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The Effect of Aging on the Cutaneous Microvasculature

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Abstract

Aging is associated with a progressive loss of function in all organs. Under normal conditions the physiologic compensation for age-related deficits is sufficient, but during times of stress the limitations of this reserve become evident. Explanations for this reduction in reserve include the changes in the microcirculation that occur during the normal aging process. The microcirculation is defined as the blood flow through arterioles, capillaries and venules, which are the smallest vessels in the vasculature and are embedded within organs and tissues. Optimal strategies to maintain the microvasculature following surgery and other stressors must use multifactorial approaches. Using skin as the model organ, we will review the anatomical and functional changes in the microcirculation with aging, and some of the available clinical strategies to potentially mitigate the effect of these changes on important clinical outcomes.

Keywords

Aging; microcirculation; arteriosclerosis; microvascular anatomy; microvascular physiology; cutaneous

I. Introduction

Aging is associated with a progressive loss of functional reserve in all organs including the skin (Braverman, 2000), central nervous system (Wahl and Schilling, 1993), cardiovascular (Goldspink, 2005), pulmonary (Lowery et al., 2013), and renal (Böhler et al., 1993) systems. Under normal conditions the physiologic compensation for age-related deficits is sufficient, but during times of stress the limitations of physiologic reserve become evident. Underlying this reduction in global organ reserve are the changes in the microcirculation that occur during the aging process (Montagna and Carlisle, 1990). The microcirculation is defined as

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the blood flow through arterioles, capillaries and venules, which are the smallest vessels in the vasculature and are embedded within organs and tissues. The microcirculation provides tissue perfusion, fluid homeostasis, and delivery of oxygen and other nutrients. It also controls temperature and the inflammatory response. Age-associated delays in microvascular responses to stressors lead to impairments in processes that are pivotal for wound healing, such as temperature regulation and tissue perfusion. Optimal healing strategies following surgery and other stressors must therefore use multifactorial approaches to address changes in the microcirculation in the older host (Bentov and Reed, 2014). Potential strategies include maintaining euthermia and euvolemia, better use of existing vessels to optimize vasodilation (e.g., physical activity, pneumatic compression, or pharmacologic mediators) (Husmann et al., 2008; Krcma et al., 2009), optimization of inflammatory and other cellular responses (e.g., stem cells) (Jadlowiec et al., 2012; Roubelakis et al., 2014), and strategies to address deficiencies in growth factors and sex steroids (Jadlowiec et al., 2012; Makrantonaki and Zouboulis, 2009; Scalia, 2013). We will review the anatomical and functional changes in the microcirculation with aging and some of the available strategies to potentially mitigate the effect of these changes on important clinical outcomes. When examining microcirculatory function and dysfunction, the cutaneous microcirculation is considered not only accessible but also representative of other organ systems (Holowatz et al., 2008). Accordingly, for the purposes of this review, we will utilize skin as the model for age-related changes in the microcirculation, and wound healing as a clinical outcome.

II. Age-related anatomical and functional changes in the microcirculation

It has long been appreciated that blood flow to the skin, the largest organ in the body, is reduced by 40% between the ages of 20 to 70 years (Tsuchida, 1993). This likely reflects changes in the microcirculation. Anatomically (following the direction of blood flow), the microcirculation is composed of arterioles, capillaries and venules. These blood vessels are lined by endothelial cells that regulate the exchange of water, nutrients, and waste products between blood and the tissues. Arterioles and venules are surrounded by smooth muscle that can contract (vasoconstriction) or relax (vasodilation) to regulate blood flow and pressure. Arterioles are 10-100μm in diameter, innervated and surrounded by smooth muscle cells. Arterioles carry the blood to the capillaries, which are 5-8 μm in diameter, not innervated and not invested by smooth muscle cells. Capillaries form the vascular bed largely responsible for the distribution of nutrients and exchange of waste products. Some capillaries are surrounded by pericytes (Rouget cells), which are a mesenchymal-type cell that has contractile properties and can also provide structural support to the capillaries (Armulik et al., 2011). Blood flows out of the capillaries into the venules that are 10-200μm in diameter and are surrounded by smooth muscle cells, but to lesser extent than arterioles. Some authors also include the lymphatic capillaries and collecting ducts, but these structures will not be discussed in this review. The following sections will highlight age-related changes in microvascular anatomy and physiology.

II a. Impaired microvascular reactivity

Not all vessels are perfused under conditions of normal metabolic demand (Chade, 2013). Consequently, non-perfused microvasculature represents a reserve that may be recruited under conditions of stress (Levy et al., 2008). Accessing this reserve is more difficult in aged organs due to impairments in the dynamic control of blood flow (Jackson et al., 2010). Reduction of arteriolar reactivity in the aged reflects changes in multiple mechanisms. For example, acetylcholine-induced endothelium-dependent vasodilatation declines with advancing age (although vasodilatation in response to bradykinin, substance P and isoproterenol is preserved) (DeSouza et al., 2002). Aging is also associated with deficits in endothelial nitric oxide availability (Feher et al., 2014) and nitric oxide synthase-dependent vasodilation of arterioles (Mayhan et al., 2008). Replacement of low estrogen levels in aged female rats can restore impairments of vasodilation (Kang et al., 2011). Reactive oxygen species signaling increases with age (Donato et al., 2007) and can impair endothelium-dependent vasodilation (Sindler et al., 2013). The availability of collateral circulation also declines in the aging vasculature. For example, collateral circulation via pial anastomoses after middle cerebral artery occlusion is reduced in an aged animal model (Yamaguchi et al., 1988).

Vasoconstrictive responses are also delayed with age. Cutaneous vasoconstriction in response to low body temperature is dependent on adrenergic stimulation by norepinephrine, which is impaired in aging (Thompson and Kenney, 2004). Interestingly, despite the limitation in dynamic responses, age is associated with chronic vasoconstriction mediated by local activation of Rho-kinase signaling (Thompson and Kenney, 2004). This form of vascular dysregulation is thought to contribute to additional age-related pathologies including hypertension and erectile dysfunction (Nunes et al., 2010).

