Plants and the Microcirculation: A Powerful New Clinical Paradigm

by Kerry Bone

We receive nearly all our tissue nourishment and oxygen via the circulation of blood. The common view is that our circulatory or cardiovascular system consists of veins, arteries and the heart. Hence, all circulatory health problems are seen to arise from malfunctions of these key structures of the macrocirculation. But missing from this perspective is any consideration for the largest, and most neglected, part of our circulatory system. This is the microcirculation, the part that actually does the job of tissue nourishment. Allied to, and intimately connected to, the microcirculation is the concept of healthy vascular endothelial function.

Gaining new insights into this overlooked topic can transform the way many patients are treated, including not only those with just circulatory problems, but an extraordinarily wide range of other common diseases. There is abundant clinical evidence that herbs and plant foods can play a key role in maintaining microcirculatory and endothelial health. In fact, at present there is much more comprehension of the benefits of plants in this context than for drugs.

In support of this contention, a recent scientific review of role of the microcirculation in health and disease observed:[1]

> 'The difficulty of accessing microcirculation in view of the extremely small dimensions of these vessels has been by far the principal reason why this enormous anatomical entity has been essentially neglected for decades……With very few exceptions, pentoxifylline and the antidiabetic metformin, no specific treatments have been developed for treating disorders at the microcirculatory level'.

What is the microcirculation?

The microvascular bed is an anatomical entity comprising countless small arterioles, capillaries and venules. Tissues such as the retina of the eye and the glomeruli of the kidney are particularly rich in microcirculation, because of their specific functions. The health of the microcirculation determines the blood supply and nutrient flow to all our vital tissues, but especially to vulnerable structures such as the long nerves that flow out of our spinal column to our limbs. Hence with diabetes (which damages the

microcirculation) these tissues are specifically affected: namely as retinopathy, nephropathy and neuropathy. These come under the general heading of diabetic microangiopathy, which is the best known expression of microvascular disease.

The vascular endothelium

The vascular endothelium is the delicate monolayer of cells lining all blood vessels. It regulates the contractile and proliferative state of underlying smooth muscle cells and the interaction of the blood vessel wall with the circulating blood (eg as the gateway for immune cells and the interactions that trigger haemostasis).[1] The multitude of tiny vessels throughout the body means the microcirculation contains the most significant proportion of the endothelial surface of the vascular bed. Hence, much of the understanding and implications of endothelial dysfunction are relevant to the consideration of microcirculatory health. If the vascular endothelial cells of the human body were aligned end to end they would go around the world four times.[2]

Microvascular physiology

The small arteries and arterioles dilate or contract to maintain a constant flow of blood to the microvascular bed.[1] Capillaries are also able to regulate their flow by transmitting signals to upstream controlling arterioles. A multitude of factors influence the contraction or relaxation of arterioles (such as innervation, insulin, melatonin, blood viscosity and metabolites), but a key factor is nitric oxide (NO). In addition to this arteriolar control of capillary blood flow, other considerations are at play in determining the effective flow of blood through the capillaries. These include the haematocrit, blood viscosity and red blood cell deformability/aggregation.

Erythrocytes are biconcave-shaped cells that have an axial diameter usually above the internal diameter of capillaries. They must elongate to cross the tube: red cell deformability is therefore a crucial parameter for normal capillary flow, as illustrated by the vascular pain crisis in sickle cell anaemia patients.[1]

Microvascular function and disease

According to the key review mentioned above:[1]

> ‘The fundamental role of microvessels is to supply target tissues with oxygen and nutrients; therefore it appears logical that microvascular disorders will impact on tissue function, given the close coupling between flow and metabolism.’

