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Age-related change in endothelial and microvessel function and therapeutic consequences

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Summary

As the absolute numbers and proportion of older adults increases across most of the developed world, a greater understanding of the aetiopathogenic mechanisms of the increased vascular risk and their therapeutic implications becomes essential to all clinicians assessing and managing the geriatric patient. The role of endothelial function and the microcirculation is increasingly recognized in the maintenance of adequate perfusion, and their dysfunction is thought to be an early and potentially reversible mechanism by which age acts to increase cardiovascular risk.

Here we review evidence that altered microvascular function appears before other recognized predictors of vascular disease, and progresses from childhood to late adult life, preceding fulminant atherosclerotic or arteriosclerotic disease. Low birth-weight babies have reduced endothelial function in skin microvessels at 3 months, and by age ten brachial artery endothelial function is reduced in comparison with normal birth-weight babies. In overweight/obese adolescent children with clustering of traditional cardiovascular disease risk factors, endothelial function is lower compared with normal weight children and this appears to persist into early adulthood. Adult ageing is associated with impaired microvessel endothelial function and an increase in capillary blood pressure, independent of brachial artery blood pressure. Biological and lifestyle factors that influence microvessel function include body fat and visceral adiposity, sex hormone status, diet and physical activity.

Exploration of the therapeutic implications for management of endothelial dysfunction remains in embryonic state. The use of ACE-inhibitors, angiotensin receptor blockers and direct renin inhibitors in patients with evidence of microvascular damage such as retinopathy and microalbuminuria has been established; however, in the general older population the benefit has yet to be established. Therefore current recommendations are to screen for microvascular damage and if present target treatments after control of other vascular risk factors such as hypertension.

Keywords: microcirculation, endothelial function, ageing.

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Introduction

Age is one of the most important risk factors for cardiovascular disease,[1] although the exact mechanism, beyond a greater accumulation of exposure to environmental pathogens, by which ageing leads to cardiovascular events is not fully understood. As the absolute numbers and proportion of older adults increases across most of the developed world, a greater understanding of the aetiopathogenic mechanisms of the increased vascular risk and their therapeutic implications becomes essential to all clinicians assessing and managing the geriatric patient. The purpose of this review is to discuss what is currently understood about the role of the endothelium and microcirculation in the ageing process.

The endothelium

Endothelial dysfunction, a key vascular change observed with advancing age, is increasingly being recognized as an important early step in the process of clinical cardiovascular disease. The endothelium, that is the monolayer of cells forming the interface between circulating blood and the intima of all blood vessels, plays a vital role in maintaining vascular homeostasis.[2] The healthy endothelium is optimally placed and is able to respond to physical and chemical signals by production of a wide range of factors that regulate vascular tone, cellular adhesion, thromboresistance, smooth muscle cell proliferation, and vessel wall inflammation.[3] In

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normal physiology the endothelium produces nitric oxide (NO), mainly in response to shear stress, but also by messengers such as bradykinin, vascular endothelial growth factor (VEGF), adenosine and serotonin. This acts as a vasodilator adapting tissue perfusion to changes in cardiac output[4] whilst inhibiting inflammation, cellular proliferation and thrombosis, thereby maintaining the vascular wall in a quiescent state. Other vasodilatory mechanisms regulated by the endothelium include prostacyclin[5] and endothelium-derived hyperpolarizing factor (EDHF).[6] EDHF can compensate for loss of NO-mediated vascular tone particularly in the microcirculation.[7] All of these vasodilatory factors are reduced with advancing age.[8–10] Further, endothelial produced vasoconstrictors such as endothelin-1, prostanoids and angiotensin II, which in health help modulate vasomotion,[11,12] are up-regulated with increasing age. Additional work has demonstrated a pro-inflammatory and oxidative stress phenotype[13,14] in impaired endothelial function of carefully screened healthy, older people.

These impairments in endothelial function are mechanistically involved in the initiation and development of atherosclerosis[3,15–17] and predict future cardiovascular disease.[18–20] Because of this, impaired vascular endothelial function with advancing age has been widely studied as a putative and potentially reversible mechanism by which age acts to increase cardiovascular risk.

Recognition of the importance of the endothelium has resulted in a considerable amount of research, mostly focusing on conduit arteries and resistance vessels, often using a forearm model. However, the majority of the vascular endothelium lies within the microvasculature, due to the large surface area of the nutritive vessels when compared with the conduit vessels. As such, the role of endothelial dysfunction in the microcirculation plays an important role in regulating tissue perfusion.