II b. Increased vascular stiffness

Medial degeneration and deposition of extracellular matrix, fats, cholesterol and other substances results in a hardening of arteries that is often referred to as arteriosclerosis. The accumulation of hyaline materials (plasma proteins including C3, lipoproteins, intercellular connective tissue and cellular debris) is exacerbated by diseases more common with aging, such as hypertension or diabetes mellitus (Sawabe, 2010). Most studies of age-related changes in the arterioles focus on cerebral and renal arterioles (rather than skin), as sclerosis in these organs results in significant clinical deficits (cerebral hemorrhage, infarctions and nephrosclerosis). It is uncertain whether sclerosis of the venules (phlebosclerosis) is an age-related process since the prevalence of phlebosclerosis is increased with aging, but no correlation exists between age and the degree of phlebosclerosis (Leu et al., 1991).

II c. Decreased vascular density and impaired vascular organization

Angiogenesis (the formation of new microvasculature from existing vessels) is impaired in aged tissues (Rivard et al., 1999; Shimada et al., 2004) leading to a reduction in the number and density of blood vessels in most organs, including the skin. A decrease in microvascular density has been implicated in age-related nephropathy (Kang et al., 2001) and in neurodegeneration (Brown and Thore, 2011). In a mouse model of femoral artery ligation, an age-dependent diminished recovery of flow was observed. The decreased flow recovery

was due to a reduction in collateral number and diameter (collateral rarefaction) (Faber et al., 2011). The importance of collateral rarefaction as a therapeutic target in older humans remains to be elucidated (Epstein et al., 2012). Aging is also associated with disorganized branching geometry of the arterioles and capillaries. The lack of microvascular organization is seen in skin (Li et al., 2006), human retinal vasculature (Stanton et al., 1995) and skeletal muscle (Frontera et al., 2000; Russell et al., 2003). It is likely, but not proven, that decreased vascular density and increased vessel disorganization contributes to age-related deficits in diffusive transport capacity of the skin vasculature.

III. Interventions that influence the aging microcirculation

The importance of a well-functioning microcirculation is underscored during stress conditions (trauma, surgery, shock states etc.), which are accompanied by loss of vascular integrity, organ dysfunction, and even death (Hinshaw, 1996). There are a range of interventions that can optimize the microcirculation to better respond to these stresses. As an example, smoking cessation is commonly accepted as a lifestyle change that reduces post-operative respiratory complications, but also decreases the risk of surgical site infection (Wong et al., 2012). The latter benefit likely represents improvement in the cutaneous microcirculation. Other strategies aimed at improving microcirculatory function include: increasing physical activity, use of pneumatic compression, optimization of inflammatory responses, and addressing deficiencies in growth factors, sex steroids, or the extracellular matrix. Measures that support the microcirculation also encompass clinical strategies that are usually provided in the acute care setting: judicious use of fluids, circulatory support with inotropes and vasopressors, maintenance of normal body temperature, and optimization of pain control. The following sections will review interventions, including lifestyle modifications, clinical practice and experimental approaches, that impact the microcirculation in aging.

III. a. Lifestyle changes

Lifestyle habits influence numerous aspects of microvascular structure and function (Payne and Bearden, 2006). Adherence to a healthier lifestyle at age 70 to 90 years old is associated with a more than 50% lower rate of all-causes and cause-specific mortality (Knoops et al., 2004).

III. a. 1. Smoking cessation—Smoking accelerates telomere shortening with age (Valdes et al., 2005), potentially due to an increase in oxidative stress (Donohue, 2006). Remarkably, the aged are less likely to be provided with smoking cessation advice and support (Buckland and Connolly, 2005). Clinical assessment of skin wrinkling/aging in an aged cohort revealed that smoking one pack/day is equivalent to a decade of chronological aging (Leung and Harvey, 2002). Smoking has a profound effect on the microcirculation by causing endothelial cell dysfunction, decreasing endothelial-dependent vasodilation and reduced blood flow due to activation of circulating leukocytes and platelet aggregation (Lehr, 2000). Smoking cessation rapidly restores (within four weeks) some of the effects on the microcirculation as well as reduces the incidence of surgical site infection (Sorensen, 2012).

III a. 2. Physical activity—Despite the documented reduction in mortality and improvement of quality of life caused by physical activity, the molecular and cellular changes in the microvasculature that occur during physical activity are still being elucidated (Schiattarella et al., 2014). Regular physical activity can, in part, abrogate age-induced endothelial dysfunction (Taddei et al., 2000). Aerobic training is associated with higher nitric oxide generation in older subjects, which improves microcirculatory endothelial-dependent function (Franzoni et al., 2004). Increased cutaneous blood flow was observed in a group of aged male individuals who exercised regularly for over a decade when compared to sedentary matched controls (Wang et al., 2001). Even a short, but regular, training schedule was shown to improve healing in experiments where aged mice exercised daily for 8 days (Keylock et al., 2008), and aged humans exercised 3 times per week for one month, prior to cutaneous wounding (Emery et al., 2005).

III. b. Clinical interventions

III b. 1. Maintenance of normal body temperature—Age is an independent risk factor for development of hypothermia (Frank et al., 1992). Mild hypothermia is associated with vasoconstriction as measured by skin temperature and subcutaneous tissue oxygen tension (Sheffield et al., 1996). Compensatory thermoregulatory responses are decreased in the aged (Hajat et al., 2007), mostly due to altered regulation of skin blood flow in the setting of a reduced microcirculation (Holowatz et al., 2010). For the same reason, rewarming of the older adult takes longer than the time required to rewarm young adults (Carli et al., 1986). During surgery and anesthesia, the initial decrease in core temperature results from the redistribution of heat to the peripheral microcirculation. External prewarming in the preoperative area might prevent redistribution of core heat (de Brito Poveda et al., 2013). Combined strategies that use multiple modalities (prewarming with use of warmed fluids and forced-air warming devices), are more effective in the aged (Moola and Lockwood, 2011). The importance of maintenance of body temperature during surgery is highlighted by the observation that maintaining normothermia during surgery results in a 3-fold risk reduction in surgical wound infection (Kurz et al., 1996).

