Cardiovascular Science

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Review

Fibrinaloid Microclots-Induced Microcirculation Dysfunction: Mechanism and Laser-Based Haemodynamic Validation

Douglas B. Kell [1,2,*], Huihui Zhao [3,4] and Etheresia Pretorius [1,2,*]

[1] Department of Biochemistry, Cell and Systems Biology, Institute of Systems, Molecular and Integrative Biology, Faculty of Health and Life Sciences, University of Liverpool, Crown St, Liverpool L69 7ZB, UK
[2] Department of Physiological Sciences, Faculty of Science, Stellenbosch University, Stellenbosch Private Bag X1 Matieland, Stellenbosch 7602, South Africa
[3] School of Traditional Chinese Medicine, Beijing University of Chinese Medicine, Beijing 10026, China; hh686@126.com (H.Z.)
[4] Institute of Ethnic Medicine and Pharmacy, Beijing University of Chinese Medicine, Beijing 10026, China

* Corresponding author. E-mail: dbk@liv.ac.uk (D.B.K.); resiap@sun.ac.za (E.P.)

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ABSTRACT: The microcirculation typically refers to those capillaries less than 100 μm in diameter. We have shown that blood can clot into an anomalous amyloid form, manifesting as microclots of typically 2–200 μm equivalent diameter that are rather resistant to fibrinolysis. Because they contain fibrin and other proteins in an amyloid form, we have referred to them as fibrinaloid microclot complexes. We have also previously developed the idea that endothelial dysfunction can both lead to and be caused by the fibrinaloid microclots so formed, such that this can slow or block entirely parts of the microcirculation. The microclots might be thought of as a 'structural' manifestation in that they are actual, observable structures. This impairment of the microcirculation is referred to in Traditional Chinese Medicine (TCM) as 'blood stasis'. It is thus desirable to have 'functional' methods that can measure these effects on the microcirculation directly. As a complement to a recent survey of nailfold capillaroscopy, the present paper provides a wide-ranging review of the utility of laser speckle imaging (LSI) and laser Doppler imaging (LDI) for assessing the microcirculation in a large variety of diseases in which it is considered to be involved. These include Long COVID, sepsis, and ischaemic stroke. In all cases in which fibrinaloid microclots have been observed, so too do these methods detect an impairment of the microcirculation. Notably, blood pressure is raised while blood flow in the microcirculation is lower; this clearly speaks to occlusion and/or capillary rarefaction, and indicates that the raised blood pressure is the effect and not the cause of the decrease in flow rate or stasis of the microcirculation. As rapid, information-rich and non-invasive methods, LSI and LDI seem to have outstanding potential for assessing the role of fibrinaloid microclots in affecting blood stasis in the microcirculation, in a huge variety of inflammatory diseases and syndromes.

Keywords: Clotting; Amyloid; Fibrinaloid; Laser-doppler imaging; Laser speckle imaging; Cross-seeding; Fibrils; Microcirculation

1. Introduction

1.1. The Microcirculation and Endothelial Dysfunction

The microcirculation represents the terminal elements of the circulation consisting of microvessels, and has been defined as those with diameters less than 20 μm [1] or (more commonly) less than 100 μm [2–6]. As with other blood vessels, the walls of microvessels consist of endothelial cells [7] (we here ignore the glycocalyx [8] and mucins [9]). The microcirculatiion is responsible for perfusing and bringing O_2 to tissues throughout the body, and especially at its extremities. By contrast, endothelial dysfunction, manifesting straightforwardly as effects on the microcirculation (e.g., [10,11]), underpins a large variety of diseases and associated symptoms. Thus, Table 1 provides a list of some diseases or syndromes in which the evidence is especially well established. Further details, in terms of the use of laser imaging methods for assessing the microcirculation in these and many other diseases, and whether or not the presence of fibrinaloid microclots has been tested or observed, are given later in Tables 2 (laser speckle imaging) and 3 (laser Doppler imaging).

Table 1. A summary of some of the diseases or syndromes in which a disruption of the microcirculation is both observed (using any means of observation) and is considered to have aetiological involvement.

Disease or Syndrome	Comments	Selected References
Age-related macular degeneration (AMD)	Also related to cardiovascular issues. Note that the proteins in drusen, that is the insoluble material often associated with AMD, include amyloid A, amyloid-β, amyloid P, α1-antitrypsin, fibrinogen, *etc*. [12–14], importantly including abundant amyloid structures [15–17] that stain with the amyloid stain thioflavin T [18,19]	[20–25]
Cancers	Many vascular changes are involved in all aspects of tumorigenesis, *etc.*	[26–32]
Cardiovascular diseases	Strong relationship with microcirculation disruption	[33–47]
Choroid thickness after haemodialysis		[48]
Chronic fatigue syndrome	Bears some similarities to Long COVID	[49–55]
Chronic venous insufficiency		[56]
COVID and post-COVID	The key to recovery	[57–69]
Diabetes, type 2	Recognised as a vascular disease	[70–81]
Diabetic complications		[82–84]
Fibromyalgia	Clear likelihood of fibrinaloid microclot deposition	[85–96]
General reviews of microcirculation disruption		[97–104]
Glaucoma	Relates to intraocular blood pressure	[105–115]
Hypertension	Capillary rarefaction is seen as a major driver, at least in later stages. Increased blood pressure but lowered flux strongly implies that the latter causes the former. Put another way, there is an increased resistance to flow. This is entirely consistent with the known role of angiogenesis inhibitors in raising blood pressure [116,117].	[41,75,116,118–138]
Inflammatory bowel disease		[139–144]
Metabolic syndrome	A comorbidity of many cardiovascular diseases	[46,47,80,145–153]
Obstructive sleep apnoea	A common co-morbidity of many of these diseases, which implies the potential for a common aetiology and a common cure	[152,154–157]