This review then goes on to list a range of diseases linked to microvascular dysfunction. These are overweight/obesity, diabetes, hypertension, low birth weight, sleep disorders, Alzheimer’s disease, gout, erythromelalgia, venous insufficiency, lupus, haemochromatosis, high ferritin, cardiometabolic syndrome, non-alcoholic steatotic hepatitis, polycystic ovary syndrome, gestational diabetes, acromegaly, rheumatoid arthritis, scleroderma, Bechet’s disease, hyperdynamic circulation, myocardial infarction, stroke, β-thalassaemia and HIV. But even this extensive list is incomplete. Based on the current literature we can credibly add the following diseases or applications: liver disease in general, kidney disease, neuropathies/neuralgias, restless leg syndrome, osteoarthritis (OA), retinal diseases, poor healing of any tissue, intervertebral disc damage, recovery from ischaemic damage, anti-ageing, athletic performance and cancer (especially to mitigate the damage caused by conventional treatments).

What damages the microcirculation?

Smoking is a key factor. A single cigarette has an immediate effect on microcirculatory control. Passive smoking (second-hand smoke) for 10 minutes from two cigarettes decreased capillary blood flow by more than 50%.[3] Based on assessment of dental surgical procedures, current smoking status was observed to adversely affect healing capacity.[4]

Other factors shown to damage vascular endothelial and microcirculatory health include poor glycaemic control (see later), hypertension, increased oxidative stress, elevated homocysteine, obesity (see later) and a high fat meal (see later).[5,6,7]

Surgical wound repair is a challenge in the elderly patient, with complications including dehiscence and infection. One proposed reason is that surgery disrupts the microvasculature of the aged skin, which already has diminished microcirculatory support. Most anaesthetics are also thought to adversely affect the microcirculation.[8]

OA and the microcirculation

One review has suggested there is mounting evidence that a microvascular pathology plays a key role in the initiation and/or progression of OA.[9] Disruption of microvascular blood flow in subchondral bone may reduce nutrient diffusion to the articular cartilage. Specifically, ischaemia in subchondral bone due to microthrombi may produce osteocyte death, bone resorption and articular damage. Another earlier review suggested that vascular disease in subchondral bone might accelerate the OA process.[10] This is either via reduced cartilage nutrition or (as per above) due to direct ischaemic effects on bone, depending on whether cartilage damage is the primary or secondary inflammatory event in OA. Bone marrow lesions, linked to a poorer prognosis for knee OA, could be secondary to such vascular events. Hence, regardless of its role in initiating OA (more relevant for prevention), microvascular disease is suggested to be highly relevant to its progression.

Heart disease and microcirculation

Coronary microvascular dysfunction (CMD) is under intense investigation because of the growing awareness of its importance. For example, in 354 patients with angina or angina-like chest pain with a normal angiogram, coronary flow reserve (a measure of heart microvascular health) was a comprehensive indicator of cardiovascular risk.[11]

More than half of women suffering from angina have no significant coronary artery obstruction. This is thought to be due to CMD.[12] In other words CMD is both a predictor of cardiovascular events and also contributes to the pathophysiology of angina.

The liver and microcirculation

There are major changes in the microcirculation of the liver with ageing. These include increased endothelial cell thickness and reduced numbers of pores (fenestrations). Such changes are thought to contribute to dyslipidaemia, vascular disease, liver degeneration and poor drug metabolism.[13,14]
An article in the newspaper *The Australian* in 2006 by journalist Jill Margo noted the following about this research:

> ‘Australian researchers have made a discovery that could prove beneficial to millions of older people. Through identifying how an ageing liver is starved of oxygen, they believe they may have uncovered an important factor in susceptibility to age-related diseases, including coronary artery diseases and nervous system disorders such as Parkinson’s....

> What they found had never been described before. They discovered that with age, tiny blood vessels in the liver undergo microscopic changes that can potentially translate into major diseases. Associate Professor David Le Couteur, a geriatrician and clinical pharmacologist at the Canberra school, says a young, healthy liver has unique blood vessels. Unlike vessels anywhere else in the body, they are very thin and full of holes and look rather like the wire mesh in flyscreen. This mesh allows oxygen being carried in the blood to pass effortlessly into the liver cells where it is used to fuel metabolic processes. With age, Le Couteur says this fine mesh-like structure changes dramatically. The vessels thicken, the holes close off and an underlying basement membrane develops. This means less oxygen can get through and that the liver cells have less oxygen to do their metabolic work (including processing toxins). ...The researcher's theory suggests that in old age these substances (toxins) can bypass the liver and deposit themselves elsewhere in the body where they can cause harm. Some fats may, for example, accumulate in coronary artery while a particular family of toxins might travel to the brain where they congregate and later manifest, perhaps as Parkinson's disease.'

