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The cardiovascular system in the ageing patient

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The ageing process is associated with important changes in the responses of the cardiovascular system to pharmacological stimuli. They are not limited to the arterial system, involved in the modulation of cardiac afterload and vascular resistance, but they also involve the low-resistance capacitance venous system and the heart. The main changes include loss of large artery compliance, dysfunction of some of the systems modulating resistance vessel tone, increased activity of the sympathetic nervous system, and reduced haemodynamic responses to inotropic agents. This review focuses on the effects of ageing on arterial and venous reactivity to drugs and hormones, the autonomic nervous system, and the cardiovascular responses to inotropic agents. Some of the age-related changes might be at least partially reversible. This may have important therapeutic implications.

Keywords: ageing, arteries, inotropes, sympathetic nervous system, veins

The effects of ageing on arterial and venous vascular reactivity (A. Moore, D. Lyons)

Introduction

Ageing has a profound effect on blood vessel structure and function. Changes in blood vessel reactivity are mediated mainly by altered responsiveness of the endothelium to the key homeostatic systems that regulate vascular tone [1]. Before describing age-related changes in arteries and veins it is important to highlight briefly their respective physiological roles.

Large arteries play an important role in converting the pulsatile output of the heart to the more continuous pattern of blood flow seen distally in the vasculature. Large arteries perform this function by virtue of their distensibility. They act as a 'sump' into which blood is temporarily stored during systole before being propelled onwards by the elastic recoil of these arteries during diastole. Therefore, the principal parameter of interest in examining large artery function is compliance. Small arteries and arterioles, on the other hand, are the principal determinants of systemic vascular resistance. Their tone is influenced by several homeostatic systems.

The venous system is a 'low-resistance' capacitance system. It contains more than half of the total blood volume. The more relevant physiological parameters in evaluating venous function therefore are not pressure or resistance but compliance and volume.

Examining relevant changes in the properties of veins and arteries requires different methodological approaches. Several different *in vivo* techniques have been used to assess vascular responses to pharmacological stimuli. Applanation tonometry is the principal technique used to measure indirect markers of large vessel compliance including pulse wave velocity and augmentation index. In resistance vessels venous occlusion plethysmography has been widely used to examine age-related changes in vascular responsiveness [2, 3]. The most widely used technique to evaluate the venous system is a linear variable differential transformer model to evaluate volume changes in dorsal hand veins [4].

Age-related changes in each of these vessel subtypes will now be examined individually.

Age-related changes in large artery reactivity

Ageing is associated with loss of compliance in the aorta and the principal arterial conduits [5]. This loss of compliance is a powerful determinant of cardiovascular risk [6, 7]. However, despite this relationship loss of compli-

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ance has not been felt to be a suitable target for pharmacological manipulation until recently. The structural changes in the large arteries of older individuals responsible for loss of compliance were felt to be largely irreversible [8, 9]. Hence any potential beneficial effects of treating this phenomenon were considered to be mediated further 'downstream' at the level of the resistance vessels. However, recent evidence suggests a role for circulating nitric oxide (NO) in regulating large artery compliance [10]. This appears to open up the possibility of modifying large artery stiffness with drug classes that can alter endothelial function by increasing NO bioavailability. Several drug classes have been shown to alter large vessel compliance. These include calcium channel blockers, ACE inhibitors, (oral) nitrates, and the potassium channel opening agent Nicorandil. There is some evidence to suggest that ACE inhibitors may have direct arterial wall effects and not produce changes in large vessel stiffness because of their blood pressure lowering effects [11, 12].

The increasing recognition that large vessel stiffness plays a central pathophysiological role in hypertension in older individuals may help to guide clinicians in treating specific subgroups of older hypertensives where evidence supporting one individual drug class over another is absent. The presence of combined isolated systolic hypertension and orthostatic hypotension in older patients provides such an example. At present no evidence base exists to guide clinicians treating this combination of conditions. An ideal antihypertensive for this group of patients should lower blood pressure by reducing large vessel stiffness without producing orthostatic hypotension. In the absence of such an ideal agent clinicians must choose between antihypertensives with a lower reported incidence of associated orthostatic hypotension within each drug class. Differences in the pharmacokinetic profiles of individual agents in each drug class should be carefully considered before commencing treatment. Agents that produce a more gradual onset of effect may be preferable. Treatment with lower doses in the initial stages appears prudent in order to minimize the risk of precipitating falls or syncope due to hypotension.