Parkinson's disease		[158]
Pre-eclampsia	Clear hypertensive disorder, albeit involving cellular senescence [159] and likely an infectious origin [160,161]	[162–165]
Psoriasis	[166,167]	
Raynaud's phenomenon	Strongly related to systemic scleroderma	[139,168–174]
Sepsis and septic shock	One of the most significant examples, with a high level of mortality. Strong evidence that lowered microcirculatory flux relates closely to mortality (and might hence offer protective treatments).	[175–204]
Sickle cell disease	Significant impacts on the microcirculation	[205–212]
Stroke (ischaemic)	Very clear evidence for a relation between microcirculation and multiple factors before and after an ischaemic stroke	[213–225]
Subarachnoid haemorrhage	Erythrocyte sedimentation rate (ESR) was the only measure predictive of a subsequent stroke in a detailed study [226]	[227–237]
Systemic sclerosis (scleroderma)	A major focus in the nailfold capillaroscopy field	[238–247]
Traumatic brain injury and other traumas		[248–252]

While it is slightly egregious to pick out specific syndromes, we would comment that some, such as ischaemic stroke, are among the main causes of human deaths. All these diseases, especially the chronic diseases [253], display multiple, similar observables, and endothelial dysfunction can both cause and be caused by oxidative stress (from hypoxia and/or reactive oxygen species) (e.g., [254–269]), mitochondrial dysfunction [270], and inflammation [258,259,271]. Endothelial dysfunction can itself be caused by cellular senescence [272–280], and in particular via infection (see Figure 1).

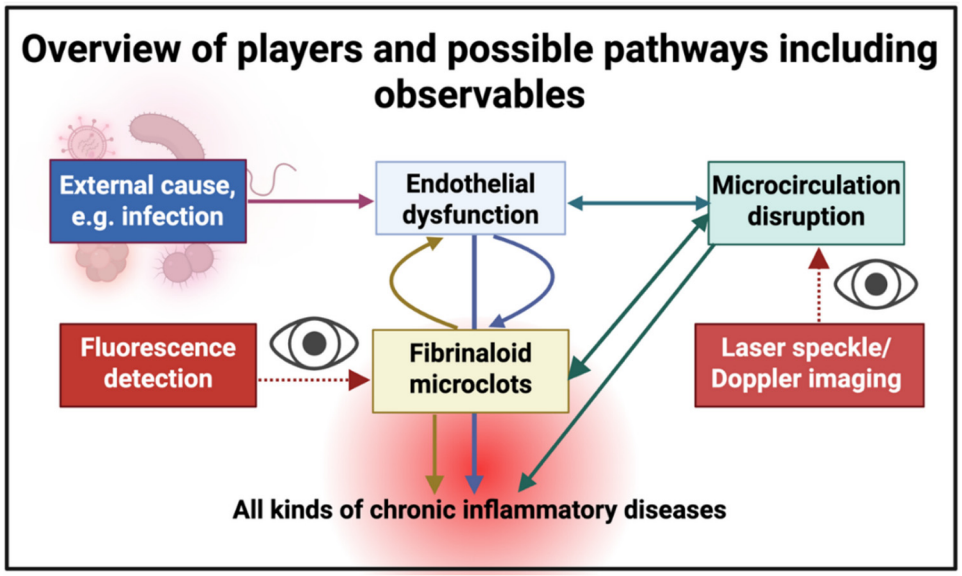

Figure 1. Overview of the relationship between microcirculation disruption and other observables.

Disseminated intravascular coagulation (DIC) is commonly an accompaniment to sepsis and is characterised by widespread microvascular thrombosis [281–299] and is associated with a high mortality. A particularly striking recent finding [300] involved the discovery of an unequivocal relationship (odds ratio > 50) between DIC and the presence of fibrinaloid microclots. The directions of causality are not yet known, but this does highlight the potential utility of microcirculation measurements in such patients.

Particular attractions of the microcirculation as an object of study are (i) that it is amenable to non-invasive measurements, in particular via the skin, tongue or retina, and (ii) that it reflects the properties of the

far less accessible macrovasculature (see e.g., [126,301–312]) and is thus effectively a surrogate for assessing the presence, likelihood, and possibly severity, of a large variety of mainly (cardio)vascular diseases.

