The aged cardiovascular risk patient

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There is no precise definition of ‘the aged’, ‘the elderly’ or ‘advanced age’. This is hardly surprising, because there is no specific clinical marker of the ‘geriatric’ patient, and ageing does not occur abruptly but represents a continuum. In fact, the ‘geriatric population’ is unique for its non-homogeneity: physical and medical heterogeneity increase with advancing age. Nevertheless, data analysis by age quintiles supports the clinical relevance of usually defining patients aged >64 yr as the elderly cohort. Approximately 15% of the Western population and about 25% of surgical patients are aged ≥65 yr. Half of these will undergo surgery in the remainder of their life time.

Age itself is an independent morbidity and mortality risk factor for a long list of diseases and injuries, hospitalization, length of hospitalization, and adverse drug reactions. With very few exceptions, age has been shown to be an independent predictor of perioperative outcome. If we are to successfully reduce age-related perioperative cardiovascular morbidity and mortality (the main contributor to overall adverse perioperative outcome) we need to define the factors that increase perioperative cardiovascular risk age-dependently. Although we might not always be able to improve underlying conditions, awareness of such additional risk factors may modify our perioperative anaesthetic management in a way that will ultimately improve outcome.

Accordingly, this review will first address the question of what constitutes perioperative cardiovascular risk, independent of age. It will then focus on factors that might affect perioperative cardiovascular outcome age-dependently. Such factors include age-related changes in cardiovascular structure and function, altered cardiovascular response to increased flow demands in the elderly, coexisting cardiovascular and other disease with advancing age, and drug therapy in older people. Finally, anaesthetic implications will be discussed.

Cardiovascular risk assessment

The preoperative assessment of perioperative cardiovascular risk relies on the evaluation of clinical markers, functional capacity and surgery-specific risk. On the basis of such evaluation, different levels of risk can be defined.

Clinical markers

Clinical markers of increased perioperative cardiovascular risk for myocardial infarction, congestive heart failure and death can be placed in three categories: major, intermediate and minor predictors (Table 1). In conjunction with the concomitant degree of functional capacity and the anticipated surgical risk, the severity of the clinical marker will influence the subsequent perioperative management (see below).

Functional capacity

In clinical practice, exercise tolerance in daily life (‘medical’ or ‘physical fitness’) best reflects the ‘quality’ of biological age. It is one of the most important predictors of perioperative outcome in the elderly surgical patient. Poor exercise tolerance may reflect the severity of the underlying disease, or a lower functional capacity. Functional status can be expressed in metabolic equivalent (MET) levels. One MET corresponds to the oxygen consumption (VO₂) of a 70 kg, 40 yr old man in a resting state, which is approximately 3.5 ml kg⁻¹ min⁻¹. Multiples of the baseline 1 MET value can be used to define the aerobic demands for specific activities (Table 2). Functional capacity is assessed by recording daily activities, and has been classified as excellent (>7 METs), moderate (4–7 METs), poor (<4 METs) or unknown. Such a clinical questionnaire provides an estimate, but not an objective measurement of functional status (such as exercise testing).
Table 1 Clinical predictors of increased perioperative cardiovascular risk (adapted from reference 43)

<table>
<thead>
<tr>
<th>Major predictors</th>
<th>Intermediate predictors</th>
<th>Minor predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>unstable coronary syndromes,</td>
<td>mild angina pectoris, previous myocardial</td>
<td>advanced age, abnormal ECG, rhythm</td>
</tr>
<tr>
<td>compensated congestive heart failure</td>
<td>infarction (&gt;30 days old), compensated or</td>
<td>other than sinus, low functional</td>
</tr>
<tr>
<td>significant arrhythmias, severe</td>
<td>previous congestive heart failure, diabetes</td>
<td>capacity, history of stroke,</td>
</tr>
<tr>
<td>valvular disease</td>
<td>mellitus</td>
<td>uncontrolled systemic hypertension</td>
</tr>
</tbody>
</table>

Table 2 Estimated energy requirements for various activities (adapted from reference 43)

- **1 MET**
  - Can you...
  - take care of yourself?
  - eat, dress or use the toilet?
  - walk indoors around the house?
  - walk a block or two on level ground at 2–3 mph (3.2–4.8 km h⁻¹)?
  - do light work around the house, like dusting or washing dishes?
- **4 METs**
  - climb a flight of stairs or walk up a hill?
  - walk on level ground at 4 mph (6.4 km h⁻¹)?
  - run a short distance?
- **>10 METs**
  - do heavy work around the house, like scrubbing floors or lifting or moving heavy furniture?
  - participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a baseball or football?
  - participate in strenuous sports like swimming, singles tennis, football, basketball or skiing?

Table 3 Perioperative cardiac risk (combined incidence of cardiac death and nonfatal myocardial infarction for noncardiac surgical procedures) (adapted from reference 43)

<table>
<thead>
<tr>
<th>Risk of procedure</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (often &gt;5%)</td>
<td>emergent major operations, particularly in the elderly; aortic and other major vascular; anticipated prolonged surgical procedures associated with large fluid shifts and/or blood loss</td>
</tr>
<tr>
<td>Intermediate (generally ≤5%)</td>
<td>carotid endarterectomy; head and neck; intraperitoneal and intrathoracic; orthopaedic; prostate</td>
</tr>
<tr>
<td>Low (generally ≤1%)</td>
<td>endoscopic procedures; superficial procedures; cataract; breast</td>
</tr>
</tbody>
</table>

Patients unable to meet a 4 MET demand during most normal daily activities have increased perioperative short-term and long-term cardiac risk.⁴³

*Surgery-specific risk*

It appears obvious that different surgical procedures would be associated with different cardiac outcome. Surgery-specific cardiac risk is related to two factors: type of surgery and degree of haemodynamic cardiac stress associated with a particular surgical procedure. Examples of high-risk (combined perioperative incidence of myocardial infarction and/or death ≥5%), intermediate-risk (reported cardiac risk generally <5%) and low-risk procedures (reported cardiac risk generally <1%) are listed in Table 3.

