receptor and fibrinogen as binder. The early platelet mass is unstable, but with the conversion of fibrinogen to fibrin, it becomes secure [88]. Damage to the tissue results in the release of tissue factor and activates factor X which in turn activates the generation of thrombin from prothrombin. Thrombin

converts fibrinogen to fibrin. Enhanced exposure and activity is the final common pathway of clot formation [87]. Activated platelets release two substances which contribute to increased expression of IIb/IIIa receptor. One is thromboxane A2 (TXA2) which can be blocked by aspirin and the other is adenosine diphosphate (ADP) which also stimulates platelet recruitment and is inhibited by clopidogrel [89]. Under high shear-stress conditions, von Willebrand factor (vWF) appears to play an important role in both platelet adhesion and aggregation [90].

The plaque (1) may undergo patchy or massive calcification and some lesions in acute coronary syndromes tend to have less calcification and hence more softness of the plaque resulting in an increase in vulnerability to shear force [91]. (2) The fissured or ulcerated lesions may develop superimposed thrombus, (3) macrophages may release metalloproteinases and other proteolytic enzymes that can weaken the fibrous cap and make them more vulnerable to rupture [81, 92]. The loss of endothelial integrity may invoke haemorrhage either an influx of blood from the vessel lumen or result from intraplaque neovascularisation which can trigger acute clinical events [93]. The haemorrhage could cause sudden expansion of the plaque [94, 95] and cause its rupture. Damage to the underlying media may result in atherosclerotic aneurysm (Fig. 1.1) [80].

The plaque instability leads to development of clinical events. Attention has been drawn recently that the fibrous cap is a strong determinant of the likelihood of plaque rupture which in turn leads to thrombosis followed by either plaque

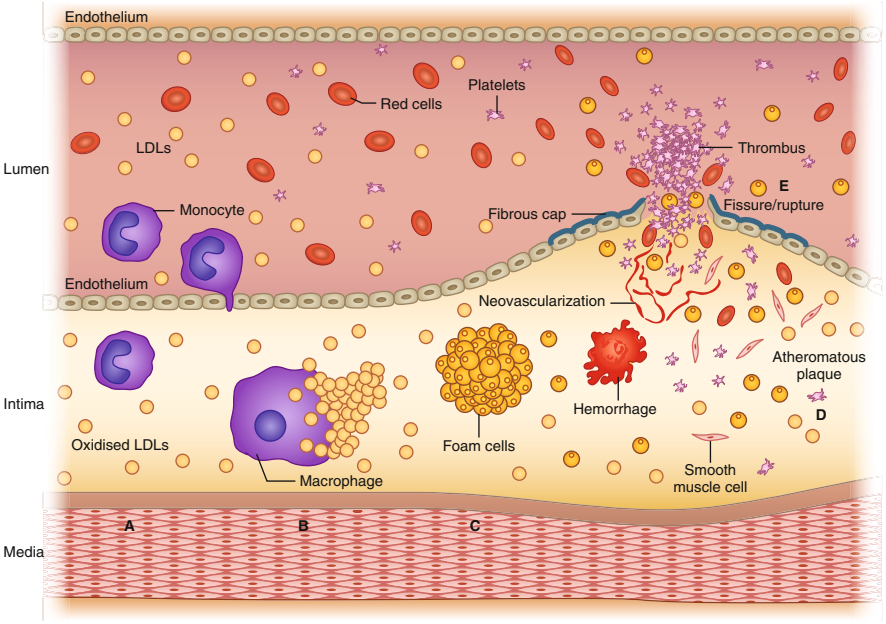

Fig. 1.1 Schematic diagram showing formation of atheromatous plaque and sequela