1.2. Fibrinaloid Microclots

We discovered long ago that blood can clot into an anomalous amyloid-like form [313–315], producing 'fibrinaloid' microclots (commonly in the range 2–200 μm in equivalent diameter [316–319]) that are relatively resistant to degradation. All such diseases in which fibrinaloid microclots formation has been studied are similarly accompanied by the above symptoms. These diseases [320] include acute COVID-19 [321–326], Alzheimer's dementia [313,327–330], diabetes mellitus type 2 [326,327,331–333], Long COVID [317–319,334–343], migraine [344], myalgic encephalopathy/chronic fatigue syndrome (ME/CFS) [345–348], Parkinson's disease [327,349,350], rheumatoid diseases [351–353], and sepsis/septic shock [300] (see also [294]). It is obvious that such particulate matter as represented by fibrinaloid microclots can block the microcirculation causing local hypoxia, and (focusing on Long COVID) this readily explains phenomena such as blood stasis [354], fatigue [334], post-exertional system exacerbation (previously post-exertional malaise) [355], auto-antibody formation [356], postural orthostatic tachycardia syndrome (POTS) [340], atrial fibrillation [357] and fibromyalgia [358]. Their amyloid nature, as well as their proteome content [335,336,359], straightforwardly explains the relative resistance of fibrinaloid microclots to fibrinolysis [360,361]. We further showed that the macroclots removed by thrombectomy following an ischaemic stroke are also amyloid in character [362,363].

Although other amyloid stains are available, fibrinaloid microclots are typically measured using the classical fluorogenic amyloid stain thioflavin T [364–367], and the fluorescence is observed using fluorescence microscopy or flow methods. These may be considered to be 'structural' methods, while a variety of more 'functional' methods are known. We recently suggested [368,369] that one 'functional' type of methods of assessing abnormalities in the microcirculation, based on nailfold capillaroscopy (see e.g., [370–377]), might make a useful complement to our 'structural' microclot assays.

In addition, other functional methods of measuring the microcirculation are known, including indocyanine green fluorescence [378–383], optical coherence tomography angiography (OCTA) [28,179,384–396], and in particular, as we focus on here, here laser speckle (contrast) imaging (LSI or LSCI) [36,397–406] and laser Doppler imaging (LDI) [239,402,407,408]. From the physics point of view, the latter two are considered essentially equivalent [409,410]. The chief purpose of this paper is thus to assess LSI and LDI and the findings made with them when they are applied in diseases known to be accompanied by fibrinaloid microclots. Explicitly, methods such as LDI and LSI that can detect the effects of microclots in lowering the rate of blood flow are to be seen as having significant clinical value in terms of admitting treatments that either remove them via fibrinolysis (see e.g., [316,334]) or stop their formationo (e.g., [411,412]). We conclude that, while they are not that cheap, they should prove to be exceptionally useful tools for determining disorders of the microcirculation. A preprint has been posted [413].

1.3. A Note on Systems Biology Explanations of Cause and Effect

We recognise, for non-systems-biologists, that if one is studying a steady state system in which all steps are proceeding at the same rate, it might be seen as odd to argue that some steps are somehow 'more important' in determining the speed or course of events than are others. However, this is in fact the case, and it can be quantified precisely. Specifically, the answer lies in what is called sensitivity analysis, in which we study the effects of a normalised change in a parameter (such as the k_{cat} of an enzymatic step) on the normalised value of a variable (in metabolism this is usually a concentration or a flux). Metabolic control analysis [414–418] is exactly such a formalism that applies this to biochemistry, and is based on what is called a local sensitivity analysis [419,420]. Even in very simple systems consisting of just three

metabolites (e.g., A → B → C) with the two steps catalysed by enzymes E_1 and E_2, it is surprisingly tricky to do this well unless one is both informed and careful (see e.g., [421–425]).

This said, in an elementary sense, blood pressure (V), peripheral resistance (R), and the rate of blood flow or flux (I) can be seen as straightforwardly related to each other in a manner entirely analogous to the standard and well-known Ohm's law relation V = IR of DC electricity. Given this relationship, it is worth pointing out that in such systems, one can establish a setup in which external control is either of the voltage or the current (also in AC systems [426]). Consequently, it is at least reasonable to ask which of the elements contributing to the observable blood flow then normally exerts the greater control. The answer is that it seems clearly to be the case that blood pressure increases that can be observed [41,75,116,118–138] seem to be caused mainly by changes in peripheral resistance, *i.e.*, the microcirculation [116,117] rather than anything else controlling the blood pressure more directly. From the perspective of the role of fibrinaloid microclots this is an extremely important recognition.

We next rehearse the role of 'blood stasis' in disorders of the microcirculation, before describing LSI.

1.4. The Microcirculation from the Point of View of 'Blood Stasis' in Traditional Chinese Medicine

The concept of "blood stasis" in TCM is closely related to microcirculatory disorders in modern medicine. Blood stasis is one of the basic pathological mechanisms in TCM, referring to the pathological state of poor blood circulation and stagnant blood. In recent years, multiple studies have shown a high degree of similarity between the concept of blood stasis and microcirculatory disorders in terms of pathophysiology. Our study on the relationship between blood stasis syndrome and microclotting [354] recognised that abnormal amyloid-like clots, known as fibrinaloid microclots, can form in the blood. These microclots appear in various chronic inflammatory diseases, and they can block microvessels, reduce tissue oxygen transport, and lead to various pathological consequences. Microclots provide a simple mechanism for slowing blood flow by obstructing the transport of red blood cells [334,354].

Blood stasis syndrome is commonly seen in various chronic diseases in TCM clinical practice, and its manifestations are highly consistent with the clinical characteristics of microcirculation disorders. Blood stasis constitution is associated with a number of metabolic abnormalities and microcirculation disorders. The complex interactions between host constitution, gut microbiota, and serum metabolites may indicate potential metabolic vulnerability, even in cases of surface health [427].