Various combinations of major, intermediate or minor clinical predictors, of excellent, moderate or poor functional capacity, and of high-risk, intermediate-risk or low-risk surgical procedure will predict the overall extent of perioperative cardiovascular risk. Obviously, the old patient with major clinical predictors and poor functional capacity undergoing a high-risk surgical procedure carries the highest perioperative cardiac risk.

**Advanced age**

*The Guidelines for Perioperative Cardiovascular Evaluation for Noncardiac Surgery* of the American College of Cardiology and the American Heart Association⁴³ are somewhat ambiguous as to the clinical significance of advanced age as an independent risk factor. Being listed as a minor clinical predictor would imply that advanced age has not been proven to increase perioperative cardiac risk independently (the definition provided for the category of minor clinical predictors). However, the very same guidelines also state that high-risk surgical procedures include ‘emergent major operations, particularly in the elderly’, and that ‘advanced age is a special risk’.⁴³ Such a statement implies that advanced age does, in fact, present an independent predictor of perioperative cardiac outcome.

**Age-related cardiovascular changes**

*Heart*

Ageing is associated with numerous molecular, ionic, biophysical and biochemical changes in the heart.³¹ ⁶³ These changes affect protein function, mitochondrial oxidative phosphorylation, Ca²⁺ kinetics, excitation–contraction coupling, myofilament activation, contractile response, matrix composition and regeneration, cell growth and size, and apoptosis (Table 4).⁶¹
Age-related changes in cardiac morphology (Table 5) are mostly the result of alterations of intracellular molecular and biochemical pathways. In turn, many of the changes in cardiac function (Table 5) with advancing age develop in response to underlying alterations in morphology. Ultimately, cardiac ageing results in decreased mechanical and contractile efficiency, prolongation of the relaxation phase, stiffening of myocardial cells, mural connective tissue and valves, decreased number of myocytes, increased myocyte size, increased rate of myocyte apoptosis and blunted β-adrenoceptor-mediated contractile and inotropic response.\(^{37, 62, 76, 111}\)

### Vasculature

Ageing affects various aspects of vascular morphology and function (Table 6).\(^{39-61, 106}\) The large arteries dilate, their walls thicken, the wall matrix changes, elastolytic and collagenolytic activity increases and smooth muscle tone increases.\(^{42, 59, 61}\) As a result, vascular stiffness increases with advancing age.\(^{59, 61}\)

### Cardiac adaptations

Increased vascular stiffness leads to elevated systolic arterial pressure and pulse-wave velocity, and to early reflected pulse pressure waves and late peak systolic pressure, thereby augmenting aortic impedance and cardiac mechanical load (Fig. 1).\(^{63}\) In this way, arterial stiffening triggers a variety of cardiac adjustments. Some of these adjustments are additional and are similar to the age-related intrinsic changes in cardiac morphology and may, therefore, be expected to worsen cardiac performance.

The chronically elevated left ventricular afterload ultimately causes left ventricular wall thickening,\(^{55}\) which is largely a result of an increase in the size of cardiac myocytes.\(^{76}\) The combination of late augmentation of aortic impedance (through early reflected pulse waves) and left ventricular hypertrophy (partly adaptive) prolongs myocardial contraction. The prolonged myocardial contraction time could contribute to preserved left ventricular pump function, as it prolongs the time available to eject blood from the heart into the stiffened vasculature.

On the other hand, prolonged myocardial contraction delays ventricular relaxation at the time of mitral valve opening, as reflected by reduced early left ventricular filling rate in older individuals.\(^{37, 79-93}\) Early diastolic filling rate declines by approximately 50% between 20 and 80 yr of age.\(^{63}\) In addition to the purely mechanical reason (i.e. prolonged contraction time), the decrease in early diastolic filling rate may, in part, be caused by a prolonged isovolumetric relaxation time between aortic valve closure and mitral valve opening, possibly because of a reduced rate of Ca\(^{2+}\) sequestration from the myoplasm to the sarcoplasmic reticulum.\(^{61}\)

An increase in late diastolic filling partly compensates for the decrease in early diastolic filling rate and helps to maintain end-diastolic volume and stroke volume in the elderly.\(^{61}\) However, this compensatory mechanism is dependent on the effective atrial contribution to late diastolic filling. The importance of atrial activity is reflected by an age-related increase in left atrial size\(^ {55} \) and enhanced atrial contribution to late ventricular filling.\(^ {37} \) The latter explains the greater dependency of stable haemodynamics on sinus rhythm with advancing age. Left atrial enlargement may contribute to the greater likelihood of lone atrial fibrillation in the elderly.

In ageing men, an elevated end-diastolic volume maintains cardiac output by increasing stroke volume in the

### Table 4 Age-related changes in cardiac cellular and biochemical mechanisms in experimental animals

<table>
<thead>
<tr>
<th>Isomyosin shift</th>
<th>Expression of fibrosis-related genes</th>
<th>Altered growth-controlling factors</th>
<th>Impaired excitation-contraction coupling</th>
<th>Impaired calcium homeostasis</th>
<th>Increased myocyte apoptosis</th>
<th>Increased atrial natriuretic peptide secretion</th>
</tr>
</thead>
</table>

### Table 5 Age-related changes in cardiac morphology and function

| Morphology | decrease in myocyte number, increase in myocyte size, decrease in matrix connective tissue, increase in left ventricular wall thickness, decrease in conduction fibre density, decrease in sinus node cell number |
| Function   | decrease in intrinsic contractility, increase in myocardial contraction time, decrease in myocardial contraction velocity, increase in myocardial stiffness, increase in ventricular filling pressures, increase in left atrial pressure/size, increase in action potential time, decrease in coronary flow reserve, decrease in β-adrenoceptor-mediated modulation of inotropy and chronotropy |

### Table 6 Age-related changes in vascular morphology and function

| Morphology | increase in diameter and stiffness of large elastic arteries, increase in medial and intimal thickness, increase in endothelial variant cells, increase in elastolytic and collagenolytic activity, change in vascular cell proliferation/migration, change in vascular wall matrix |
| Function   | decrease in β-adrenoceptor, flow-dependent, endothelium-dependent and atrial-natriuretic-peptide mediated vasodilation, decrease in nitric oxide production/effect, increase in vascular impedance, increase in pulse wave velocity, early reflected pulse waves |
Fig 1 Cardiac adjustments to arterial stiffening during ageing. LV=left ventricular. \( \text{MD}_{\text{O}_2} / \text{MV}_{\text{O}_2} \) balance. LV hypertrophy