III b. 2. Judicious use of fluids—Assessing intravascular volume status is challenging in the aged (McGee et al., 1999). The consequences of extreme intravascular volume have deleterious effects; both hypovolemia (Arkilic et al., 2003) and excessive fluid administration (Brandstrup et al., 2003) are associated with microcirculatory impairments. Patients received more fluids and accumulated more collagen in their surgical incisions (Hartmann et al., 1992) when fluid administration was guided by markers of microcirculatory function (subcutaneous oxygen tension) rather than clinical criteria. However, increased fluid administration was not associated with reduced surgical wound infection rate (Kabon et al., 2005) or consistent improvements in other clinical parameters (Bundgaard-Nielsen et al., 2009). The need for more accurate determination of volume status is underscored by studies that show judicious use of fluids improves outcomes more in the older population than in the younger population (Spahn and Chassot, 2006). Noninvasive assessment of microvascular blood flow may help to identify patients who will benefit from fluid therapy (Pranskunas et al., 2013). Regardless of the method used to assess

volume status, a strategy of administering fluids in a manner that optimizes the microcirculation and maintains end organ perfusion is recommended.

Intravascular volume is also affected by anemia, which is common in the older population. Over 8% of men and 6% of women greater than 65 years of age, and without severe comorbidities, have anemia as defined by hemoglobin levels below 10g/dl (Endres et al., 2009). Low hemoglobin in young healthy subjects does not reduce subcutaneous tissue oxygenation (Hopf et al., 2000), but the hemoglobin level that optimizes the cutaneous microcirculation in older patients remains to be determined.

III b. 3. Pain control—Alleviating pain has a profound effect on the microvasculature. For example, anesthesia causes vasodilation by direct effects on the peripheral microcirculation (Kobayashi et al., 1990) and indirectly by central inhibition of vasoconstriction (Xiong et al., 1996). Agents used to treat pain show a broad array of effects on the microcirculation. Opioids induce the release of nitric oxide (Stefano et al., 1998), directly relax smooth muscle cells (White et al., 1990), and activate the VEGF receptor (Singleton et al., 2006). The effect of opioids on angiogenesis itself is still under investigation. Some suggest that opioids inhibit angiogenesis (Lam et al., 2008), whereas other data indicates that opioids might promote blood vessel formation (Faramarzi et al., 2009).

The response of the microcirculation to local anesthetic agents is not consistent. The first known local anesthetic, cocaine (Calatayud and Gonzalez, 2003), induces vasoconstriction, even at small doses, by inhibition of norepinephrine uptake (Lange et al., 1989). Modern local anesthetics (lidocaine (Johns et al., 1985) and bupivacaine (Johns et al., 1986)) have a dose dependent biphasic effect: low concentrations cause vasoconstriction of arterioles, while high concentrations cause vasodilation. Local anesthetics can be detrimental to angiogenesis by an anti-proliferative effect on mesenchymal cells (Lucchinetti et al., 2012). However, local anesthetics may have an overall positive influence on the microcirculation by reducing the stress response associated with pain (Bamigboye and Hofmeyr, 2009). Intra-articular lidocaine, used for pain management after knee surgery, increased subcutaneous tissue oxygen tension indicating improved microvascular flow (Akca et al., 1999). Human studies suggest that the dose-dependent properties of local anesthetics may be more pronounced in older tissues as a result of age-related decreases in hepatic blood flow and clearance (Nation et al., 1977).

III b. 4. Inotropes and vasopressors—Norepinephrine and epinephrine induce vasoconstriction (Jensen et al., 1985) and have effects on subsequent biological processes that influence the integrity of the microcirculation. For example, the microcirculation to the skeletal musculature and skin is impaired in patients suffering from end stage congestive heart failure due to high circulating levels of catecholamines, which increase afterload. This impairment is partially reversed by infusion of inotropic agents that increase cardiac output (Nanas et al., 2008). Monitoring blood pressure is not sufficient to evaluate flow in the microcirculation. In sepsis, it has been shown that maintaining systemic blood pressure with vasopressors did not result in improvement in microcirculatory parameters (for example, lactate levels, tissue dysoxia and regional intestinal capnography) (Spronk et al., 2004).

Interestingly, early microcirculatory perfusion indices did predict survival in humans with severe sepsis and septic shock (Trzeciak et al., 2007).

III. Experimental Interventions

III c. 1. Pneumatic compression—Age is an important risk factor for developing venous thromboembolism (Rosendaal, 1999) due to deficits in the microvascular responses and changes in circulating mediators that affect coagulation. Guidelines for older adults advise that intermittent pneumatic compression should be started before surgery and continue until fully ambulatory (Aronow, 2004). Intermittent pneumatic compression of the foot in the dependent position improves microcirculatory function, as measured by laser Doppler flux and transcutaneous oxygen tension (Abu-Own et al., 1993). Several mechanisms are proposed to mediate the effects of pneumatic compression on the microcirculation. In a study of patients suffering from claudication, pneumatic compression resulted in transient suspension of peripheral sympathetic autoregulation and enhanced release of nitric oxide, which results in increased blood flow (Delis and Knaggs, 2005). In a mouse model of arterial ligation, two weeks of treatment with intermittent pneumatic leg compression enhanced blood flow to collateral-dependent tissues (Roseguini et al., 2012). A single session of pneumatic compression was sufficient to regulate transcription of genes associated with inflammation and vascular remodeling in older humans (Sheldon et al., 2012)