The main method of treating blood stasis syndrome in TCM is to promote blood circulation. Many TCM herbal formulas have shown significant effects in improving the microcirculation, not least XueFu ZhuYu (reviewed in [354]). Danshen is another commonly used TCM for promoting blood circulation and removing blood stasis, and studies have shown that it has various pharmacological effects on improving microcirculation [428,429]. *Salvia miltiorrhiza* extract and its pure compounds have many effects, such as anti atherosclerosis, anti arrhythmia, anti thrombosis, anti hypertension, anti ischemia reperfusion injury, and protection of endothelial function [430]. These effects are closely related to improving the microcirculation [431].

Dang-gui-Si-Ni (DGSN) decoction is another typical formula for promoting blood circulation and removing blood stasis. DGSN can prolong clotting time (PT, TT, and APTT) and reduce fibrinogen (FIB) content. In *in vivo* experiments, low-dose (500 $\mu g \cdot mL^{-1}$) DGSN significantly enhanced cardiac output and blood flow velocity. These findings indicate that DGSN can significantly improve hemodynamics and downregulate coagulation factors, thereby improving the microcirculation [432].

In the treatment of chronic coronary syndrome (CCS), the TCM compound Danshen Dripping Pills has shown significant cardioprotective effects. Compared with Western medicine treatment alone, the combination of TCM and Western medicine improved the effectiveness of electrocardiogram by 8318%, the effectiveness of angina by 20%, and the cessation or reduction of nitroglycerin tablet use by 20%. These

effects are likely related to improving coronary microcirculation [433]. Overall, the microcirculation is seen within TCM as contributing strongly to the phenomena of blood stasis. We now turn to LSI.

1.5. Laser Speckle (Contrast) Imaging (LSI/LSCI)

When laser light illuminates an object, the scattered light produces a 'random' (actually deterministic, but massively complex) interference effect referred to as a speckle pattern. If the object is moving, the speckles necessarily fluctuate in intensity. Similarly, if the speckle pattern is imaged with an exposure time longer than the shortest speckle fluctuation time, the fluctuations cause a blurring of the speckle, leading to a reduction in the local speckle contrast. This thus encodes the velocities and the distributions thereof as speckle contrast variations; for higher velocity, the speckle contrast is reduced [397,434,435]. Given the size of the speckles, the magnification used, and the typical blood flow rates (~1 $mm \cdot s^{-1}$ in capillaries [436]), exposure times are typically in the range of 1–10 ms [437]. Typically, the range thereby covered is 0.1–10 $mm \cdot s^{-1}$. Specific implementations of the general technique are variously referred to as laser speckle imaging (LSI), laser speckle contrast imaging (LSCI), laser speckle contrast analysis (LASCA) and laser speckle flowgraphy (LSFG) (there are slight variations in implementation); we shall normally use the first terminology., and not discriminate them in any real detail A particular attraction is that interrogation can be over a wide area simultaneously (*i.e.*, no scanning or rastering is necessary).

Instruments can be used in 'spatial mode' or 'temporal model' [397]. Typically, when used in 'spatial mode', the speckles are mapped over a small grid of detector pixels (typically 5 × 5) and the contrast is assessed as the standard deviation (SD) of pixel intensities (average pixel intensity = I); SD is low for fast moving speckles (high blood flow) where the image is blurred, and SD is high for slow moving speckles (low blood flow) where the image is not so blurred. The basic formula for LSCI assessment of tissue is thus Flux $\propto (<I>/SD)^2$. Note that flux differs from velocity as it also takes into account the concentration of the scattering particles.

In 'temporal mode', the intensities of individual pixels during at least 25 successive images are used to calculate average intensities and SDs. Compared to a 5 × 5-pixel set-up, this mode is necessarily at least 25 times slower than spatial mode, but its linear resolution is, of course, 5 times greater.

A typical speckle pattern (taken from [397]) is given in Figure 2, while Figure 3 illustrates the general principle.

Figure 2. A typical 'instantaneous' laser speckle pattern, which changes over time in response to particle motion. Taken from the Open Access CC-BY3.0 publication [397] (DOI:10.1117/1.JBO.18.6.066018).