<table>
<thead>
<tr>
<th>Table 7</th>
<th>Changes in cardiovascular physiology in healthy individuals at rest between the ages of 20 and 80 yr; LV=left ventricular (adapted from reference 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic volume</td>
<td>LV end-diastolic volume increases (c.20%) in males, no change in females</td>
</tr>
<tr>
<td>LV end-systolic volume</td>
<td>LV end-systolic volume increases (c.20%) in males, no change in females</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>Ejection fraction no change</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>Stroke volume increases (c.20%) in males, no change in females</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Heart rate decreases (c.10%) in males, decreases (c.15%) in females</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>Cardiac output increases (c.15%)</td>
</tr>
<tr>
<td>Stroke work</td>
<td>Stroke work decreases (c.50%)</td>
</tr>
<tr>
<td>Early diastolic filling rate</td>
<td>Early diastolic filling rate increases (c.15%)</td>
</tr>
<tr>
<td>Systolic arterial pressure</td>
<td>Systolic arterial pressure no change in males, increases (c.45%) in females</td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td>Systemic vascular resistance</td>
</tr>
</tbody>
</table>

presence of an age-related decline in heart rate (Table 7).61 As there is no comparable increase in end-diastolic volume in women, cardiac output decreases modestly in ageing females.28

The heterogeneity in filling among left ventricular segments increases with age.8 The normal ageing process seems to have similar effects on right and left ventricular diastolic performance.55 At rest, mild diastolic dysfunction has little adverse effect on systolic myocardial performance in healthy elderly people.28 61 as reflected by maintained ejection fraction, stroke volume and stroke work, and only marginally elevated end-systolic volume in men (Table 7).28 At times of cardiovascular stress, however, the limited cardiac reserve capacity of the elderly becomes apparent (see below).

An age-related increase in left ventricular systolic stiffness (as determined by the end-systolic elastance, \( E_s \)) seems to accompany the age-related increase in vascular stiffness (as determined by the effective arterial elastance, \( E_a \)), even in the absence of cardiac hypertrophy.14 Comparative increases in \( E_s \) and \( E_a \) with age maintain the \( E_s / E_a \) ratio,14 an index of ventricular–arterial coupling. Ageing increases \( E_a \) principally by its effects on pulsatile loading, with an additional but smaller age-dependent effect from mean resistance.14 34

Although the increase in \( E_a \) maintains the \( E_s / E_a \) ratio with age, the increase in both parameters imposes a limitation on net ventricular–arterial interaction, in as much as systolic arterial pressure becomes more sensitive to changes in ventricular filling. Even small blood volume shifts from heart to peripheral vessels can result in considerable changes in arterial pressure.14

Since contractile reserve is also linked to increases in \( E_a \), age-related elevation of baseline \( E_a \) might limit some of this contractile reserve and may contribute to the blunting of end-systolic volume decline during exercise (see below).28
Furthermore, the age-related increase in ventricular stiffness may contribute to the increased prevalence of hypotension with normal physiological stresses like postural shift,77 and enhanced pressure changes with excess sodium intake or restriction109 and diuretics.73 Thus, ventricular and arterial stiffening may well amplify the adverse effects of diastolic, autonomic and baroreflex dysfunction (see below) on cardiovascular compensatory mechanisms.

**Coronary circulation**
Ageing is associated with structural and functional changes in the coronary vasculature, which could affect myocardial perfusion with advancing age. The gradual age-related decline in coronary flow reserve may be a result of elevated baseline cardiac work and myocardial blood flow18 or abnormal vasodilator capacity. Such a reduced dilator reserve may be the result of impaired endothelium-dependent dilation of large epicardial and resistance coronary vessels,25 decreased basal and stimulated release of nitric oxide by the coronary endothelium,2 or increased coronary vasoconstrictor effect of endothelin-1 (ET-1).41 Endothelin plasma concentrations increase with increasing age.71

**Autonomic nervous system**
Ageing is accompanied by a variety of neurohumoral changes (Table 8). Increased basal sympathetic outflow23 and norepinephrine plasma concentrations26 suggest an up-regulation of sympathetic outflow.23 Such sympathetic overactivity leads to desensitization of β-adrenoceptors, which may account for the blunted postsympathetic responsiveness to β-adrenergic stimuli with ageing.61 64 109

Whereas the vasodilatory response to β-adrenoceptor stimulation decreases with age, the contractile response to α-adrenoceptor stimulation appears to be unaltered, or may even increase with age. The precise mechanism for this observation remains uncertain. It may be related to an age-related increase in arterial (but not venous) α1-adrenoceptor density.90

Ageing affects autonomic cardiovascular control mechanisms in different ways.94 109 Attenuated respiratory sinus arrhythmia with advancing age23 56 suggests a decrease in parasympathetic influence on sinus node function. Age-related increases in catecholamine plasma concentrations26 and in the basal rate of sympathetic neural firing23 reflect increased sympathetic nerve activity and suggest blunted sinoaortic baroreflex sensitivity that reduces the restraint on sympathetic outflow. Preservation of the sympathetic limb of the baroreflex (i.e. sympathetic reflex response to changes in the peripheral circulation) with advancing age23 would suggest reduced tonic baroreceptor function (i.e. less inhibitory afferent signals at a given arterial pressure) but maintained gain during arterial pressure perturbations. In contrast, the heart rate reflex response to alterations in arterial pressure is clearly impaired with advancing age.

**Table 8 Age-related neurohumoral changes**

<table>
<thead>
<tr>
<th>Sympathetic nerve activity increases</th>
<th>Parasympathetic nerve activity decreases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma catecholamine concentration increases</td>
<td>Baroreceptor reflex activity decreases</td>
</tr>
<tr>
<td>β1-Adrenoceptor responsiveness decreases</td>
<td>α1-Adrenoceptor responsiveness increases (?)</td>
</tr>
</tbody>
</table>

Age-related autonomic and baroreflex dysfunction may compromise arterial pressure homeostasis in response to diuretic therapy, altered fluid intake and postural stress.97 107 Age-related changes in heart rate response to posture, hypotension and various other physiological stimuli have also been reported.15 Blunted baroreceptor reflex response may contribute to sinus node depression, carotid sinus syndrome and syncope in the elderly.