III c. 2. Sex hormones—The lower incidence of cardiovascular disease in premenopausal women, relative to age-matched men, suggests a significant role for female gonadal hormones in the regulation of the vasculature (Mendelsohn and Karas, 2005). The finding of sex-specific differences in microvascular flow and vasodilatory capacity are observed even in newborn preterm infants (Stark et al., 2008). In an experimental model of hepatic ischemia/reperfusion, microvascular injury was more pronounced in male rats than in female rats. Treatment of the male rats with estrogen before ischemia reversed some of the deleterious effects on the microcirculation (Burkhardt et al., 2008). Menopause is associated with abnormal endothelial function, which can be reversed by long-term estrogen (but not progesterone) administration (Campisi et al., 2002). The effect of testosterone is unclear as it can improve (Worboys et al., 2001) or worsen (Hutchison et al., 1997) endothelial dysfunction.

III c. 3. Growth factors—Angiogenesis and microvascular function are dependent on cell proliferation, migration and regulation of the extracellular matrix. These processes are modulated by a number of growth factors; for example, transforming growth factor-beta (Beck et al., 1993), vascular endothelial growth factor (Gavin et al., 2006), platelet-derived growth factor (Andrae et al., 2008), insulin-like growth factor-1 (Thum et al., 2007) and basic fibroblast growth factor (Lederman et al., 2002). Age-related deficiencies in angiogenesis are due, in part, to decreased availability of some of these angiogenic growth factors in the extracellular milieu (Arthur et al., 1998). Clinical trials of growth factors for therapeutic angiogenesis continue to be evaluated (Ferrara and Kerbel, 2005), but have been largely disappointing (Barrientos et al., 2008). One exception is topical platelet-derived growth factor, which accelerates cutaneous wound closure (Saba et al., 2002) in part by

enhancing nitric oxide mediated vasodilation (Maejima et al., 2011). Further studies are needed to determine the optimal combination of angiogenic and other growth factors that are needed to improve the microcirculation and subsequent healing of wounds in older persons.

IV d. Stem Cells and Extracellular Matrix

It has been nearly 2 decades since stem cell therapies were first proposed to support the microcirculation by providing precursors that can promote angiogenesis in ischemic tissues. Initially, endothelial progenitor cells were isolated from human peripheral blood and shown to differentiate into mature endothelial cells (Asahara et al., 1997). These findings led to studies that evaluated implanted bone marrow cells to attain therapeutic angiogenesis in patients suffering from limb ischemia (Tateishi-Yuyama et al., 2002). However, aging is also associated with deficits in the regulatory networks of mesenchymal stromal cells, underscoring the complexity of interventions to enhance angiogenesis in aged tissues (Lepperdinger, 2011). Subsequent clinical trials have been slow to evolve due to insufficient data showing consistent benefit (Moazzami et al., 2011), and concerns that activation of this cascade could promote neoplastic processes (Quante et al., 2011).

Age-related changes in the millieu surrounding the microvasculature reflect deficits in cellular biosynthesis as well as the expression of growth factors, cytokines, extracellular matrix, and matrix metalloproteinases (Ambati et al., 2003; Bentov and Reed, 2014; Gurtner et al., 2008). As an example, matrix metalloproteinases promote cell proliferation and vessel ingrowth by degrading the existing extracellular matrix. Metalloproteinases activity is balanced, in part, by endogenous tissue inhibitors of metalloproteinases. Aged tissues are associated with a tendency toward overexpression of metalloproteinases activity (Ashcroft et al., 1997b) and reduced levels of tissue inhibitors of metalloproteinases (Ashcroft et al., 1997a), but these changes are tissue specific. Any approaches to enhance the microcirculation in aged tissues will require attention to this dysregulation of metalloproteinase expression and activity (Gargioli et al., 2008).

Conclusion

Aging is associated with dramatic changes in the anatomy and function of the microcirculation. The microcirculation plays a seminal role in tissue hemostasis and the response to stress and injury. Age-associated deficits in microvascular anatomy and function contribute to deficits in tissue healing in the older population. A wide spectrum of clinical interventions is already utilized, and additional therapies are under investigation, to reverse deficits in the microvascular response to stress in the older host. Successful approaches will undoubtedly require a multi-faceted strategy that addresses age-related changes in vessel density, organization, and physiology in order to optimize the microcirculation in aging.

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References

Abu-Own A, et al. Effects of intermittent pneumatic compression of the foot on the microcirculatory function in arterial disease. Eur J Vasc Surg. 1993; 7:488–92. [PubMed: 8405490]

Akca O, et al. Postoperative pain and subcutaneous oxygen tension. Lancet. 1999; 354:41–2. [PubMed: 10406365]

Ambati J, et al. Age-related macular degeneration: etiology, pathogenesis, and therapeutic strategies. Surv Ophthalmol. 2003; 48:257–93. [PubMed: 12745003]

Andrae J, et al. Role of platelet-derived growth factors in physiology and medicine. Genes Dev. 2008; 22:1276–312. [PubMed: 18483217]

Arkilic CF, et al. Supplemental perioperative fluid administration increases tissue oxygen pressure. Surgery. 2003; 133:49–55. [PubMed: 12563237]

Armulik A, et al. Pericytes: developmental, physiological, and pathological perspectives, problems, and promises. Dev Cell. 2011; 21:193–215. [PubMed: 21839917]

Aronow WS. The Prevention of Venous Thromboembolism in Older Adults: Guidelines. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2004; 59:M42–M47.