Diabetic microangiopathy

Diabetic microangiopathy is directly linked to hyperglycaemia, and can be detected in people with only marginally raised blood glucose levels. A popular theory focuses on postprandial hyperglycaemia: the rise in blood sugar after meals can interfere with normal blood vessel function even in healthy people. Inadequate eating (fat and/or sugar-rich meals) can, over time, damage the endothelial cells lining the microcirculation.[1]

As mentioned above, type 2 diabetes (T2DM) causes microvascular disease. But there is a growing school of thought that microvascular dysfunction might actually be a fundamental cause of insulin resistance, leading eventually to T2DM. For example, retinal vascular calibre is one of several surrogate measures of microvascular dysfunction. A meta-analysis including more than 44,000 individuals found obesity was significantly linked to narrower arteriolar and wider venular calibres.[15] We also know that obesity is a risk factor for insulin resistance.[16]Another study concluded that the data: [17]

> '…indicate that various estimates of microvascular dysfunction were associated with incident T2DM and, possibly, impaired fasting glucose, suggesting a role for the microcirculation in the pathogenesis of T2DM.'

Alzheimer's disease

One theory gaining increasing credibility is that the cause of Alzheimer's disease lies in the cardiovascular system. Some researchers are focussing on the role of the subcortical white matter lesions (WMLs) of the brain that result from cerebral small vessel disease. WMLs are indicated by areas of rarefaction or low attenuation on brain computed tomography (CT) scans. They are also described as white matter hyperintensities because on magnetic resonance imaging (MRI) they show up as a more intense signal. The vulnerability of the white matter to ischaemia is due to the fact that it is supplied by long penetrating end arterioles from the surface and base of the brain that travel for a long distance, with very few interconnections. CT of the brain shows that 30% of people aged 85 years have evidence of low attenuation of white matter. In contrast, MRI shows an incidence approaching 100% at age 85. Studies demonstrate that normal people with white matter ischaemia could have subtle neuropsychological deficits, such as a slower rate of mental processing and impaired attention and concentration.[18] For example, a recent meta-analysis of 27 published studies examined studies in older adults who had a clinical diagnosis of cognitive impairment due to a vascular cause (WMLs), but not serious enough to impair their ability to function (no dementia).[19] Results demonstrated that those individuals show weaknesses across all cognitive domains relative to healthy controls, with the greatest impairment in the domain of processing speed, and the least affected being working memory and visuospatial construction. The authors concluded that disruption to subcortical white matter impairs more cognitive processes than typically thought. White matter ischaemia is also closely associated with vascular or so-called multi-infarct dementia. The key difference is that a patient need not show a history of strokes to have a cognitive impairment brought about by ischaemia.[19] Hence it is appropriate to describe it as a quiet saboteur of the brain.[20]

Another related concept is the origin of Alzheimer-like dementias (ALDs) from capillary haemorrhages.[21] The theory elevates the role of the microcirculation to a high importance in the aetiology of Alzheimer's disease. To quote from a paper from Jonathon Stone, an Australian scientist championing this line of thinking:

> "This paper proposes that the formation of each plaque is initiated by bleeding from a cerebral capillary, which creates the conditions for formation of an amyloid-rich plaque. Specifically, it is argued that ischaemia caused by the haemorrhage upregulates the expression of beta-amyloid by local neural cells, and that haemoglobin released into the

neuropil binds to the beta-amyloid and promotes its oligomerisation. The premise that the event that initiates plaque formation is vascular explains why the risk factors for ALDs and cardiovascular diseases overlap; why drugs and lifestyle changes with vaso-protective effects protect against dementia; and why oxidative stress is prominent early in the genesis of Alzheimer-like dementias. The vascular premise also suggests that the anatomical substrate for the spread of plaque formation is the capillary bed of the cerebral cortex, and provides an explanation of why plaque formation is age-related, occurring as the capillary bed becomes fragile with age. The more specific premise, that haemorrhage creates the conditions for plaque formation, explains many of the features of plaques: their small and relatively uniform size, each being at the site of a capillary bleed; why plaques form around capillaries; why haem is found in every plaque; why an inflammatory response is prominent where plaques form; why plaque formation and haemorrhagic stroke commonly co-occur in both sporadic and familial dementias; why plaques form around vessels in mouse models of plaque formation induced by transgenes that mimic the mutations that cause familial disease; why the acute petechial bleeding caused by brain trauma can lead to the formation of plaques. The hypothesis also suggests an explanation of how ALD's can occur without plaque formation, as when the cerebral capillaries become blocked or constricted in flow, without haemorrhage. Advances in the prevention of dementia will be gained, it is argued, from understanding of why the cerebral capillary bed becomes unstable with age, and how that instability can be prevented, delayed or slowed. Advances in the treatment of dementia will be gained from techniques that minimise the neural damage caused by a multitude of tiny strokes."

To quote further from Dr Stone in radio interview:

"The beat of our heart is symbolic of life, of energy, of courage and determination. Yet… if we live to old age, the heart destroys us. And it does so in a terrible way, pummelling the brain beat after beat until its small blood vessels burst, and lesions, tens of thousands of them, erode its circuitry, until the brain shrinks around the debris, its function failing. Slowly, relentlessly – this evidence goes - the beat of the heart destroys the memory, the intellect and the personality of the person it had so long served to keep alive."[22]

In other words brain microbleeds result from pulse-induced damage to the cerebral vessels. The pulse becomes increasingly destructive with age because of the age-related stiffening of the aorta and great arteries, which causes an increase in the intensity of the pulse pressure.[23] This hypothesis highlights the dementia-preventing role of agents that maintain arterial elasticity, lower blood pressure, improve microvascular integrity and protect the brain from microscopic ischaemic damage.

Endothelial function and disease

Closely allied to microcirculatory dysfunction is poor endothelial health. It is now thought that the key initiating event in the development of atherosclerosis is endothelial damage, followed by an inflammatory response. In support of this, endothelial dysfunction appears to predict arterial (large vessel) disease and the risk of a hard cardiovascular event (heart attack or stroke). Endothelial function can be measured by a number of techniques, including flow-mediated dilatation (FMD) and peripheral arterial tonometry (PAT). The latter is also known as the reactive hyperaemia index (RHI) (and sometimes called RH-PAT). [24] The former (FMD) tests endothelial function in large conduit blood vessels, while the latter tests such function in small arteries and the microcirculation.

A recent review concluded that traditional cardiovascular (CV) risk factors based on the Framingham study do not adequately predict future CV events.[25] As per above, RH-PAT, a non-invasive measurement of endothelial function, is emerging as a promising tool in CV risk prediction. Improvements in endothelial function have recently been linked to lower CV morbidity and mortality. A poor RHI has also been linked to the presence of vulnerable plaque, which is more likely to rupture and cause an acute CV event.

Erectile dysfunction (ED) in an otherwise healthy man is a warning sign of poor vascular endothelial health. In particular, endothelial NO production is typically impaired.