**Response to increased oxygen demand**
The haemodynamic response to cardiovascular stress is influenced by various factors, including the nature of the cardiovascular stimulus, the posture in which the cardiovascular system is challenged, gender, fitness and cardiovascular health. Besides these factors, age plays a significant role.28 75 112

In healthy, sedentary individuals, maximum work capacity and oxygen consumption (VO2max) decrease by approximately 10% per decade after the age of 20 yr.97 At a given VO2max, increases in heart rate and ejection fraction, and peripheral vasodilation are blunted in the elderly. The decrease in maximum physical capacity may not result solely from limitations in the central circulation (i.e. cardiac reserve capacity), but may also be related to peripheral factors (i.e. redistribution of blood to working muscles, impaired ability of muscle to extract and use oxygen).27 61 The cardiac element of the diminished VO2max in healthy individuals is caused primarily by an age-related decline in the maximum heart rate.28 92

One of the major age-associated alterations in the cardiovascular response to exercise is a striking decrease in heart rate and contractile response, as reflected by decreases in peak heart rate and peak ejection fraction, and by a progressively blunted exercise-induced decrease in end-systolic volume with advancing age (Table 9).28 The Frank–Starling mechanism is the major mechanism that maintains stroke volume in the elderly: peak end-diastolic volume during exercise increases progressively with advancing age and is considerably (c.30%) larger in old than in young individuals (Table 9).28 The augmentation of end-diastolic volume preserves stroke volume but attenuates the increase in ejection fraction.28

The age-associated decline in maximal heart rate and left ventricular contractility during vigorous exercise probably reflects diminished β-adrenergic modulation of contractility, chronotropy and vasomotor tone with advancing age. β-
Table 9 Cardiorespiratory responses to exhaustive upright exercise; LV=left ventricular; SVR=systemic vascular resistance (adapted from references 28 and 61)

<table>
<thead>
<tr>
<th></th>
<th>Peak response at 20 yr</th>
<th>Change in peak response between 20 and 80 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic volume</td>
<td>no change, or decrease</td>
<td>increase (c.30%) in males, no change in females</td>
</tr>
<tr>
<td>LV end-systolic volume</td>
<td>decrease</td>
<td>decrease (c.100%)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>increase</td>
<td>decrease (c.15%)</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>increase</td>
<td>no change</td>
</tr>
<tr>
<td>Heart rate</td>
<td>increase</td>
<td>decrease (c.25%)</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>increase</td>
<td>decrease (c.25%)</td>
</tr>
<tr>
<td>Stroke work</td>
<td>increase</td>
<td>increase (c.30%) in males, no change in females</td>
</tr>
<tr>
<td>SVR</td>
<td>decrease</td>
<td>no change in males, increase (c.10%) in females</td>
</tr>
<tr>
<td>Systolic arterial pressure</td>
<td>increase</td>
<td>increase</td>
</tr>
<tr>
<td>Oxygen consumption</td>
<td>increase</td>
<td>decrease (c.50%)</td>
</tr>
<tr>
<td>Plasma catecholamines</td>
<td>increase</td>
<td>decrease (c.60%)</td>
</tr>
<tr>
<td>Myocardial contractility</td>
<td>increase</td>
<td></td>
</tr>
<tr>
<td>β-Adrenergic modulation</td>
<td>fully functional</td>
<td></td>
</tr>
</tbody>
</table>

![Diagram](image_url)

Fig 2 Cardiac response to increased flow demand in the young and the elderly. The young meet the increased flow demand primarily by β-adrenoceptor-mediated augmentation of heart rate and contractility, thus preserving preload reserve via the Frank-Starling mechanism. In contrast, the elderly employ primarily the preload reserve to augment cardiac performance, thereby losing additional cardiovascular reserve and becoming susceptible to cardiac insufficiency. EDV=end-diastolic volume; LV=left ventricular; Δ=change.

Adrenoceptor blockade effectively converts the haemodynamic profile of young men to that more typical of older men across submaximal work rates. This finding supports the hypothesis that blunted β-adrenoceptor responsiveness underlies the attenuated increases in heart rate and myocardial contractility, and the cardiac dilation that occur during exhaustive exercise in older individuals.

The clinical implications of blunted β-adrenoceptor responsiveness with advancing age are considerable. The young respond to increased flow demands primarily with sympahtoadrenergic activation, followed by β-adrenoceptor-mediated modulation of cardiovascular performance (Fig. 2). Such a mechanism maintains heart size despite increases in heart rate, venous return and systolic arterial pressure. As preload reserve is preserved, additional flow demands can be met by activation of the Frank-Starling mechanism, i.e. by increasing end-diastolic volume.

In contrast, in the elderly, the increased peripheral flow demand is met primarily by activation of the preload reserve (Fig. 2). As no further compensatory mechanism exists, additional flow demands may result in cardiovascular insufficiency. Such reduced cardiovascular reserve capacity explains the higher incidence of acute and chronic heart failure in the elderly. The cardiovascular response to exercise in the elderly is comparable to disease states such as congestive heart failure. It emphasizes the importance of peripheral vasodilation.

The clinically most relevant alterations in cardiovascular physiology with ageing are increased myocardial and vascular stiffness, blunted β-adrenoceptor-mediated modu-
lation of inotropy, chronotropy and vasomotor tone, and autonomic reflex dysfunction. The increase in myocardial stiffness decreases left ventricular compliance which, in turn, impairs diastolic function. These changes are reflected by reduced early diastolic filling rate, elevated end-diastolic volume in elderly men and a tendency for higher cardiac filling pressures. Despite maintained stroke volume and ejection fraction, the increase in end-systolic volume in elderly men reflects an age-dependent decline in intrinsic myocardial contractility.