Arthur WT, et al. Growth factors reverse the impaired sprouting of microvessels from aged mice. Microvasc Res. 1998; 55:260–70. [PubMed: 9657926]

Asahara T, et al. Isolation of putative progenitor endothelial cells for angiogenesis. Science. 1997; 275:964–7. [PubMed: 9020076]

Ashcroft GS, et al. Human ageing impairs injury-induced in vivo expression of tissue inhibitor of matrix metalloproteinases (TIMP)-1 and -2 proteins and mRNA. J Pathol. 1997a; 183:169–76. [PubMed: 9390029]

Ashcroft GS, et al. Age-related differences in the temporal and spatial regulation of matrix metalloproteinases (MMPs) in normal skin and acute cutaneous wounds of healthy humans. Cell Tissue Res. 1997b; 290:581–91. [PubMed: 9369533]

Bamigboye AA, Hofmeyr GJ. Local anaesthetic wound infiltration and abdominal nerves block during caesarean section for postoperative pain relief. Cochrane Database Syst Rev. 2009 CD006954.

Barrientos S, et al. PERSPECTIVE ARTICLE: Growth factors and cytokines in wound healing. Wound Repair and Regeneration. 2008; 16:585–601. [PubMed: 19128254]

Beck L, et al. One systemic administration of transforming growth factor-beta 1 reverses age-or glucocorticoid-impaired wound healing. Journal of Clinical Investigation. 1993; 92:2841. [PubMed: 8254038]

Bentov I, Reed MJ. Anesthesia, microcirculation, and wound repair in aging. Anesthesiology. 2014; 120:760–72. [PubMed: 24195972]

Böhler J, et al. Renal functional reserve in elderly patients. Clinical nephrology. 1993; 39:145–150. [PubMed: 8462202]

Brandstrup B, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. Ann Surg. 2003; 238:641–8. [PubMed: 14578723]

Braverman IM. The Cutaneous Microcirculation. J Investig Dermatol Symp Proc. 2000; 5:3–9.

Brown WR, Thore CR. Review: Cerebral microvascular pathology in ageing and neurodegeneration. Neuropathology and Applied Neurobiology. 2011; 37:56–74. [PubMed: 20946471]

Buckland A, Connolly MJ. Age-related differences in smoking cessation advice and support given to patients hospitalised with smoking-related illness. Age and Ageing. 2005; 34:639–642. [PubMed: 16267193]

Bundgaard-Nielsen M, et al. ‘Liberal’ vs. ‘restrictive’ perioperative fluid therapy--a critical assessment of the evidence. Acta Anaesthesiol Scand. 2009; 53:843–51. [PubMed: 19519723]

Burkhardt M, et al. The effect of estrogen on hepatic microcirculation after ischemia/reperfusion. International Journal of Colorectal Disease. 2008; 23:113–119. [PubMed: 17665206]

Calatayud J, Gonzalez A. History of the development and evolution of local anesthesia since the coca leaf. Anesthesiology. 2003; 98:1503–8. [PubMed: 12766665]

Campisi R, et al. Noninvasive assessment of coronary microcirculatory function in postmenopausal women and effects of short-term and long-term estrogen administration. Circulation. 2002; 105:425–30. [PubMed: 11815423]

Carli F, et al. An investigation of factors affecting postoperative rewarming of adult patients. Anaesthesia. 1986; 41:363–9. [PubMed: 3706684]

Chade AR. Renal vascular structure and rarefaction. Compr Physiol. 2013; 3:817–31. [PubMed: 23720331]

de Brito Poveda V, et al. A systematic review on the effectiveness of prewarming to prevent perioperative hypothermia. J Clin Nurs. 2013; 22:906–18. [PubMed: 22978458]

Delis KT, Knaggs AL. Duration and amplitude decay of acute arterial leg inflow enhancement with intermittent pneumatic leg compression: an insight into the implicated physiologic mechanisms. J Vasc Surg. 2005; 42:717–25. [PubMed: 16242560]

DeSouza CA, et al. Evidence for agonist-specific endothelial vasodilator dysfunction with ageing in healthy humans. J Physiol. 2002; 542:255–62. [PubMed: 12096067]

Donato AJ, et al. Direct evidence of endothelial oxidative stress with aging in humans: relation to impaired endothelium-dependent dilation and upregulation of nuclear factor-kappaB. Circ Res. 2007; 100:1659–66. [PubMed: 17478731]

Donohue JF. Ageing, smoking and oxidative stress. Thorax. 2006; 61:461–462. [PubMed: 16738041]

Emery CF, et al. Exercise Accelerates Wound Healing Among Healthy Older Adults: A Preliminary Investigation. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2005; 60:1432–1436.

Endres HG, et al. Prevalence of anemia in elderly patients in primary care: impact on 5-year mortality risk and differences between men and women. Curr Med Res Opin. 2009; 25:1143–58. [PubMed: 19317606]

Epstein SE, et al. Effects of aging on the collateral circulation, and therapeutic implications. Circulation. 2012; 125:3211–3219. [PubMed: 22733335]

Faber JE, et al. Aging causes collateral rarefaction and increased severity of ischemic injury in multiple tissues. Arteriosclerosis, thrombosis, and vascular biology. 2011; 31:1748–1756.

Faramarzi N, et al. Opioid receptor antagonist promotes angiogenesis in bile duct ligated rats. J Gastroenterol Hepatol. 2009; 24:1226–9. [PubMed: 19486259]

Feher A, et al. Age-related impairment of conducted dilation in human coronary arterioles. Am J Physiol Heart Circ Physiol. 2014; 306:H1595–601. [PubMed: 24778172]

Ferrara N, Kerbel RS. Angiogenesis as a therapeutic target. Nature. 2005; 438:967–974. [PubMed: 16355214]

Frank SM, et al. Epidural versus general anesthesia, ambient operating room temperature, and patient age as predictors of inadvertent hypothermia. Anesthesiology. 1992; 77:252–7. [PubMed: 1642343]

Franzoni F, et al. Effects of age and physical fitness on microcirculatory function. Clin Sci (Lond). 2004; 106:329–35. [PubMed: 14588072]

Frontera WR, et al. Aging of skeletal muscle: a 12-yr longitudinal study. Journal of Applied Physiology. 2000; 88:1321–1326. [PubMed: 10749826]

Gargioli C, et al. PlGF-MMP-9-expressing cells restore microcirculation and efficacy of cell therapy in aged dystrophic muscle. Nature medicine. 2008; 14:973–8.