The microcirculation

The microcirculation comprises flow within the arterioles and venules $<150\ \mu$m in diameter, which show a myogenic reduction in lumen diameter in response to increase in pressure, and capillaries.[21] It provides the interface for the delivery of oxygen and nutrients, the removal of waste products and carbon dioxide, transvascular exchange and tissue fluid economy.[22] Organs, tissues and most cells depend on adequate perfusion by the microcirculation and thus adequate microvessel function is essential for the cardiovascular system to fulfil this fundamental role.[22] As such, changes in microvessel function with age may have important consequences for organ function and overall human health. The structure and function of the microcirculation have been covered elsewhere in detail.[22–24]

The contribution of endothelial function to alterations in microvascular structure and function with advancing age has been the subject of increased interest in recent years. This is partly due to recognition of the importance of microcirculation in cardiovascular and metabolic diseases. Abnormalities of the microcirculation have been reported in a number of disease states including hypertension,[25,26] insulin resistance,[24] and type I and II diabetes.[27] Framingham Risk Score is also associated with impaired skin microvessel endothelium-dependent vasodilatation in healthy older men and women.[28]

Clinically, elevated urinary albumin excretion rate (AER), an indirect marker of renal microvascular damage, independently predicts total and cardiovascular mortality in diabetes,[29] hypertensive patients,[30] postmenopausal women,[31] elderly patients,[32] and the general (largely non-diabetic) population, right into the normal range of AER.[33–35] Similarly, microvascular retinopathy is associated with a 3-fold increase in risk of heart failure even in people without pre-existing coronary heart disease, diabetes or hypertension.[36] Cerebral microvascular disease indicated by the presence of white matter lesions or leukoariaosis on magnetic resonance imaging[37] were associated with increased risk of stroke in the Atherosclerosis Risk In Communities (ARIC) study. This study also showed that if retinopathy was also present the risk ratio rose from 2.6 to 18.1,[38] suggesting that greater risk might be conferred by systemically abnormal microvascular function.

Microvessel ageing across the human lifespan

Current evidence indicates that a number of factors contribute to alterations in microvascular function from birth to older age. These include genetic factors, developmental factors, age-related

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biological factors, environmental and lifestyle factors as well as the interaction of disease processes that probably combine to determine microcirculatory health.

Genetic factors

Studies of parents and offspring suggest that children of hypertensives have attenuated maximal cutaneous microvascular perfusion and capillary recruitment compared with those of normotensive parents, and offspring who go on to develop hypertension have further blunting of responses compared with those who remain normotensive.[39] As such, a genetic predisposition to poor microvessel function may constitute an important part of the inheritance and development of hypertension in these individuals. In contrast to children of hypertensive subjects, offspring of normotensive parents who themselves develop hypertension demonstrate no difference in microvessel function.[39]

Ethnic differences in microvascular function also suggest a genetic component to microvascular function. Women of African-Caribbean descent have poorer maximal cutaneous microvascular perfusion than European counterparts, and men and women of African-Caribbean descent have poorer post-occlusive microvascular reactive hyperaemia (i.e. the microvascular response to tissue ischaemia) compared with European counterparts after correcting for conventional risk factors.[40] Left ventricular hypertrophy is also greater in African-Caribbeans and some of this difference is explained by poorer microvessel function.[41] The mechanisms underlying inherited differences in microvessel function are uncertain[42] but these inherited differences may have important implications for appropriate risk stratification and clinical management of disease.

Developmental factors

Foetal development may also influence microvessel function. Low birth-weight babies born at full term have lower maximal hyperaemia at 3 months of age compared with babies of higher birth-weight.[43] This persists into childhood[44] and may contribute to increased cardiovascular risk associated with low birth-weight.[45] Impaired endothelial function and increased arterial stiffness have also been reported in adults with low birth-weight,[46] suggesting that low birth-weight is associated with systemically poor micro- and macrovascular function.

During puberty, microvascular function adapts during pubertal development probably because of the greater hydrostatic challenge incurred as a result of the growth spurt and progression towards adult height.[47] Lowering the leg from a supine position to below heart level induces vasoconstriction in healthy post- but not pre-pubertal children. Children with type I diabetes do not fully acquire this microcirculatory adaptation during puberty, even if they are free of diabetic complications.[47] Similarly, adult diabetics do not display this compensatory mechanism resulting in capillary hypertension upon standing,[47,48] potentially leaving the foot microcirculation exposed to high hydrostatic pressures associated with upright posture, perhaps contributing to the pathophysiology of the diabetic foot. These findings suggest that microvascular function during development and childhood may have important implications for disease pathophysiology and importantly precede other indicators of cardiovascular and metabolic diseases.