Although the cardiac adaptation to arterial stiffening will help to maintain systolic function and myocardial oxygen supply/demand balance, diastolic function will be impaired even further. In general, however, despite evidence of impaired diastolic and systolic function in elderly males, overall cardiac performance is adequately maintained at rest during advancing age. Despite arterial stiffening, pump function is maintained via various adaptations which include a moderate increase in left ventricular wall thickness, prolonged contraction, atrial enlargement, enhanced atrial contribution to left ventricular filling and elevated end-diastolic volume in males. The age-related alteration in cardiovascular response to a change in posture or exercise is probably caused more by autonomic reflex dysfunction and blunted β-adrenoceptor responsiveness with advancing age than by impaired myocardial function.

**Age and cardiovascular disease**

Ageing affects cardiovascular risk factors, incidence and clinical manifestation of cardiac disease, treatment strategies and prognosis. Cardiovascular disease is superimposed on age-associated changes in cardiac and vascular characteristics. The final pathophysiological mechanism and clinical presentation result from an interaction between age-related changes in cardiovascular physiology and cardiovascular disease.

**Chronic ischaemic heart disease**

The diagnosis of ischaemic heart disease may be more difficult in the elderly. Reduced physical activity with age limits the occurrence of demand angina. Possibly related to the age-related changes in myocardial compliance and diastolic relaxation, dyspnoea, rather than pain, may dominate the clinical picture of myocardial ischaemia and infarction. The predictive value of a negative exercise stress test is low in a population with a high prevalence of ischaemic heart disease. As many elderly people are unable to exercise to 85–90% of their predicted maximum heart rate, a pharmacological stress test with thallium scan or echocardiogram is often of greater diagnostic accuracy.

Although the goal and choice of anti-ischaemic treatment are generally similar in young and old patients, the elderly must be expected to be more sensitive to the hypotensive effects of certain anti-ischaemic drugs because of blunted baroreceptor reflex activity and sympathetic responsiveness, and increased myocardial and vascular stiffness. As a result of the same age-related decrease in sympathetic responsiveness, myocardial ischaemia is less likely to be provoked by adrenergic-mediated increases in myocardial oxygen demand and the benefit derived from treatment with β-adrenoceptor blockers may be reduced.

**Acute myocardial infarction**

In the elderly, in-hospital and subsequent mortality, reinfarction and complications are all increased. Likewise, perioperative myocardial infarction carries a considerably higher mortality in the elderly. In addition, age is an independent predictor of adverse outcome following various therapeutic interventions, such as percutaneous transluminal angioplasty (PTCA), coronary stenting and thrombolysis.

Increased mortality and morbidity in the elderly after myocardial infarction and therapeutic cardiovascular interventions have many causes. They include greater impairment of baseline left ventricular function, more advanced multivessel disease, higher rate of major complications, greater risk of cardiac rupture despite comparable infarct size (probably on the basis of age-related morphological changes), higher rate of vascular complications, increased incidence of non-cardiac complications (e.g. stroke and haemorrhage), greater likelihood of interventions being performed under emergency conditions, lower procedural success, more contraindications to thrombolytic therapy, longer times between onset of symptoms and presentation for evaluation and treatment, blunted catecholamine response, impaired renal and respiratory reserve, and coexisting diseases.

**Congestive heart failure**

Determination of whether there is predominantly a systolic or a diastolic component to heart failure is particularly important in the elderly because approximately 40% of patients aged >60 yr with symptoms of congestive heart failure have preserved systolic function. The treatments for systolic and diastolic dysfunction are different, and older people are less able to compensate for adverse cardiovascular drug effects.

**Arrhythmias**

Arrhythmias occur more frequently and are more often associated with haemodynamic compromise in older people. Atrial fibrillation is the most common supraventricular arrhythmia in individuals aged >65 yr. It often impairs cardiac performance because ageing people become progressively dependent on atrial contribution to diastolic filling. Any compromise in cardiac output or arterial
Table 10 Possible relationships between age-related cardiovascular changes and clinical impairment; LV=left ventricular; LA=left atrial (modified from reference 61)

<table>
<thead>
<tr>
<th>Cardiovascular change</th>
<th>Pathophysiology</th>
<th>Clinical impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cardiac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>increased myocardial stiffness</td>
<td>decreased LV compliance</td>
<td>lower threshold for dyspnoea</td>
</tr>
<tr>
<td>altered conduction system morphology</td>
<td>irregular conduction</td>
<td>greater prevalence of arrhythmias</td>
</tr>
<tr>
<td>increased LA size</td>
<td>increased LA pressure/ distension</td>
<td>greater prevalence of lone atrial fibrillation</td>
</tr>
<tr>
<td>2. Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>increased vascular stiffness</td>
<td>increased aortic impedance</td>
<td>systolic hypertension, LV hypertrophy</td>
</tr>
<tr>
<td>3. Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>increased myocardial stiffness</td>
<td>decreased cardiovascular reserve</td>
<td>decrease in exercise tolerance</td>
</tr>
<tr>
<td>+ increased vascular stiffness</td>
<td>decreased baroreceptor reflex activity</td>
<td>lower threshold for, and greater severity of heart failure</td>
</tr>
<tr>
<td>+ autonomic dysfunction</td>
<td></td>
<td>greater susceptibility to postural hypotension and syncope</td>
</tr>
<tr>
<td>+ decreased β-adrenoceptor responsiveness</td>
<td></td>
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</tbody>
</table>

Although the diagnostic and therapeutic principles of managing cardiac disease are comparable in older and younger patients, accompanying diseases, changes in lifestyle habits and altered pharmacokinetics and pharmacodynamics (see below) render overall management more difficult in older patients. Relevant data are lacking, so an evidence-based approach to cardiovascular care in the elderly is difficult.82

It is to be expected that age-related cardiovascular changes are associated with cardiovascular diseases (Table

Fig 3 Changes in vasculature and heart with ageing, leading to cardiovascular disease with advancing age. The line bisecting the top and bottom parts indicates the point when ‘normal’ ageing (below the line) will produce symptoms of disease (above the line). (Reproduced with permission from Lakatta EG. Aging effects on the vasculature in health. Risk factors for cardiovascular disease. Am J Geriatr Cardiol 1994; 3: 11–17.)
Table 11 Age-related changes in non-cardiovascular organ function