Gavin T, et al. Soleus, plantaris and gastrocnemius VEGF mRNA responses to hypoxia and exercise are preserved in aged compared with young female C57BL/6 mice. Acta Physiologica. 2006; 188:113–121. [PubMed: 16948798]

Goldspink DF. Ageing and activity: their effects on the functional reserve capacities of the heart and vascular smooth and skeletal muscles. Ergonomics. 2005; 48:1334–1351. [PubMed: 16338704]

Gurtner GC, et al. Wound repair and regeneration. Nature. 2008; 453:314–321. [PubMed: 18480812]

Hajat S, et al. Heat-related and cold-related deaths in England and Wales: who is at risk? Occup Environ Med. 2007; 64:93–100. [PubMed: 16990293]

Hartmann M, et al. Effect of tissue perfusion and oxygenation on accumulation of collagen in healing wounds. Randomized study in patients after major abdominal operations. Eur J Surg. 1992; 158:521–6. [PubMed: 1360822]

Hinshaw LB. Sepsis/septic shock: participation of the microcirculation: an abbreviated review. Crit Care Med. 1996; 24:1072–8. [PubMed: 8681576]

Holowatz LA, et al. Aging and the control of human skin blood flow. Front Biosci (Landmark Ed). 2010; 15:718–39. [PubMed: 20036842]

Holowatz LA, et al. The human cutaneous circulation as a model of generalized microvascular function. Journal of Applied Physiology. 2008; 105:370–372. [PubMed: 17932300]

Hopf HW, et al. Subcutaneous perfusion and oxygen during acute severe isovolemic hemodilution in healthy volunteers. Arch Surg. 2000; 135:1443–9. [PubMed: 11115350]

Husmann M, et al. Integrity of venoarteriolar reflex determines level of microvascular skin flow enhancement with intermittent pneumatic compression. J Vasc Surg. 2008; 48:1509–13. [PubMed: 18829220]

Hutchison SJ, et al. Testosterone Worsens Endothelial Dysfunction Associated With Hypercholesterolemia and Environmental Tobacco Smoke Exposure in Male Rabbit Aorta 1. Journal of the American College of Cardiology. 1997; 29:800–807. [PubMed: 9091527]

Jackson DN, et al. Blunting of rapid onset vasodilatation and blood flow restriction in arterioles of exercising skeletal muscle with ageing in male mice. The Journal of physiology. 2010; 588:2269–2282. [PubMed: 20375140]

Jadlowiec C, et al. Stem cell therapy for critical limb ischemia: what can we learn from cell therapy for chronic wounds? Vascular. 2012; 20:284–9. [PubMed: 23086986]

Jensen JA, et al. Epinephrine lowers subcutaneous wound oxygen tension. Curr Surg. 1985; 42:472–4. [PubMed: 4075834]

Johns RA, et al. Lidocaine constricts or dilates rat arterioles in a dose-dependent manner. Anesthesiology. 1985; 62:141–4. [PubMed: 3970363]

Johns RA, et al. Dose-dependent effects of bupivacaine on rat muscle arterioles. Anesthesiology. 1986; 65:186–91. [PubMed: 3740507]

Kabon B, et al. Supplemental intravenous crystalloid administration does not reduce the risk of surgical wound infection. Anesth Analg. 2005; 101:1546–53. [PubMed: 16244030]

Kang D-H, et al. Impaired angiogenesis in the aging kidney: Vascular endothelial growth factor and Thrombospondin-1 in renal disease. American Journal of Kidney Diseases. 2001; 37:601–611. [PubMed: 11228186]

Kang LS, et al. Aging and estrogen alter endothelial reactivity to reactive oxygen species in coronary arterioles. Am J Physiol Heart Circ Physiol. 2011; 300:H2105–15. [PubMed: 21441309]

Keylock KT, et al. Exercise accelerates cutaneous wound healing and decreases wound inflammation in aged mice. Am J Physiol Regul Integr Comp Physiol. 2008; 294:R179–84. [PubMed: 18003791]

Knoops KB, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly european men and women: The hale project. JAMA. 2004; 292:1433–1439. [PubMed: 15383513]

Kobayashi Y, et al. Effect of enflurane on contractile reactivity in isolated canine mesenteric arteries and veins. Anesth Analg. 1990; 70:530–6. [PubMed: 2331070]

Krcma M, et al. Effect of mild increase of physical activity on microvasculary reactivity in obese subjects with diabetes mellitus type 2. Exp Clin Endocrinol Diabetes. 2009; 117:150–2. [PubMed: 19053020]

Kurz A, et al. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. New England Journal of Medicine. 1996; 334:1209–1216. [PubMed: 8606715]

Lam C-F, et al. Prolonged use of high-dose morphine impairs angiogenesis and mobilization of endothelial progenitor cells in mice. Anesthesia & Analgesia. 2008; 107:686–692. [PubMed: 18633053]

Lange RA, et al. Cocaine-induced coronary-artery vasoconstriction. N Engl J Med. 1989; 321:1557–62. [PubMed: 2573838]

Lederman RJ, et al. Therapeutic angiogenesis with recombinant fibroblast growth factor-2 for intermittent claudication (the TRAFFIC study): a randomised trial. The Lancet. 2002; 359:2053–2058.