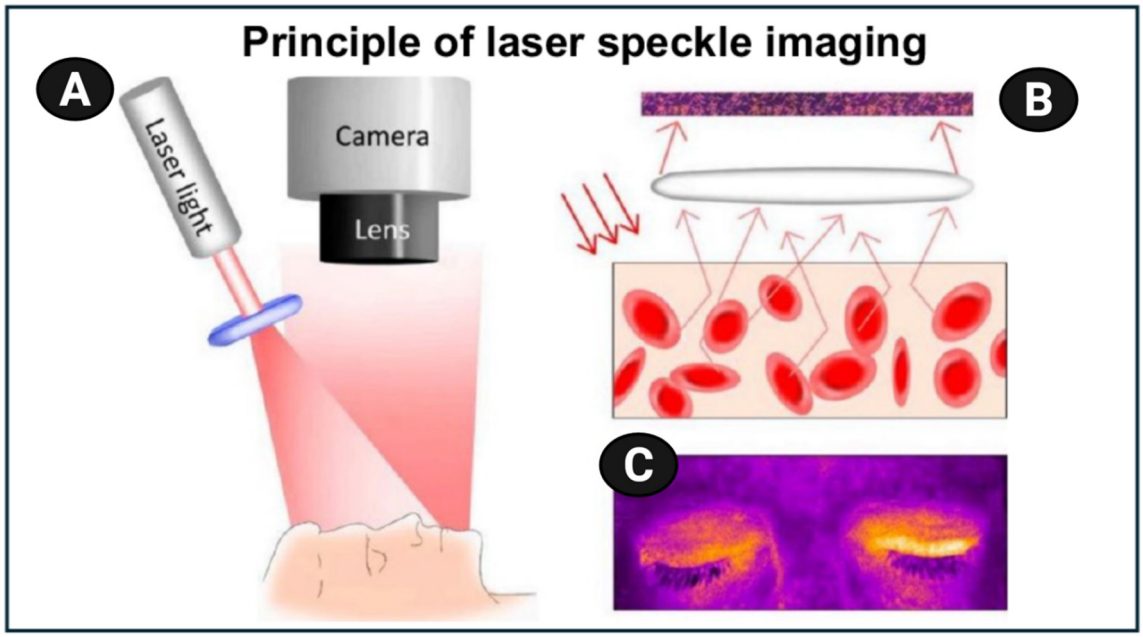

Figure 3. Schematic representation of laser speckle contrast imaging (LSCI). (**A**) The technique relies on the interference of light backscattered from an interrogation zone, which may include moving particles, creating distinct dark and bright areas (a speckle pattern) that is captured by a camera. The greater the blur or spatial homogeneity, the faster the blood flow. (**B**) Variations in the speckle pattern, specifically the amount of blur that is observable following a specific imaging window, are predominantly driven by the movement of red blood cells, enabling interpretation as perfusion, whose rate can be estimated. (**C**) Analysis of speckle-pattern variations yields an image displayed on the monitor, where white and yellow depict areas with high perfusion, contrasting with darker areas indicating lower perfusion areas. Taken from the CC-BY 4.0 publication [401], originally from [438]. For interrogating the subject's face, only particularly low-power lasers are to be used.

As with our previous review on nailfold capillaroscopy [368,369], we think that the most illuminating strategy for our purposes is to compare diseases assessed using LSCI with those in which fibrinaloid microclots are known to exist experimentally, so as to see how much overlap is already documented. Table 2 sets out such an analysis. Note, of course, that many of these syndromes are diseases of ageing, and that microvascular properties do decline with age [439–442], so a comparison with age-matched controls is (as usual [443]) required.

Table 2. Some disorders involving the microcirculation in which laser speckle contrast imaging has been found to have diagnostic utility or where fibrinaloid microclots have been demonstrated. Disorders in which fibrinaloid microclots have been demonstrated are rendered in bold face; note that every disorder in which microclots have been demonstrated has microcirculation anomalies when assessed using laser speckle imaging (where this has been applied).

Disease or Syndrome	**Comments**	**Selected Laser Speckle Imaging References**	**Selected Fibrinaloid Microclot References (Where Tested)**
Acute COVID-19	Significant evidence of microvascular dysfunction	[57,444,445]	[321–326]
Acute respiratory distress syndrome	Severity correlates with lowered microcirculation	[57,446]	
Age-related macular degeneration	Also related to glaucoma	[447,448]	
Alzheimer's dementia (including mild cognitive impairment)	Significantly lowered cerebral blood flow in Alzheimer's dementia	[449–457]	[313,327–330]

Antineutrophil Cytoplasmic Antibody-Associated (ANCA) Vasculitis	Impaired microvascular function and blunted reactivity after occlusion	[458]	
Atopic dermatitis	Review showing marked differences, and treatment	[459]	
Behçet's disease	Higher baseline flux	[458]	
Biliary cirrhosis	Significant microcirculation lesions	[460]	
Burns	Lesions can occur at places distal to the burn site. Faster though less common than LDI. Useful in burn depth diagnosis.	[461–475]	
Cancers	There is a large literature, indicating issues with the microcirculation. A very small number of reviews at right.	[401,476]	
Chronic smokers	Led to Buerger's disease, successful diagnosed (and cured)	[477]	
Cold urticaria	Attenuated response to cold challenge in patients with cold urticaria	[478]	
Connective tissue disorders	Includes Ehlers-Danlos syndrome	[479–483]	
Coronary heart disease		[484–488]	
Dermatomyositis		[482,489]	
Diabetes mellitus, type 1	Decreased microcirculation flux. Can be ameliorated by a Chinese herbal formula.	[490–493]	
Diabetes mellitus, type 2	Impaired microcirculation. Correlates with glycosylated haemoglobin A1c levels	[76,494–498]	[326,327,331–333]
Diabetic complications	Review	[499]	
Diabetic foot		[500–502]	
Diabetic nephropathy	Decreased blood flow despite no lowering of vessel diameter (consistent with microclots)	[72]	
Diabetic neuropathy		[497,498,503,504]	
Diabetic retinopathy	Decreased blood flow despite no lowering of vessel diameter (consistent with microclots). Microcirculation decrease precedes retinopathy.	[72,505–507]	
Digital ulcers		[508–514]	
Endothelial (dys)function		[515–518]	[342]
Erythromelalgia		[519]	
Fibromyalgia	Seemingly, no studies have been done.		See [358], and for amyloid deposition in skeletal muscle [520]
Gaucher disease	Seemingly, no studies have been done.		
General reviews		[36,246,401,406,434,480,521–524]	
Glaucoma	Evidence for vasculopathies	[106–108,525–528]	
Heart failure		[484,529–533]	
Hepatitis, viral	Seemingly, no studies have been done.		