Herbs and plant foods that benefit microcirculatory and endothelial health

The bilberry (*Vaccinium myrtillus)* has a long-held reputation for benefitting vision, and a significant part of this probably arises from its support of the microcirculation. For example, in open trials, bilberry extract improved symptoms caused by decreased capillary resistance (microvascular bleeding, bruising and faecal occult blood),[26] reduced the microcirculatory changes induced by cortisone therapy in patients with asthma and chronic bronchitis,[27] and improved diabetic retinopathy with a marked reduction or

even disappearance of haemorrhages.[28] Post-operative complications from surgery of the nose were reduced in patients who received bilberry extract administered for 7 days before and 10 days after surgery. This was probably because of its benefits for the microcirculation.[29] In placebo-controlled trials, bilberry extract has improved early-phase diabetic retinopathy.[30]

We could also add the blueberry (*Vaccinium corymbosum*) here as a less active alternative. Indeed, a controlled clinical study involving 21 healthy men found that blueberry polyphenol intake improved FMD, with significant increases at 1 to 2 hours and then 6 hours after consumption (possible reflecting the differing pharmacokinetics of the various polyphenolic metabolites).[31] Relevant to the previously noted vascular theory of Alzheimer's disease, an 8-week, randomised, double blind, placebo-controlled clinical trial (n = 40) found that daily blueberry consumption (22 g freeze dried powder) improved blood pressure, plasma nitric oxide and arterial stiffness in postmenopausal women with early hypertension.[32]

Garlic (*Allium sativum*, particularly as the fresh-crushed raw clove or as an allicin-releasing powder) is good for both the microcirculation and microcirculatory flow. For example, in a controlled clinical trial a single 900 mg dose of garlic powder significantly increased capillary skin perfusion by 55%.[33] Another study found that garlic powder (600 mg/day) administered for 7 days increased calf blood flow by approximately 15%.[34]

Two controlled trials have investigated the activity of gotu kola (*Centella asiatica*) actives (triterpenoids) in patients with microvascular damage due to diabetes. The largest trial involved 100 patients with or without neuropathy and 40 healthy controls, and compared the extract with placebo over 12 months.[35] The herbal actives were significantly more effective at improving microcirculatory measures and oedema. A smaller trial in 50 patients compared a similar dose of gotu kola actives to placebo or no treatment over 6 months.[36] There was significant improvement in the active treated group in measures linked to microscopic vascular damage, including capillary permeability.

Clinical studies of ginkgo (*Ginkgo biloba*) in retinal problems best illustrate its positive effect on microcirculation. For example, improved retinal artery and capillary flow rates have been observed,[37,38] which probably would explain its beneficial effect on vision in patients with glaucoma,[39] since glaucoma results in poor blood flow to the retina. In earlier research, a single dose of standardised Ginkgo extract (112.5 mg) resulted in a significant increase in blood flow in the nail capillaries of healthy volunteers.[40]

Another study demonstrated an increased blood flow to the forearms of volunteers.[41] These studies confirm the ability of Ginkgo to enhance microcirculatory flow.

Numerous clinical trials using doses of between 100 and 150 mg/day of OPCs from grape seed (*Vitis vinifera*) have demonstrated a beneficial effect on capillary resistance and capillary permeability.[42] For example, 100 mg/day of OPCs was administered to elderly patients with capillary fragility. Very good results were achieved in 67%, good in 17% and moderate in 13%. More recently, grape seed extract at 133 mg/day for 14 days reduced leg swelling in healthy women during prolonged sitting (6 hours).[43]

There are several studies suggestive of cocoa's (*Theobroma cacao*) positive effect on the microcirculation and endothelium. In one clinical trial, the impairment of endothelial function caused by a glucose challenge was reduced by dark chocolate, but not white chocolate.[44] Dark chocolate also reduced endothelial dysfunction in breath-hold divers.[45] A single dose of a flavanol-rich cocoa improved cerebral perfusion in 18 healthy older adults (placebo-controlled, crossover trial).[46] A randomised, controlled trial in 60 healthy young volunteers found that 10g of dark chocolate a day (75% cocoa) for one month improved pulse wave velocity, arterial stiffness index and FMD.[47]

The beetroot (*Beta vulgaris*) is one of the richest sources of dietary nitrate. It is now realised that a specific pathway in the body can make NO from dietary nitrate: the nitrate-nitrite-NO pathway. [48] This has profound implications for microcirculatory and endothelial health, and for regulating blood pressure, as many clinical studies have already demonstrated.