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>increased chest wall rigidity, increased work of breathing, decreased respiratory muscle strength and endurance (c.20% decrease by 70 yr), decreased functional alveolar surface area (c.15% decrease by 70 yr), decreased response to hypoxaemia and hypercapnia, decreased vital capacity (c.20–40 ml yr⁻¹), increased residual volume (c.30% of total lung capacity at 70 yr), increased closing volume, decreased gas exchange (c.0.5% yr⁻¹)</td>
</tr>
<tr>
<td>Renal</td>
<td>reduction in number of nephrons (c.0.5–1.0% yr⁻¹, mostly cortical), reduced glomerular filtration rate (c.30–50% decrease by 70 yr), decrease in renal blood flow, decrease in urine-concentrating ability, reduction in ability to conserve sodium, decreased tubular secretion, reduction in total body water (c.10–15% decrease by 80 yr), lower thirst perception</td>
</tr>
<tr>
<td>Hepatic</td>
<td>reduction in hepatic mass (c.40% decrease by 80 yr), reduction in hepatic and splanchnic flows (c.40% decrease by 80 yr), decrease in activity of microsomal demethylation pathway, decrease in activity of hepatic cholinesterase</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>reduction in skeletal mass, lower metabolic requirement (c.10–15% lower by 80 yr), reduced body heat production, decrease in thermoregulatory vasconstriction, reduction in number of neurons (c.15% decrease by 80 yr), reduced adrenal mass (c.15% decrease by 80 yr), reduced cortisol secretion (c.15% decrease by 80 yr)</td>
</tr>
</tbody>
</table>

10). Figure 3 illustrates the continuum between the ‘normal’ ageing process (below the line bisecting top and bottom parts) and clinically perceived disease (above the line). At some point, ‘normal’ ageing will produce signs and symptoms that we usually equate with disease. In old age, the pathophysiology of age-independent cardiovascular disease is superimposed on the age-related alterations in cardiovascular structure and function. Such an interaction may change the typical clinical presentation of a given disease in a way that delays diagnosis and treatment, and thereby even worsens long-term outcome. There will obviously be a time when the patient will have relevant cardiovascular alterations that are not apparent at rest, but which become clinically relevant at times of increased cardiovascular stress.

Age-related changes in non-cardiac organ function

Respiration

Age-related changes in structure and function of the respiratory system have been well described (Table 11). The clinical implications are multiple and may well affect cardiovascular risk in the elderly. In the presence of impaired cardiovascular compensatory mechanisms, delayed excretion as well as conservation of free water and salt render the aged patient prone to hyper- and hypovolaemia, hypertension and hypotension, and heart failure.

The age-related decreases in thirst, renin response and urine-concentrating ability facilitate sodium and volume depletion. Any sodium depletion may impair the Starling mechanism on which the elderly depend to maintain cardiac output and arterial pressure during various forms of cardiovascular challenge. Concurrent diseases also associated with sodium and volume loss (e.g. diarrhoea, vomiting, short-term renal losses) may further unmask the limited adaptive cardiovascular capacity in the elderly. All of this may predispose the elderly to syncope. Attention to fluid and electrolyte balance is particularly important in the elderly.

It is conceivable that the insufficient cardiovascular response to postural changes serves as a non-osmotic stimulus for the release of vasopressin, possibly resulting in hyponatraemia. This electrolyte imbalance is not uncommon in the elderly during disease, treatment with diuretics, or in the perioperative period.

Liver

Age-related hepatic changes (Table 11) may impair the functional hepatic reserve to meet the increased demands of metabolism, biotransformation and protein synthesis after surgery and its complications.

Thermoregulation

Advancing age predisposes a patient to perioperative hypothermia. Contributing factors include frail constitution, reduced metabolic rate, reduced subcutaneous fat layer, major and long operations, and impaired thermoregulation. Adverse effects of perioperative hypothermia include prolonged drug action, negative postoperative nitrogen balance, impaired coagulation, immune dysfunction and subsequent increased incidence of wound infection, leftward shift of the haemoglobin–oxygen saturation curve.
increased vascular resistance, cardiac arrhythmia, and up to four-fold increases in cardiac output and VO₂ associated with rewarming and shivering. Several of these factors impose a high load on the cardiovascular system. Not surprisingly, even in the absence of shivering, mild intraoperative hypothermia can be associated with an increased incidence of postoperative myocardial ischaemia and angina in older patients.⁵²

As part of the ‘normal’ ageing process, most organ systems lose approximately 1% of their function per year, beginning at around 30 yr. However, there is considerable individual variability in decline. The hallmark of ageing is not necessarily a decline in resting levels of performance, but a lack of functional reserve and inability of organ systems to respond to external stress. Ageing organ systems may not have the functional reserve to meet increased perioperative oxygen demands, and may thus contribute to perioperative cardiovascular morbidity.

### Drug therapy

The incidence of adverse drug reactions is two to three times higher in the elderly,⁷² this is probably related to the reduced physiological reserve of most organ systems with advancing age, greater severity of disease to be treated, coexisting diseases, altered pharmacokinetics and pharmacodynamics, polypharmacy and intake of drugs with low therapeutic index (e.g. digoxin, antiarrhythmics).

Pharmacokinetics are largely dependent on drug distribution, hepatic metabolism and renal excretion. All of these change with advancing age in an unpredictable manner (Table 12). Drug distribution is affected by age-related decreases in total body water and lean body mass, relative increase in body fat, decrease in serum albumin, increase in α₁-acid glycoprotein, decrease in cardiac output and reduction in blood volume. Drugs that are usually highly protein bound (e.g. lidocaine, propranolol, thiopental, etomidate, propofol, alfentanil and fentanyl) may have an exaggerated clinical effect because a greater proportion of the drug is free (unbound). The decreased distribution volume of water-soluble drugs (e.g. digoxin) may result in adverse reactions because of increased initial plasma concentrations. The increased distribution volume of fat-soluble drugs (e.g. thiopental, diazepam and midazolam) prolongs drug action. Injection of drugs into a contracted blood volume will produce higher initial plasma concentrations.