Age-related changes in resistance vessel vasoconstriction

The principal mediators of vasoconstriction in arterioles are the catecholamine α_1-adrenergic sympathetic nervous system, the endothelin-1/endothelin receptor system and the renin-angiotensin system (RAS). These systems differ in their onset of action and duration of effect. Endothelin-1 has the slowest onset of action and the longest duration of effect and therefore its principal role is in control of basal vascular tone [12]. By contrast, the effects mediated at α_1-adrenergic receptors are the most rapid in onset but shortest in duration of effect. Stimulation of postsynaptic α_1-adrenergic receptors within blood vessels leads to activation of a secondary messenger system and intracellular phospholipase Cβ [13]. In addition, stimulation of postsynaptic α_2-adrenergic receptors also produces resistance vessel vasoconstriction [14]. Stimulation of presynaptic α_2-adrenoceptors inhibits the release of noradrenaline from presynaptic storage terminals. Conversely stimulation of postsynaptic β_2-adrenergic receptors produces vasodilatation [14]. As a result, administration of β-adrenergic receptor antagonists produces reduced vasodilator tone in resistance vessels. Blockade of α_2-adrenoceptors increases release of noradrenaline from presynaptic terminals [14]. Age-related changes have been described in several of these systems.

Sympathetic nervous system

The responsiveness of arterioles to the catecholamine α_1-adrenergic receptor decreases with ageing [15, 16]. As a result, administration of intra-arterial noradrenaline in healthy older volunteers produces less vasoconstriction than in younger adults. The precise mechanism through which this decreased responsiveness is mediated is unclear. Although an age-related decrease in the activity

Table 1 Age-related changes in resistance vessel responsiveness.

Homeostatic system	*Principal function*	*Age-related change*
L-arginine nitric oxide system	Determines basal vasodilator tone and acute changes in vasodilation	↓ responsiveness in healthy older adults
α_1-adrenergic receptor/ catecholamine system	Mediates acute changes in vasoconstriction (rapid onset and short duration of effect)	↓ responsiveness to infused noradrenaline in healthy older adults
Renin-angiotensin system	Mediates subacute changes in vasoconstriction (intermediate length and duration of effect)	Responsiveness preserved in healthy older adults. Responsiveness variable, dependent on regional vascular bed studied in animal models.
Endothelin-1 ET A/ET B receptor system	Influences basal vasoconstrictive tone (slow onset and long duration of effect)	No age-related human data available. One study showing ↓ responsiveness in older adult rats

of the postsynaptic receptor G protein-phosphokinase system for β-adrenergic receptors has been demonstrated [17], the available data suggest that α-receptors show less age-related functional change than β-receptors.

Endothelin system

Age-related data on changes in responsiveness to endothelin are limited. One study has shown diminished vasoconstriction in older rats using a nerve blood flow model in response to endothelin compared with younger rats [18]. No age-related studies in humans have been reported, however.

Renin-angiotensin system

The relationship between ageing and vascular responsiveness to angiotensin II is unclear. Animal studies have shown conflicting results. Responses to infused angiotensin II appear to depend on which regional vascular bed is used as an experimental model. In mesenteric vessels responsiveness is decreased in elderly rats [19]. Responses in renal arterioles and in the coronary circulation, however, are preserved in elderly rats [20, 21]. In humans two studies addressing this relationship have been reported [22, 23]. No differences in the responsiveness of resistance vessels to angiotensin II were observed between younger and older adults in either study.

Age-related changes in resistance vessel vasodilatation

The principal mediator of vasodilator tone is the L-arginine–nitric oxide system. NO is synthesized in the vascular endothelium from L-arginine. It diffuses to underlying smooth muscle where it produces vasorelaxation [24, 25]. In addition, it mediates the effects of several vasodilating substances such as substance P, bradykinin and acetylcholine [26]. Healthy ageing has been shown to be associated with decreased total body production of NO [15] and decreased responsiveness to NO [27, 28].

The diminished responsiveness of resistance vessels to circulating catecholamines associated with ageing may partly explain the higher prevalence of adverse effects demonstrated by older patients to α_1-adrenergic receptor antagonist. This combination, of reduced resistance vessel responsiveness to catecholamines and α_1-adrenergic receptor antagonism, prevents an adequate increase in systemic vascular resistance from occurring in older individuals during orthostasis. Older individuals have been reported to have greater sensitivity to the postural hypotensive effects of prazosin and terazosin [29, 30], which have been cited as a frequent cause of drug-induced orthostatic hypotension in older people [31]. Agents within this drug class with a slower onset of action, such as doxasocin, cause less orthostatic hypotension [32]. Therefore, their use appears preferable in older patients.

The age-related decrease in NO responsiveness at resistance vessels has important implications for older individuals with common vascular conditions associated with endothelial dysfunction. Any pharmacological agent that can improve NO bioavailability at resistance vessel level is likely to modify endothelial function and produce beneficial secondary neurohumoral effects.

