The physiology of ageing

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Abstract

Britain's ageing population is growing at its fastest rate to date, making it increasingly important for clinicians to understand the physiological changes associated with ageing and recognize the difference between changes secondary to ageing and changes that occur as a result of disease. Ageing is characterized by a progressive and heterogeneous decline in physiological reserve of all organ systems, albeit at different rates, which vary in different individuals. Cellular senescence, although beneficial early in life, is likely to contribute. An age-related decline in reserve and compromise of homeostasis have important clinical implications for the interpretation of physiological findings and for understanding the atypical presentations of illnesses in older patients.

Keywords Ageing; frailty; physiology; senescence

Key points

- All organ systems undergo physiological ageing albeit at different rates
- Age associated decline in renal excretory function is arguably the most clinically relevant change
- Cardiovascular ageing causes increased vascular stiffness associated with increasing pulse pressure; postural fall in systolic BP is another feature
- Reduction in muscle bulk and strength is an important physiological change that underlies the increasing fall rate in old age

Introduction

Individuals age at different rates and there is significant heterogeneity in physiological response. The hallmark of ageing is the progressive reliance on homeostatic reserves. Most organ systems show a physiological reduction in function with age, although the rate varies between systems within an individual as well as between individuals. There is reduced redundancy of function and ability to repair. The increased risk from loss of functional reserve is worsened by the increased prevalence of coexisting disease. An understanding of the relationship between physiological ageing and disease is often helpful in interpreting physical signs and investigation results. It is sometimes difficult to differentiate between physiological ageing and disease states. This article focuses on the physiological changes of ageing that have most clinical relevance.

The cardiovascular system

Cardiovascular ageing results in attenuated mechanical and contractile efficiency. Specific changes include arterial wall thickening, changes in vascular matrix composition with increased elastolytic and collagenolytic activity, and an increase in smooth muscle tone. Ultimately, vessels 'stiffen' with age, resulting in elevated systolic arterial pressures, increased systemic vascular resistance and increased cardiac afterload. These changes account for the common finding of isolated systolic hypertension, and, as the left ventricle has to work harder to eject blood into the stiffer aorta, the increased workload can eventually lead to left ventricular hypertrophy. Coupled with these changes, plasma renin activity (PRA) and aldosterone concentration both fall with age. In addition, the PRA response to upright posture is reduced or even absent, and the aldosterone response to sodium restriction is also markedly reduced.

Hypertrophy of myocytes in response to elevated afterload lengthens contraction time, with subsequent effects on the remainder of the cardiac cycle. Ventricular relaxation is delayed at the time of mitral valve opening, contributing to diastolic dysfunction. Early diastolic filling rate decreases with age and is partly compensated for by an increase in the rate of late diastolic filling, which is dependent on atrial contractile activity. This contributes to the positive correlation between left atrial size and age, the increased likelihood of lone atrial fibrillation and the greater effect of a change from sinus rhythm to atrial fibrillation on cardiac output.

Cardiac output is dependent on heart rate and stroke volume. Stroke volume falls, resulting in a fall in cardiac output. With exercise, the heart rate response falls, exaggerating the effect on cardiac output. In addition, there is progressive decline in the number of atrial pacemaker cells resulting in a decrease in intrinsic automaticity, which can predispose to the development of conduction defects and rhythm disturbances. Resting cardiac output remains stable with age, but the increase in cardiac output that is associated with exercise is attenuated, even in healthy ageing.

The venous system acts as a reservoir, holding 70% of circulating blood volume. Veins also stiffen progressively with age, reducing their compliance. The elderly patient is therefore particularly susceptible to abrupt changes in intravascular volume, as the venous capacitance system is less well equipped to buffer marked changes. Thus, physiological changes such as those associated with micturition, assuming an upright posture and following a meal are associated with more significant falls in blood pressure with increasing age.

These changes contribute to the reduced efficiency of the baroreflex – the extent to which heart rate rises in response to falls in blood pressure. Thus, ageing is associated with less

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efficient maintenance of cardiac output in the face of falls in blood pressure.

The nervous system

Central nervous system

Ageing produces a decrease in neural density. An estimated 30% loss of brain mass occurs by the age of 80 years, primarily involving grey matter. There is reduced production of important central neurotransmitters, including catecholamines, serotonin and acetylcholine, with secondary effects on mood, memory and motor function. There is an age-related deficiency of dopamine uptake sites and transporters, in addition to depletion of cortical serotonergic, α_2-adrenergic, β-adrenergic and γ-aminobutyric acid binding sites. These changes result in age-associated reduction in speed of processing and memory.