Adult ageing and the influence of biological and lifestyle factors

A common misconception is that microvascular function is a marker, whether cause or effect, of brachial arterial hypertension. However, a study exploring young and older normotensive and hypertensive subjects demonstrated impairment in endothelial-dependent (but not endothelial-independent) cutaneous microvascular vasodilatation and an increased capillary pressure in the older normotensive adults compared with their younger counterparts, but importantly no difference in capillary pressures or vascular function between the older adults with and without hypertension.[49] This suggests strongly that microvascular dysfunction is independent of brachial artery blood pressure. Microvessel dilatation in response to skin heating, used as a measure of maximal physiological tissue perfusion, is also diminished with age.[50] This appears to be mediated at least partly through alterations to nitric oxide signalling, but non-nitric oxide signalling mechanisms were also important.[51]

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Increasing weight is a recognized consequence of western ageing,[52] such that approximately 44% of over-65s in the UK are overweight and a third are obese. In women, obesity is associated with impaired capillary recruitment and endothelium-dependent vasodilatation both in the basal state and during experimental hyperinsulinaemia.[53] This attenuation of microvascular vasodilatation in response to insulin will necessarily attenuate nutritive supply to tissues and is thought to represent 'vascular insulin resistance'[53] and contribute to the development of hypertension.[54] Visceral adiposity appears to be particularly detrimental to microvessel function, most likely mediated by a pro-inflammatory state,[55] although the associated elevated circulating free fatty acid concentrations also are likely to contribute.[56] Finally, although not directly related, the high dietary salt usually associated with increased calorific intake is thought to influence microvessel function, most likely through increased activation of the renin angiotensin aldosterone system.[57] Angiotensin II acts on the endothelial cell wall to increase vasoconstriction through endothelin-1; however, at least part of this is mediated through the local angiotensin system, rather than the systemic renal controlled system.[22,58]

Aerobic exercise has been reported to attenuate the age-related decline in resistance vessel endothelial function through a nitric oxide-dependent mechanism.[59] A similar finding has recently been reported in skin microvessels studied using microdialysis. Microvessel function was worse in older sedentary compared with older active or younger men and this was attributable to impaired nitric oxide signalling.[60] An exercise training programme in the sedentary older cohort restored microvessel function and improved nitric oxide signalling.

In women, hormone status may impart important influences on microvessel function. Capillary pressure is lower in women compared with men below age 50 years but there is no difference between the sexes after age 50.[61] However, hormone replacement therapy does not appear to improve microvessel function in healthy post-menopausal women and may be detrimental to the microcirculation in diabetic women.[62] Impaired cutaneous post-occlusive reactive hyperaemia predicts increased cardiovascular risk as assessed by the Framingham risk scores, although it is unclear whether this is simply confounded by obesity and insulin resistance.[63] Clinical markers of microvascular dysfunction appear to play a stronger prognostic role in women than men. An elevated urinary albumin excretion rate after a myocardial infarction is associated with a 1.7-fold relative death risk in men, whereas in women, after all other conventional risk factors such as obesity, hypertension, lipid profile, renal function and smoking had been adjusted for, the relative death risk is 3.3, more than twice that of men. Similarly in normotensive type 2 diabetes the vascular event rate in women with microalbuminuria is over three times that of comparable men.[64] These data suggest that the microcirculation may play a more important role in the pathogenic mechanisms of vascular disease in women.

Therapeutic implications

Risk stratification

Measuring surrogates for microvascular and endothelial function is now commonplace in the assessment of patients at higher cardiovascular risk, such as those with diabetes, hypertension and chronic kidney disease.[65] Retinal microvascular changes due to ageing, hypertension and other processes appear to reflect cerebral microvascular disease[66] and are associated with stroke independent of other risk factors.[67] Although this is clearly in place caution should be exercised with interventions, particularly in the elderly, as currently the evidence for targeting microvascular and endothelial function remains in embryonic form.

Lifestyle modifications, including the prescription of aerobic exercise, dietary modifications, caloric restriction, and weight loss, can improve endothelial function.[68–70] These lifestyle modifications have also been reported to improve prognosis in a whole range of cardiovascular and other conditions; however, as yet the proportionate risk reduction due to this improvement in microvascular function is unclear.