Age-related changes in venous compliance

The pharmacological responsiveness of several key homeostatic systems in the venous system (and hence capacitance) was first described by Collier [33]. Noradrenaline, adrenaline and serotonin were reported to cause venoconstriction in precongested veins. Angiotensin II, a potent constrictor of arterioles, only caused venoconstriction at high doses with marked tachyphylaxis. It appears to exert its effects by augmenting sympathetically induced vasoconstriction [34]. Bradykinin, acetylcholine, isoprenaline and histamine all caused venodilation when infused into a preconstricted vein but had no effect on relaxed veins. Age-related changes have been described for most of these agents, although results have not been consistent between studies. This reflects the principal difficulty with the dorsal hand vein technique, which is that considerable interindividual variability exists in venous responsiveness to pharmacological stimuli [35].

Age-related changes in venoconstriction

Older subjects exhibit equivalent venoconstrictive responses to noradrenaline to younger adults [36, 37]. However dorsal hand vein responses to neuropeptide Y, a sympathetic neurotransmitter released in veins with noradrenaline during sympathetic stimulation, have been reported to be decreased in older individuals [38].

Age-related changes in venodilation

Age-related changes in response to the mediators of venodilator tone have also been described [39–41]. Bradykinin, which produces NO-mediated effects, has been reported to produce equivalent venodilation in older to that in younger adults [41]. Eichler *et al.* demonstrated no age-related differences in preconstricted dorsal hand vein responses to intravenous nitroglycerin. However, Gascho *et al.* reported decreased venous distensibility and a diminished response to nitroglycerin in older subjects using a similar technique in upper limb veins after precongestion with upper arm cuffs [40]. The reason for the

different results obtained between these studies is not clear, but may reflect the considerable interindividual response to pharmacological stimuli, making comparisons between groups within a study or comparison between studies problematic.

Summary

Loss of large artery compliance accompanies increased age. This age-related change may prove to be more reversible than once thought and may have significant implications for clinicians managing common vascular conditions in older patients. Ageing is also associated with selective dysfunction of two homeostatic systems controlling resistance vessel tone: the L-arginine NO system and the catecholamine α_1-adrenergic receptor system. However, this age-related loss of responsiveness is not universal to all homeostatic systems. Responsiveness to infused angiotensin II appears to be preserved in healthy old age. The relationship between ageing and the third controlling influence on vasoconstrictor tone, the endothelin system, has yet to be characterized.

The influence of ageing upon venous compliance is less clearly defined. This reflects the principal difficulty with the most commonly used technique used to evaluate response to pharmacological stimuli. The evidence suggests that venous responsiveness to the principal determinant of venoconstrictor tone (the catecholamine α_1-adrenergic receptor system) is preserved. The effect of ageing on the principal mediator of venodilator tone (the L-arginine nitric oxide system) remains unclear.

Autonomic nervous system

(A. A. Mangoni, S. H. D. Jackson)

Sympathetic activity

A large body of evidence supports the view that ageing is associated with an increased activity of the sympathetic nervous system. This phenomenon has been demonstrated by using different techniques for assessment of sympathetic activity, such as measurement of the rate of appearance (spillover) of noradrenaline into the plasma compartment [42, 43] and the direct (intraneural) recordings of postganglionic sympathetic nerve activity to skeletal muscle [44, 45]. Plasma noradrenaline concentrations are elevated in elderly subjects due to a combination of augmented noradrenaline spillover and reduced metabolic clearance [42, 43, 46]. The increase in muscle sympathetic nerve activity occurs even in normotensive subjects and almost doubles between the ages of 25 and 65 years [47, 48]. This increase is observed in both men and women [47, 48]. Sympathetic tone is elevated in the heart with age in humans. This is apparently due to both reduced neuronal uptake of noradrenaline and increased sympathetic nerve discharge [49]. At present, there is no striking evidence that sympathetic activity to the kidney is elevated in healthy elderly subjects [49].

Plasma adrenaline concentrations, on the other hand, either become slightly lower or do not change across the adult age range [50]. After taking into account age-related changes in adrenaline clearance, adrenaline secretion from the adrenal medulla was 40% lower in older compared with young subjects [51].

The age-related increases in sympathetic nervous system activity under resting conditions seem to be related mainly to a primary increase in central sympathetic nerve discharge rather than impairment in tonic baroreflex inhibition of central sympathetic outflow [52–54]. The age-related responses of the sympathetic nervous system differ somewhat from the data available during resting conditions. Absolute increases of sympathetic activity in response to stress do not differ between young and older healthy adults [47, 54, 55]. A possible exception is represented by the increases in cardiac noradrenaline spillover, which seem to be greater in elderly subjects. By contrast, the absolute increases in adrenaline secretion during stress are significantly attenuated with advancing age [54].