Peripheral nervous system

Motor, sensory and autonomic fibres are lost. There is a significant reduction in afferent and efferent conduction velocities, with a progressive decline in signal transduction rate within the brainstem and spinal cord. The number of muscle cells innervated by each axon falls, leading to denervation and muscle atrophy.

Autonomic nervous system

In youth, baseline autonomic tone is largely regulated by the parasympathetic division. With increasing age, tonic parasympathetic outflow decreases and sympathetic tone increases. Increased sympathetic nervous system activity contributes to increased systemic vascular resistance. Despite this increase in sympathetic activity, ageing is associated with a blunted response to β-adrenergic stimulation.

There is reduced ability of aortic arch and carotid sinus baroreceptors to transduce changes in arterial pressure, resulting in an attenuated heart rate response to changes in arterial pressure.

This combination of age-related autonomic and baroreflex dysfunction compromises haemodynamic homeostasis, as is evident in elderly patients who are taking diuretics or have a reduced fluid intake. This dysfunction is also associated with increased postural and postprandial hypotension. Diminished baroreceptor reflex activity also contributes to sinus node depression, carotid sinus syndrome and syncope in otherwise healthy elderly people.

The kidneys

Renal mass is approximately 50 g at birth, peaks at 400 g during the fourth decade and then gradually decreases to about 300 g by the ninth decade. Loss of renal mass is primarily cortical with relative sparing of the medulla, and correlates with the reduction in body surface area. With diminished glomerular lobulation and sclerosis of the glomeruli, there is reduced surface area available for filtration, contributing to an age-related decline in glomerular filtration rate (GFR). Glomerular basement membrane permeability increases, with a secondary increase in microalbuminuria and proteinuria. This occurs even in the absence of diabetes mellitus, hypertension and chronic kidney disease.

After the age of 30 years, renal blood flow declines progressively at a rate of 10% per decade. A greater proportion of the decline in renal blood flow occurs in the cortex, with a relative increase in blood flow to the juxtamedullary region. In the ageing population, the ability to vasodilate the afferent renal artery to increase renal plasma flow and GFR is impaired. This largely results from an imbalance between vasodilatory and vasoconstrictive influences in ageing kidneys.

Age-related structural changes in the kidney

- Reduction in renal mass
- Decreased cortical thickness
- Reduction in number of glomeruli
- Diminished glomerular lobulation
- Global glomerular and vascular sclerosis
- Tubular atrophy and fibrosis

Table 1

Age-related changes in structure and renal haemodynamics (Table 1) compromise the ability of the kidney to adapt to acute ischaemia and heighten susceptibility to acute kidney injury, including normotensive ischaemic nephropathy. It also sets the stage for progressive chronic kidney disease.

Davies and Shock — in a classic cross-sectional inulin clearance study — demonstrated that GFR decreases by about 8 ml/minute/1.73 m^2 per decade from the fourth decade onwards.[1] There is wide inter-individual variability in the age-related fall in estimated GFR, further amplified by the presence of vascular and renal disease.

Creatinine clearance is influenced by nutritional status, protein intake, muscle mass, body weight, gender and ethnicity.[2] As people age, muscle mass is reduced and daily urinary creatinine excretion decreases, accompanied by an age-related reduction in creatinine clearance. This means that interpretation of estimated GFR needs to be accompanied by a clinical assessment of muscle mass.

The combined effect of these changes is that declining GFR in older patients is accompanied by lower rises in serum creatinine than would occur in younger patients.

The respiratory system

A number of key age-related changes have been described (Table 2). Loss of elastic support of the airways contributes to increased collapsibility of the alveoli and terminal conducting airways, and accounts for varying effective lung volumes.[3] The closing capacity during normal tidal ventilation gradually increases and encroaches on the tidal volume, resulting in ventilation/perfusion mismatch and reduced arterial oxygen tension.

Key age-related changes in the respiratory system

- Decline in elasticity of the bony thorax
- Loss of muscle mass, weakening of the muscles of respiration and reduced mechanical advantage
- Decrease in surface area for alveolar gas exchange
- Decrease in central nervous system responsiveness

Table 2

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