Green tea (*Camellia sinensis*) for two weeks improved forearm endothelial dysfunction in smokers.[49] There was a significant increase in plasma NO. Green tea (4 weeks) improved FMD (from 5.7 ± 2.7% to 8.7 ± 3.5%) in patients with chronic kidney disease.[50]

Outcomes of some clinical trials suggest that Korean red ginseng (KRG, *Panax ginseng*) also improves microcirculation. For example, a randomised, placebo-controlled trial in 80 women found that 6 g/day of KRG for 8 weeks significantly increased the skin temperature of the hands and feet.[51] Another trial found 1.5 g/day of KRG extract for 8 weeks decreased the imbalance in local thermal distribution of the body (as assessed by digital infrared thermal imaging).[52] The authors suggested this was evidence that KRG improves circulation (and more specifically microcirculation). In a pilot trial KRG (3 g) improved FMD, an effect reproduced by the equivalent dose of isolated ginsenosides.[53]

Insights from the Indian Paradox also point to other herbs that might be beneficial for microcirculatory and endothelial health. Briefly put, the prevalence of T2DM in India is relatively high and with poor glycaemic control (average HbA_{1C} 9.2%). Yet microvascular complications such as retinopathy are only 16.6%,[54] compared with Europe, Japan, the US and Australia at around 30%.[55] Could it be that the many spices in the Indian diet, especially turmeric (*Curcuma longa*), cayenne (*Capsicum annuum*) and ginger (*Zingiber officinale*), support microcirculatory health? The Physiomedicalists described ginger as a 'diffusive stimulant', directly pointing to its effect on the microcirculation. Consumption of spicy foods was inversely associated with total mortality and deaths from cancer, heart disease and respiratory disease in a large population based cohort study conducted in China.[56]

The 5-Point Microvascular Phytonutrient Protocol

Based on the above evidence, a five-point dietary plan (in conjunction with herbs such as gotu kola, grape seed extract and Ginkgo as additional treatments) is recommended for patients with poor microvascular/endothelial health. The plan is as follows:

- Boost dietary nitrate: green leafy vegetables, but especially beetroot as juice or a supplement.
- Increase cocoa intake: 85% chocolate, 20 g/day.
- Increase berry anthocyanin intake: 50 to100 g/day of blueberries, strawberries, raspberries and blackberries.
- Fresh-crushed raw garlic: ½ to 1 clove/day.
- Increase herbs and spices: especially green tea (3 to 4 cups/day), turmeric and ginger.

A case history

A 61-year-old man presented with the main problem of declining kidney function. As well as having high blood pressure (controlled by multiple drugs), he also had T2DM, although this was well-controlled with just diet. Although his poor kidney function could have been caused by the diabetes, a medical specialist advised that some type of autoimmune damage to the glomeruli might be at play as well. In addition, tests showed that the tissue around his glomeruli exhibited a high degree of fibrosis, leading to a main diagnosis of arterionephrosclerosis. His glomerular filtration rate (eGFR) was quite abnormal at 35 and his plasma creatinine was elevated. His renal specialist had advised that he will probably be needing dialysis in 18 to 24 months.

The patient was recommended to follow the five-point dietary plan above. In addition, he was prescribed tablets containing high doses of *Echinacea* root (for the autoimmune aspects), turmeric (anti-inflammatory and protective of the kidneys) and grape seed, gotu kola and ginkgo for his microcirculation. He was also advised to take a high-dose fish oil supplement for its anti-inflammatory omega-3 fatty acids.

The man had another blood test conducted by his medical specialist 5 months later. To both their surprise, his creatinine level had fallen by 33% and his eGFR had risen to 51. His specialist commented that it was very rare for the eGFR to come back in this way, especially with his damaged kidneys. Normally it is a one-way decline. Eighteen months after the patient's initial presentation for herbal treatment his eGFR was normal at 74. Four years later it is maintained at around these normal levels.

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