Lehr HA. Microcirculatory dysfunction induced by cigarette smoking. Microcirculation. 2000; 7:367–84. [PubMed: 11142334]

Lepperdinger G. Inflammation and mesenchymal stem cell aging. Curr Opin Immunol. 2011; 23:518–24. [PubMed: 21703839]

Leu HJ, et al. Phlebosclerosis: disorder or disease? Vasa. 1991; 20:230–6. [PubMed: 1950139]

Leung WC, Harvey I. Is skin ageing in the elderly caused by sun exposure or smoking? British Journal of Dermatology. 2002; 147:1187–1191. [PubMed: 12452869]

Levy BI, et al. Impaired Tissue Perfusion: A Pathology Common to Hypertension, Obesity, and Diabetes Mellitus. Circulation. 2008; 118:968–976. [PubMed: 18725503]

Li L, et al. Age-related changes of the cutaneous microcirculation in vivo. Gerontology. 2006; 52:142–53. [PubMed: 16645294]

Lowery EM, et al. The aging lung. Clin Interv Aging. 2013; 8:1489–96. [PubMed: 24235821]

Lucchinetti E, et al. Antiproliferative effects of local anesthetics on mesenchymal stem cells: potential implications for tumor spreading and wound healing. Anesthesiology. 2012; 116:841–56. [PubMed: 22343474]

Maejima D, et al. Platelet-Derived Growth Factor (PDGF)-BB Produces NO-Mediated Relaxation and PDGF Receptor β-Dependent Tonic Contraction in Murine Iliac Lymph Vessels. Microcirculation. 2011; 18:474–486. [PubMed: 21535294]

Makrantonaki E, Zouboulis CC. Androgens and ageing of the skin. Curr Opin Endocrinol Diabetes Obes. 2009; 16:240–5. [PubMed: 19390323]

Mayhan WG, et al. Age-related alterations in reactivity of cerebral arterioles: role of oxidative stress. Microcirculation. 2008; 15:225–36. [PubMed: 18386218]

McGee S, et al. The rational clinical examination. Is this patient hypovolemic? JAMA. 1999; 281:1022–9. [PubMed: 10086438]

Mendelsohn ME, Karas RH. Molecular and cellular basis of cardiovascular gender differences. Science. 2005; 308:1583–7. [PubMed: 15947175]

Moazzami K, et al. Local intramuscular transplantation of autologous mononuclear cells for critical lower limb ischaemia. The Cochrane database of systematic reviews. 2011 CD008347.

Montagna W, Carlisle K. Structural changes in ageing skin. Br J Dermatol. 1990; 122(Suppl 35):61–70. [PubMed: 2186788]

Moola S, Lockwood C. Effectiveness of strategies for the management and/or prevention of hypothermia within the adult perioperative environment. Int J Evid Based Healthc. 2011; 9:337–45. [PubMed: 22093385]

Nanas S, et al. Inotropic agents improve the peripheral microcirculation of patients with end-stage chronic heart failure. J Card Fail. 2008; 14:400–6. [PubMed: 18514932]

Nation RL, et al. Lignocaine kinetics in cardiac patients and aged subjects. Br J Clin Pharmacol. 1977; 4:439–48. [PubMed: 901735]

Nunes KP, et al. RhoA/Rho-kinase and vascular diseases: what is the link? Cellular and molecular life sciences. 2010; 67:3823–3836. [PubMed: 20668910]

Payne GW, Bearden SE. The Microcirculation of Skeletal Muscle in Aging. Microcirculation. 2006; 13:275–277. [PubMed: 16611593]

Pranskunas A, et al. Microcirculatory blood flow as a tool to select ICU patients eligible for fluid therapy. Intensive Care Med. 2013; 39:612–9. [PubMed: 23263029]

Quante M, et al. Bone marrow-derived myofibroblasts contribute to the mesenchymal stem cell niche and promote tumor growth. Cancer cell. 2011; 19:257–272. [PubMed: 21316604]

Rivard A, et al. Age-dependent impairment of angiogenesis. Circulation. 1999; 99:111–20. [PubMed: 9884387]

Roseguini BT, et al. Intermittent pneumatic leg compressions enhance muscle performance and blood flow in a model of peripheral arterial insufficiency. 2012

Rosendaal FR. Risk factors for venous thrombotic disease. Thromb Haemost. 1999; 82:610–9. [PubMed: 10605758]

Roubelakis MG, et al. Platelet-Rich Plasma (PRP) Promotes Fetal Mesenchymal Stem/Stromal Cell Migration and Wound Healing Process. Stem Cell Rev. 2014

Russell JA, et al. Effects of aging on capillary geometry and hemodynamics in rat spinotrapezius muscle. 2003

Saba AA, et al. Topical platelet-derived growth factor enhances wound closure in the absence of wound contraction: an experimental and clinical study. Ann Plast Surg. 2002; 49:62–6. discussion 66. [PubMed: 12142597]

Sawabe M. Vascular aging: From molecular mechanism to clinical significance. Geriatrics & Gerontology International. 2010; 10:S213–S220. [PubMed: 20590836]

Scalia R. The microcirculation in adipose tissue inflammation. Rev Endocr Metab Disord. 2013; 14:69–76. [PubMed: 23378133]

Schiattarella GG, et al. Physical activity in the prevention of peripheral artery disease in the elderly. Front Physiol. 2014; 5:12. [PubMed: 24624088]

Sheffield CW, et al. Centrally and locally mediated thermoregulatory responses alter subcutaneous oxygen tension. Wound Repair Regen. 1996; 4:339–45. [PubMed: 17177730]

Sheldon RD, et al. Acute impact of intermittent pneumatic leg compression frequency on limb hemodynamics, vascular function, and skeletal muscle gene expression in humans. Journal of Applied Physiology. 2012; 112:2099–2109. [PubMed: 22442025]

Shimada T, et al. Angiogenesis and vasculogenesis are impaired in the precocious-aging klotho mouse. Circulation. 2004; 110:1148–1155. [PubMed: 15302783]