The effect of age on drug metabolism and excretion is related to changes in hepatic and renal function. Decreases in hepatic mass, hepatic blood flow, activity of the microsomal demethylation pathway, and presystemic metabolism of drugs with a high rate of hepatic extraction, will result in greater bioavailability of drugs with high intrinsic hepatic clearance, where the rate-limiting step in metabolism is hepatic blood flow (e.g. lipid-soluble β-adrenoceptor blockers, antiarrhythmics, most major tranquillizers and tricyclic antidepressants).⁵⁰ ⁷² Age-related decreases in renal blood flow, glomerular filtration rate, tubular secretion and urine-concentrating ability contribute to reduced clearance of quinidine, digoxin and atenolol, diminished diuretic response to furosemide, and volume depletion.⁶⁰

Advancing age alters pharmacodynamics. This may render the elderly more sensitive to a given concentration of drug. However, whereas the sensitivity to sedatives, inhalational anaesthetics and anticoagulants increases with advancing age, the responsiveness to β-adrenoceptor agonists and antagonists, and to digoxin decreases.⁵⁰ ⁷² Nevertheless, the therapeutic window for digitalis is narrower in older people because of a decreased inotropic effect without a change in arrhythmogenic potential. Use of non-steroidal anti-inflammatory drugs is associated with a higher incidence of hyperkalaemia, renal failure and death from gastrointestinal bleeding.

Underlying age-related changes in cardiovascular function and compensatory mechanisms, and increased prevalence of coexisting diseases render older patients more sensitive to the side-effects of cardiovascular drugs. Pre-existing volume contraction and decreased baroreceptor reflex function contribute to greater hypotensive and/or bradycardic responses to calcium channel blockers, nitrates and diuretics. Preexisting conduction system disease or left ventricular dysfunction increase the likelihood of side-effects following treatment with β-adrenoceptor blockers and certain calcium channel blockers.⁶⁰ Advanced age predisposes to clinically relevant volume depletion, hypokalaemia, hyponatraemia and hypomagnesaemia after diuretic therapy. As a result of marked heterogeneity of drug response in the elderly, no strict age-related rules can be applied across the entire geriatric population.

### Anaesthetic implications

As with a young patient, perioperative anaesthetic management of an aged patient will be determined primarily by the
Preoperative assessment

As the likelihood of adverse perioperative events increases with advancing age, preoperative assessment of organ function reserve becomes particularly important in the elderly. If there is evidence of cardiac impairment, quantification of such impairment is critical because the clinical presentation of the cardiac disease may be very atypical and may lead to a wrong diagnosis.

Preoperative risk stratification is particularly important in the elderly patient because often even the short- and intermediate-term prognosis is limited. It makes very little sense to subject an aged patient with severely reduced organ function to a major operation, knowing that the perioperative morbidity and mortality are prohibitively high. Effective preoperative risk stratification may modify preoperative therapy, surgical approach, choice of anaesthetic technique and agents, perioperative monitoring and postoperative care.

When major predictors (Table 1) are present, surgery is usually cancelled or delayed until the cardiac problem has been diagnosed and appropriately treated. In the presence of intermediate predictors, further management depends on the patient’s functional capacity (Table 2) and the surgery-specific risk (Table 3). Poor functional capacity or a high-risk surgical procedure justify preoperative cardiac assessment by additional non-invasive testing (e.g. exercise stress testing, pharmacological stress testing such as dipyridamole-thallium myocardial perfusion imaging or dobutamine stress echocardiography). The need for additional coronary angiography will depend on the results of the non-invasive testing. Subsequent care (e.g. cancellation or delay of surgery, revascularization, intensified medical management) is dictated by the findings of non-invasive testing and coronary angiography, and by the response to treatment.

Although minor predictors per se have not been proven to predict negative perioperative cardiac outcome independently, additional preoperative non-invasive cardiac testing and possibly (depending on the results) coronary angiography may, when combined with a high-risk surgical procedure, be justified. Such a consideration also applies to advanced age.

The number of clinical markers, degree of functional capacity and extent of surgery-specific risk will influence preoperative management (e.g. adjustment or initiation of medical therapy, need for additional non-invasive or invasive cardiac testing), perioperative cardiac monitoring (e.g. right-heart catheterization, transoesophageal echocardiography, real-time ST-segment monitoring) and postoperative care (e.g. admission to an intensive care unit, intense pain control, continuation or initiation of cardiovascular medication). Such modification of perioperative management should improve the short-term and long-term perioperative cardiovascular outcome.

The identification of candidates for possible preoperative coronary revascularization (by PTCA, stenting or bypass grafting) is difficult and remains a topic of considerable controversy. In general, the indication for coronary revascularization in the perioperative setting should be identical to that in the medical setting. If it is confirmed that aggressive perioperative therapy with β-adrenoceptor blockers is effective in successfully reducing perioperative cardiac morbidity and mortality in cardiac high-risk patients, the role of preoperative coronary angiography and revascularization may greatly diminish.

Anaesthetic management

Older patients often come to the operating room with depleted volume because of overly conservative nil-by-mouth orders, reduced thirst, age-related decline in renal capacity to conserve water and salt, disease-associated fluid and electrolyte losses, inadequate intravenous fluid substitution and more frequent use of diuretics. Intravascular volume sensitivity has been repeatedly demonstrated in the elderly. Older individuals made hypovolaemic by diuretics and salt restriction exhibit a greater decline in arterial pressure in response to upright tilting than both young hypovolaemic or old normovolaemic subjects.

Likewise, because of decreased left ventricular compliance and limited β-adrenoceptor responsiveness, the elderly, particularly those with hypertension, must be expected to be more sensitive to fluid overload. Careful volume assessment before induction of anaesthesia is, therefore, even more important in the elderly than in the young, especially when major fluid shifts are anticipated.

Anaesthesia itself, and all intravenous and volatile anaesthetics, interfere with cardiovascular performance in one way or another. Induction of sleep withdraws sympathetic nerve activity on which the aged with impaired cardiac performance may depend to maintain adequate perfusion pressure. In addition to this indirect effect, all anaesthetic drugs interfere with cardiovascular performance, either by direct effects on the heart and vasculature, or indirectly by modifying the neurohumoral control mechanisms of the circulation. The direct effects include negative inotropy, impairment of diastolic function, and arterial and venous vasodilation. The indirect effects include decrease in central sympathetic outflow, interference with vagal control of heart rate, vagal stimulation and depression of baroreceptor reflex control.