Targeting microalbuminuria

The Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study demonstrated reduction in albuminuria translated to a reduction in cardiovascular endpoints.[71] This accounted for approximately 30% of the benefit that losartan

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provided over atenolol in the study and was independent of blood pressure control. This has also been demonstrated in diabetes and renal failure where reductions in microalbuminuria are proportionate to reductions in risk of future vascular events.[72] As such, microalbuminuria has become a therapeutic target in its own right in diabetes at least,[73] by the routine use of ACE-inhibitors, angiotensin receptor blockers and recently the direct renin inhibitor, aliskiren. This latter class is of particular interest because as well as having its safety and tolerability assessed specifically in an elderly cohort,[74] it has an anti-proteinuric effect at least as good as the ACE-inhibitor or ARB[75] and additional benefit, when added to the ARB, losartan, of 20% further reduction in urinary albumin excretion.[76] This benefit is independent of blood pressure and is thought to represent an effect on the aforementioned local renin-angiotensin activity. Additional therapy with non-dihydropyridine calcium channel blockers (i.e. verapamil and diltiazem) have consistently demonstrated reductions in proteinuria not achieved with the dihydropyridines (e.g. amlodipine, felodipine, nifedipine).[77]

From what has been presented thus far, it would be easy to imagine a simple argument that microvascular function declines with advancing age; ACE-inhibitors improve microvascular function, therefore all elderly patients should receive ACE-inhibitor therapy. Unfortunately this is not the case. The Antihypertensive and Lipid Lowering Treatment to prevent Heart Attack Trial (ALLHAT), the single biggest antihypertensive trial conducted, did not demonstrate any benefit from ACE-inhibitor-based therapy over thiazide-type diuretic or amlodipine.[78] A potential explanation for this is the lack of diuretics used in the ACE-inhibitor arm of ALLHAT. It is well recognized that, in order to get maximal antihypertensive effect of ACE-inhibition or ARBs, the renin-angiotensin system must be first stimulated with a diuretic. This does challenge the hypothesis of ubiquitous ACE-inhibitor therapy to improve microvascular function though, rather it justifies a targeted approach for those who have persistent microalbuminuria after adequate blood pressure control.[79]

Statins or cholesterol reduction

Cholesterol reduction with statin therapy has become almost ubiquitous in patients at high cardiovascular risk; however, early studies exploring the effects of cholesterol reduction were less than conclusive. Indeed a meta-analysis of diet, cholestyramine and fibrate therapies could demonstrate no reduction in mortality and only a non-significant ($P = 0.06$) trend in reduced cardiovascular events.[80] Subsequently many cholesterol-reducing studies using statins have demonstrated reductions in cardiovascular events and mortality,[81–83] and more recently have suggested benefits in conditions outside of the classic cardiovascular system such as Alzheimer's disease.[84] The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) Trial demonstrated a significant cardiovascular risk reduction despite all subjects having a 'normal' cholesterol but elevated high sensitivity C-reactive protein (hsCRP).[85] This hsCRP is a recognized marker of vascular inflammation that is tightly associated with endothelial dysfunction, suggesting the statin benefit was maximized in those with ongoing vascular damage, rather than absolute cholesterol concentration.

Endothelial function in diabetes

Endothelial dysfunction is common in diabetes and newer hypoglycaemic drugs have attempted to address this. The use of peroxisome proliferator-activated receptor-gamma agonists is associated with improved endothelial function;[86] however, they also cause fluid retention, through mechanisms as yet unknown, and weight gain that has counteracted the potential benefits.

There has been recent interest in therapies that influence the glucagon-like peptide (GLP)-1 pathway. Endogenous GLP-1 has been demonstrated to improve endothelial function in those with diabetes,[87] mediated directly through GLP-1 receptors located in the myocardium and vascular endothelium, and other, as yet unidentified, pathways.[88] Drugs that increase GLP-1, such as the DPP-4 inhibitors (gliptins) and GLP-1 analogues, are particularly useful in elderly patients as in addition to their potential benefits on endothelial function, they come with excellent tolerability in elderly and reduced hypoglycaemia risk.[89,90] In animal models they have also been demonstrated to reduce endothelial reperfusion injuries post-myocardial infarction, leading investigators to

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consider their use as a vascular protection in normoglycaemic individuals.[91,92]

Conclusion

The role of endothelial and microcirculatory dysfunction is increasingly recognized as an early step in the pathogenesis of vascular target organ damage. Elderly patients are at elevated risk, due to increased exposure to environmental risk factors and accumulation of multiple co-morbid conditions each adversely affecting pathways within vascular homeostasis. Clinically available tools for assessing microvascular function, such as urinary albumin excretion rate, should be utilized as part of risk stratification processes, in the hope that early targeted treatment may prevent or delay progression of cardiovascular disease and maintain health into old age.

Conflicts of interest

There are no conflicts of interest for any author.

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