Hypertension and hypertensives	As expected, raised blood pressure correlates with lower flow rates (implying that the latter is a cause of the former)	[534–541]	
Long COVID	Observable effects on the microcirculation well after the acute phase. Surprisingly few studies.	[444,542]	[317–319,334–342]
Lupus (systemic lupus erythematosus, SLE)	Functional and morphological microvascular impairments in patients with SLE	[480,543–546]	
Migraine	Significant microcirculation changes relative to controls	[547–552]	[344]
Myalgic encephalopathy/chronic fatigue syndrome	Despite the fact that it is clearly an endotheliopathy associated with a deranged microcirculation, and with similarities to Long COVID [52,345,553], we have found no relevant studies		[279,346–348,359]
Obstructive sleep apnoea		[152,157,497,554]	
Parkinson's disease	Allowed analysis of the function of vasomotor small fibers	[555]	[327,349,350]
Polycythemia vera		[556]	
Polymyositis		[482,489]	
Port wine stain	Convenient non-invasive measurement/diagnostic	[557]	
Pre-eclampsia	Microcirculation impaired	[558–560]	
Psoriasis	Perilesional increased perfusion and perfusion inhomogeneity predictive of lesion expansion after two weeks	[561–564]	
Pulmonary arterial hypertension		[509–511,565]	
Raynaud's disease or Raynaud's phenomenon (a transient digital ischaemia, often related to systemic sclerosis)	Laser speckle analysis is a little-known relative to nailfold capillaroscopy [173].	[245,546,566–571]	
Rheumatoid arthritis		[572–575]	[351–353]
Sarcopenia		[576–578]	
Sepsis and septic shock	Can discriminate sepsis from septic shock, and lowered blood flow is a high predictor of mortality. The odds ratio of predicting survival based on the presence of fibrinaloid microclots was more than 5 [300].	[579–583]	[300] and see [294]
Sickle cell disease	Microcirculation significantly impaired	[205,584–586]	
Stroke (ischaemic)	Very useful technique for monitoring and prediction	[578,584,587–598]	
Subarachnoid haemorrhage		[599]	
Systemic sclerosis	Also, the commonest area for nailfold capillaroscopy	[241,508–513,600–607]	
Traumatic brain injury	Clear effects in decreasing microcirculation	[608–611]	

The widespread occurrence of alterations in the microcirculation, as judged by LSI, is also accompanied by inflammation and oxidative stress, indicating how extensive this is in multiple syndromes (Figure 4), and we would argue that they likely share common causes [97]. In particular, where it was tested, all examples in which fibrinaloid microclots have been measured in plasma also show disorders of the microcirculation, as we would expect. This said, despite extensive detection of microclots in diseases such as myalgic encephalopathy/chronic fatigue syndrome (ME/CFS) and Parkinson's, laser speckle imaging seems not to have been assessed. This clearly provides some tremendous opportunities.