For these reasons, more frequent and severe hypotension on induction of anaesthesia must be anticipated in the elderly because the direct and indirect effects of the anaesthetics occur on top of age-related impaired cardio-
vascular compensatory mechanisms. In this regard, the haemodynamic stability after administration of etomidate in patients with heart disease is remarkable. Preserved sympathetic nerve activity and autonomic reflexes may contribute to this stability. Etomidate may, therefore, be the induction agent of choice in aged patients with limited cardiovascular reserve.

The dose requirement of many hypnotic and analgesic drugs used in anaesthesia is reduced in elderly patients as a result of age-related changes in pharmacokinetics, pharmacodynamics or both. In old age, anaesthetics may exert quantitatively as well as qualitatively different cardiovascular effects. For example, isoflurane becomes more cardiodepressant than halothane with advancing age. The cardiovascular depression caused by propofol can be rather pronounced in the elderly. Therefore, more judicious use and selection of agents, and slow titration of reduced doses during induction and maintenance of anaesthesia, are required with advancing age.

The incidence and severity of adverse drug interactions between anaesthetic and chronically administered cardiovascular drugs are likely to be greater in the elderly because of diminished cardiovascular reserve, more frequent use of cardiovascular medication (often with a narrow therapeutic window) and altered pharmacokinetics and pharmacodynamics. If the choice and dose of anaesthetic are not adjusted accordingly, arterial pressure and heart rate can decline considerably, and bradyarrhythmias may develop in patients aggressively treated with β-adrenoceptor blockers, calcium channel blockers, inhibitors of angiotensin-converting enzyme, and angiotensin receptor antagonists.

Transition from spontaneous to controlled ventilation will acutely reduce venous return and, subsequently, cardiac filling in patients who rely more heavily on adequate preload than the young. Hyperventilation must therefore be avoided in the elderly. Whenever practical, maintenance of spontaneous respiration is preferred to controlled ventilation in the aged cardiovascular risk patient. The combination of generous use of induction agents and aggressive ventilation may result in disastrous hypotension in the elderly.

Monitoring
As cardiac performance in the elderly becomes progressively dependent on preload conditions, the margin of safety declines with advancing age. As a result of age-related myocardial and vascular stiffness, reduced β-adrenoceptor responsiveness and autonomic dysfunction, inappropriately low preload will lead to a marked fall in cardiac output and arterial pressure (and, thus, in perfusion of vital organs), whereas inappropriately high preload can quickly provoke signs and symptoms of left ventricular insufficiency (e.g. impaired oxygenation, alveolar oedema or dyspnoea). More liberal use of monitoring devices that permit determination of various indices of preload and afterload (i.e. pulmonary artery catheter, transoesophageal echocardiography) may therefore be indicated in the elderly. This is particularly true for old patients with limited exercise tolerance who undergo a surgical procedure that is expected to cause considerable cardiovascular stress.

Anti-ischaemic prophylaxis
Maintenance of, or initiation of, β-adrenoceptor blocker therapy in the perioperative period with the aim of maintaining heart rate at <80 beats min⁻¹ must now be considered standard practice in the perioperative management of the aged patient at increased risk for, or having, ischaemic heart disease.

Summary
It is mostly acknowledged that ‘normal’ or ‘healthy’ ageing of the cardiovascular system is distinct from the increasing incidence and severity of cardiovascular disease with advancing age (e.g. hypertension, ischaemic heart disease and congestive heart failure). It is also recognized that chronological and biological age may differ considerably. Nevertheless, even in the absence of overt coexisting disease, advanced age is always accompanied by a general decline in organ function, and specifically by alterations in structure and function of the heart and vasculature that will ultimately affect cardiovascular performance. Actual biological age is thus the net result of the interaction between age-related and concomitant disease-associated changes in organ function. As cardiovascular performance at a given moment is the net result of interactions between heart rate, intrinsic contractility, diastolic and systolic function, ventricular afterload and coronary perfusion, it is important to be aware of the age-related changes in each of these variables, independent of disease, as they determine cardiac performance at rest and its response to stress in the elderly.

The most relevant age-related changes in cardiovascular performance for perioperative management are the stiffened myocardium and vasculature, blunted β-adrenoceptor responsiveness and impaired autonomic reflex control of heart rate. These changes are of little clinical relevance at rest, but may have considerable consequences during superimposed cardiovascular stress. Such stress can take the form of increased flow demand (as in exercise or postoperatively), demand for acute autonomic reflex control (as in change of posture) or severe disease (as during myocardial ischaemia, tachyarrhythmias or uncontrolled hypertension). It may interfere with diastolic relaxation (i.e. ventricular filling), systolic contraction (i.e. ventricular emptying) and vasoconstriction (i.e. arterial pressure homeostasis).

Three factors contribute most to the increased perioperative risk related to advanced age. First, physiological ageing
is accompanied by a progressive decline in resting organ function. Consequently, the reserve capacity to compensate for impaired organ function, drug metabolism and added physiological demands is increasingly impaired. Functional disability will occur more quickly and take longer to be cured.

Second, ageing is associated with progressive manifestation of chronic disease which further limits baseline function and accelerates loss of functional reserve in the affected organ. Some of the age-related decline in organ function (e.g. impaired pulmonary gas exchange, diminished renal capacity to conserve and eliminate water and salt, or disturbed thermoregulation) will increase cardiovascular risk. The unpredictable interaction between age-related and disease-associated changes in organ functions, and the altered neurohumoral response to various forms of stress in the elderly may result in a rather atypical clinical presentation of a disease. This may, in turn, delay the correct diagnosis and appropriate treatment and, ultimately, worsen outcome.

Third, related to the increased intake of medications and altered pharmacokinetics and pharmacodynamics, the incidence of untoward reactions to medications, anaesthetic agents, and medical and surgical interventions increases with advancing age.

On the basis of various clinical studies and observations, it must be concluded that advanced age is an independent predictor of adverse perioperative cardiac outcome. It is to be expected that the aged cardiovascular risk patient carries an even higher perioperative cardiac risk than the younger cardiovascular risk patient. Although knowledge of the physiology of ageing should help reduce age-related complications, successful prophylaxis is hindered by the heterogeneity of age-related changes, unpredictable physiological and pharmacological interactions and diagnostic difficulties.

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