Many of the effects of ageing on sympathetic nervous system activity also occur in patients with chronic heart failure (CHF). Serum noradrenaline increases with CHF progression [56]. In addition, microneurographic evidence of increased sympathetic nervous system activity has also been reported [57]. Both ageing and CHF reduce heart rate and vasodilatation responses to infused β agonists. Both are associated with downregulation of myocardial β-adrenergic receptors and uncoupling of β_2-receptors from intracellular secondary messenger systems [58]. In patients with CHF, β receptor downregulation and excess sympathetic nervous system activity can be reversed with administration of nonselective β-blockers [59]. These similarities may explain why the emerging evidence of mortality benefits of β-blockers in patients with CHF extends to older as well as younger and middle-aged adults, as reviewed recently by Aronow [60].

Cardiovascular effects of positive inotropic drugs (A. A. Mangoni, S. H. D. Jackson)

Cardiac glycosides

The contractile response to digitalis decreases with advancing age. The age-related haemodynamic effects of ouabain and digoxin have been studied in animal models [61, 62]. Ouabain administration induced a rise in left ventricular end-diastolic pressure, which increased progressively with ageing, and an elevation in left ventricular

developed pressure, which decreased progressively with ageing [61]. Ouabain also reduced coronary blood flow. The amount of this reduction increased progressively with age [61]. The haemodynamic effects of digoxin were studied in neonatal and adult dogs [62]. Two indices of systolic function were calculated: the systolic time interval (pre-ejection period/ejection time) and total electromechanical systole (pre-ejection period + ejection time). The effects of digoxin on heart rate, systolic time interval, and total electromechanical systole were age dependent [62]. Previous studies done in animals showed that the sensitivity to the cardiotoxic effects of digitalis-like compounds is increased with advancing age. This phenomenon seems to be related to a reduction in the sarcolemmal content of Na,K-adenosine triphosphatase. This might reduce the reserve capacity of the Na+ pump and thus the extent of digitalis-induced pump inhibition required before the onset of toxicity [63, 64].

Isoprenaline

The effects of age on the haemodynamic effects of isoprenaline have been studied in both animals and humans. In the rat, the heart rate and cardiac output increased in young animals, whilst only smaller increases in heart rate and no significant changes in cardiac output were observed in old animals [65]. Moreover, the regional blood flow increase observed in the young group was not present in the old group, suggesting a reduced response to β-adrenergic stimulation with advancing age [65]. In humans, the effects of progressively higher doses of isoprenaline were assessed by echocardiography. The slopes of the fractional shortening–end-systolic wall stress relationships were steeper in young compared with older males [66]. Furthermore, the magnitude of the age-associated differences in these slopes was larger in males than in females, suggesting a greater decline in the contractile response to isoprenaline with age in males [66].

Adrenaline and noradrenaline

Intravenous infusion of adrenaline cause similar increases in heart rate in young and elderly subjects. However, the increase in stroke volume, ejection fraction, cardiac index, and systolic blood pressure is significantly greater in young subjects. The reduction in end-systolic wall stress and diastolic blood pressure is also greater in this group [67]. Older females show the smallest increases in stroke volume index and ejection fraction [68]. Similarly, an age-related decrease in the inotropic effects and a displacement of dose–effect relationship to the right were observed during noradrenaline infusion in adult and old pig heart preparations [68]. In humans there is evidence that the age-associated reduced responsiveness of cardiac β-adrenoreceptors and vascular α_1-adrenoreceptors is only unmasked when the counterregulatory action of the parasympathetic nervous system is removed [69]. However, in one study the cardiac chronotropic sensitivity to isoprenaline was significantly reduced in elderly compared with young subjects before, but was similar after autonomic blockade with atropine and clonidine [70].

Dopamine

Studies of the effects of age on the inotropic effects of dopamine have provided conflicting results. In spontaneously beating right atria rat preparations, the maximal inotropic response following single and cumulative doses of dopamine was significantly reduced with advancing age [71]. In another study, the responses of heart rate and atrioventricular conduction to dopamine infusion were studied in Langedorff perfused rat hearts. Greater increases in heart rate and atrioventricular conduction times were observed in aged hearts, whereas the contractile responses were impaired in this group [72].

Dobutamine

There are no data on the effect of age on heart rate response to dobutamine in patients with heart disease. After administration of stepwise incremental infusions of dobutamine in healthy volunteers aged 22–90 years, no significant reduction in β-adrenergic sensitivity was observed with advancing age [73]. By contrast, animal studies showed an age-associated reduction in the chronotropic effects of dobutamine [71].

Summary

The current available evidence on the effects of advancing age on the structure and function of the cardiovascular system and the responses to pharmacological stimuli has been discussed. Some of these effects, such as the reduction in arterial compliance and endothelial function, might contribute at least partly to the dramatic increase in cardiovascular morbidity and mortality observed in elderly subjects. Notably, recent data support a direct role for NO in the modulation of arterial compliance and, hence, cardiac afterload. This suggests the potential for pharmacological treatment. Clinical trials are required to support this hypothesis.

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