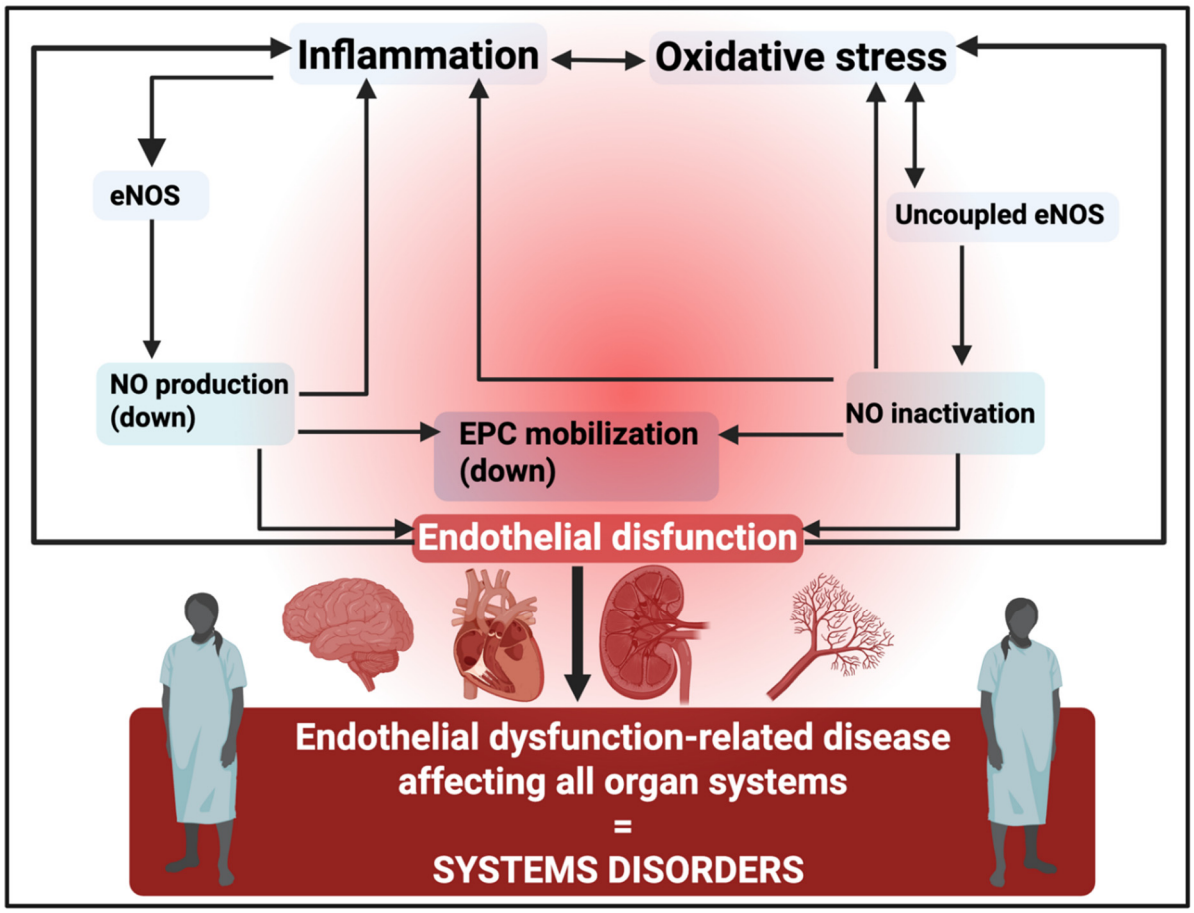

Figure 4. Widespread inflammation, oxidative stress, and endothelial dysfunction may cause systemic disease that may affect all organ systems and lead to a plethora of systems disorders. Redrawn in part from the CC-BY 4.0 Open Access paper [259].

1.6. Laser Doppler Imaging (LDI)

Detecting properties of moving objects via the Doppler effect is, of course, a method dating back to the 19th century, and a suite of methods referred to under the term laser Doppler imaging (LDI) has also been applied to the non-invasive estimation of blood flow.

Figure 5 illustrates typical arrangements for LDI. In this case, rastering is required, using either a point scan (Figure 5A) or a line scan (Figure 5B).

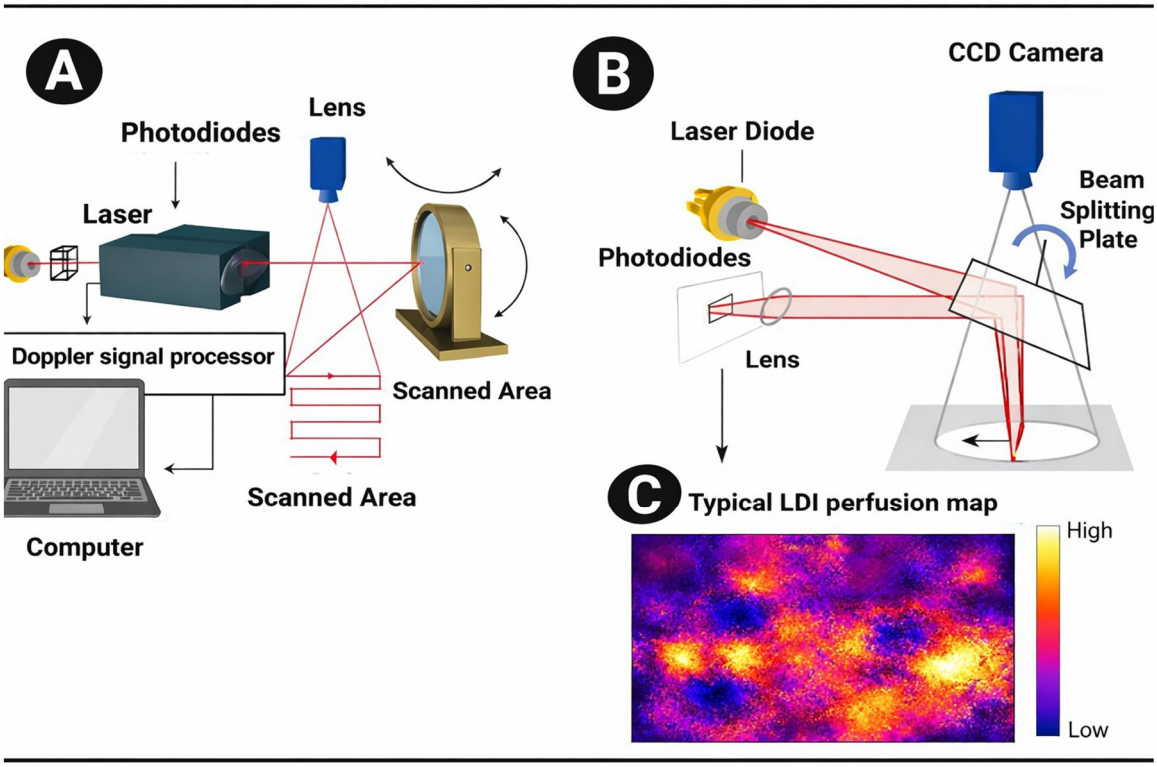

Figure 5. Two styles of laser Doppler imaging in which rastering is achieved via (**A**) a point scan or (**B**) a line scan. Figure taken, with permission, and redrawn, from a document provided by Moor Instruments at https://www.moor.co.uk/support/theory/ (accessed on 14 April 2026). Panel (**C**) shows a representative false-colour perfusion map derived from Doppler signal processing, illustrating the spatial heterogeneity of microvascular blood flow; regions of reduced signal (blue) may reflect locally diminished erythrocyte flux or intermittent capillary obstruction.