Sindler AL, et al. Age and exercise training alter signaling through reactive oxygen species in the endothelium of skeletal muscle arterioles. J Appl Physiol (1985). 2013; 114:681–93. [PubMed: 23288555]

Singleton PA, et al. Methylnaltrexone inhibits opiate and VEGF-induced angiogenesis: role of receptor transactivation. Microvasc Res. 2006; 72:3–11. [PubMed: 16820176]

Sorensen LT. Wound healing and infection in surgery. The clinical impact of smoking and smoking cessation: a systematic review and meta-analysis. Arch Surg. 2012; 147:373–83. [PubMed: 22508785]

Spahn DR, Chassot PG. CON: Fluid restriction for cardiac patients during major noncardiac surgery should be replaced by goal-directed intravascular fluid administration. Anesth Analg. 2006; 102:344–6. [PubMed: 16428519]

Spronk PE, et al. Bench-to-bedside review: sepsis is a disease of the microcirculation. Crit Care. 2004; 8:462–8. [PubMed: 15566617]

Stanton AV, et al. Vascular network changes in the retina with age and hypertension. J Hypertens. 1995; 13:1724–8. [PubMed: 8903640]

Stark MJ, et al. Sex-specific differences in peripheral microvascular blood flow in preterm infants. Pediatr Res. 2008; 63:415–9. [PubMed: 18356749]

Stefano GB, et al. Antagonism of LPS and IFN-gamma induction of iNOS in human saphenous vein endothelium by morphine and anandamide by nitric oxide inhibition of adenylate cyclase. J Cardiovasc Pharmacol. 1998; 31:813–20. [PubMed: 9641464]

Taddei S, et al. Physical activity prevents age-related impairment in nitric oxide availability in elderly athletes. Circulation. 2000; 101:2896–901. [PubMed: 10869260]

Tateishi-Yuyama E, et al. Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: a pilot study and a randomised controlled trial. Lancet. 2002; 360:427–35. [PubMed: 12241713]

Thompson CS, Kenney WL. Altered neurotransmitter control of reflex vasoconstriction in aged human skin. J Physiol. 2004; 558:697–704. [PubMed: 15181162]

Thum T, et al. Age-dependent impairment of endothelial progenitor cells is corrected by growth hormone mediated increase of insulin-like growth factor-1. Circulation research. 2007; 100:434–443. [PubMed: 17234973]

Trzeciak S, et al. Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: relationship to hemodynamics, oxygen transport, and survival. Ann Emerg Med. 2007; 49:88–98. 98, e1–2. [PubMed: 17095120]

Tsuchida Y. The effect of aging and arteriosclerosis on human skin blood flow. J Dermatol Sci. 1993; 5:175–81. [PubMed: 8241073]

Valdes A, et al. Obesity, cigarette smoking, and telomere length in women. The Lancet. 2005; 366:662–664.

Wahl, M.; Schilling, L. Regulation of Cerebral Blood Flow — A Brief Review. In: Unterberg, A., et al., editors. Monitoring of Cerebral Blood Flow and Metabolism in Intensive Care. Vol. Vol. 59. Springer; Vienna: 1993. p. 3-10.

Wang JS, et al. Tai Chi Chuan training to enhance microcirculatory function in healthy elderly men. Archives of physical medicine and rehabilitation. 2001; 82:1176–80. [PubMed: 11552187]

White DA, et al. Decrease in vascular resistance in the isolated canine hindlimb after graded doses of alfentanil, fentanyl, and sufentanil. Anesth Analg. 1990; 71:29–34. [PubMed: 2141970]

Wong J, et al. Short-term preoperative smoking cessation and postoperative complications: a systematic review and meta-analysis. Canadian Journal of Anesthesia/Journal canadien d'anesthésie. 2012; 59:268–279.

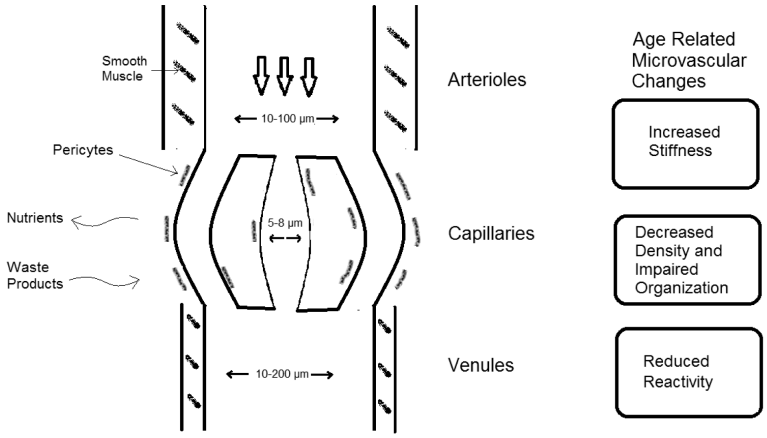
Worboys S, et al. Evidence that parenteral testosterone therapy may improve endothelium-dependent and-independent vasodilation in postmenopausal women already receiving estrogen. The Journal of Clinical Endocrinology & Metabolism. 2001; 86:158–161. [PubMed: 11231994]

Xiong J, et al. Isoflurane produces marked and nonlinear decreases in the vasoconstriction and shivering thresholds. Anesthesiology. 1996; 85:240–5. [PubMed: 8712437]

Yamaguchi S, et al. Effect of aging on collateral circulation via pial anastomoses in cats. Gerontology. 1988; 34:157–64. [PubMed: 3181764]

Highlights

1. Age related changes in the microcirculation lead to reduced reserve during stress.
2. Age related changes include decreased density, lack of organization and impaired reactivity.
3. Current approaches to improve the microcirculation focus on optimizing vascular reactivity.
4. Future directions will need a multifactorial approach to improve microvascular function.



The aging microcirculation

The microcirculation consists of arterioles, capillaries and venules. Age-related changes in microvascular anatomy and physiology are noted in the figure.