In point-scan LDI (Figure 5A), a focused laser beam sequentially interrogates individual pixels across the tissue surface using galvanometric mirrors or mechanical scanning. At each position, the Doppler frequency broadening of backscattered light—arising from moving red blood cells—is recorded to yield a local perfusion signal. A full perfusion map is then reconstructed pixel-by-pixel. This approach provides high spatial resolution and flexible sampling density, but acquisition is relatively slow, making it more susceptible to motion artefacts and limiting temporal resolution. In line-scan LDI (Figure 5B), the laser is shaped into a line (e.g., via cylindrical optics) and projected across the tissue, while a linear detector array (or fast camera) captures Doppler signals simultaneously along that line. The scan proceeds orthogonally to the line direction to build up a 2D image. This parallelisation enables substantially faster acquisition and improved temporal resolution, facilitating dynamic studies of blood flow, albeit sometimes at the expense of spatial resolution and with greater sensitivity to optical heterogeneity along the illuminated line.

In both modalities, the resulting signal is typically expressed in arbitrary perfusion units and reflects an ensemble average over the sampling volume. Importantly, in pathological states characterised by non-uniform or intermittently obstructed microcirculation, the Doppler signal may exhibit non-Gaussian fluctuations and heavy-tailed distributions, reflecting heterogeneous flow velocities and vessel occupancy. The choice of scanning modality therefore influences not only spatial and temporal resolution but also the statistical structure of the measured signal, with implications for quantitative interpretation and for downstream computational analyses, including AI-based detection of abnormal perfusion patterns. These differences are particularly relevant when probing diseases involving microvascular occlusion, where distinguishing true perfusion deficits from sampling or averaging artefacts is critical for linking imaging phenotypes to underlying clot structure and composition.

Our interest again resides in determining the spatial variation of the microcirculation and assessing diseases in which LDI has been used to detect microcirculation dysfunction and where microclots have also been observed. To this end, Table 3 is presented in the style of Table 2, but where the measurement technique is now laser Doppler imaging rather than laser speckle imaging. As with LSI, there is an age dependence in the observables [612] that needs to be taken into account.

Table 3. Some disorders involving the microcirculation in which laser Doppler imaging has been found to have diagnostic utility or where fibrinaloid microclots have been demonstrated. Disorders in which fibrinaloid microclots have been demonstrated are rendered in bold face; note again that every disorder in which microclots have been demonstrated has microcirculation anomalies when assessed using laser Doppler imaging (where this has been applied).

Disease or Syndrome	**Comments**	**Selected Laser Doppler Imaging References**	**Selected Fibrinaloid Microclot References (Where Tested)**
Acute COVID-19	Significant evidence of microvascular dysfunction	[58,60,64,613–616]	[321–326]
Acute respiratory distress syndrome	Few studies, but low microcirculation is clearly observable	[617,618]	
Alzheimer's dementia (including mild cognitive impairment)	Significantly lowered cerebral blood flow in Alzheimer's dementia. Many more studies than with LSI. Care needed with age matching, though [612]. Vascular impairment is clearly related to Aβ deposition.	[452,619–631]	[313,327–330]
Antineutrophil Cytoplasmic Antibody-Associated (ANCA) Vasculitis	Impaired microvascular function	[632]	
Atopic dermatitis	Evidence of impaired microvascular function, but surprisingly little recent literature	[633,634]	
Biliary cirrhosis	Significant microcirculation lesions	[635,636]	
Burns	Utility in burn depth assessment for assisting clinical judgement. Microcirculation problems also occur at distal sites. Seemingly more frequently used here than LSI.	[464,474,637–649]	
Cancer	Somewhat lesser literature than for LSI (given the importance to tumours of vascularisation), but there are issues with the microcirculation in cancer and its treatment. A very small number of articles on the right.	[650–652]	
Chronic smokers	Impaired microcirculation (many more papers than for LSI)	[653–658]	
Connective tissue disorders		[648,659–663]	
Coronary heart disease	Surprisingly little directly	[664–667]	
Dermatomyositis	Lowered flow rate correlates with disease severity	[174,240,668,669]	
Diabetes mellitus, type 1	A large literature implicating microcirculation defects	[74,670–672]	
Diabetes mellitus, type 2	Impaired microcirculation. Correlates with glycosylated haemoglobin A1c levels	[73,311,654,655,670,672–677]	[326,327,331–333]
Diabetic complications	Reviews (note that most complications follow from impaired microcirculation)	[499,672]	
Diabetic foot (ulcers)		[402,678–681]	
Diabetic nephropathy	Decreased blood flow despite no lowering of vessel diameter (consistent with microclots)	[682]	

Diabetic neuropathy		[683,684]	
Diabetic retinopathy	Decreased blood flow despite no lowering of vessel diameter (consistent with microclots). Microcirculation decrease precedes retinopathy.	[685,686]	
Digital ulcers	Often coupled to systemic sclerosis	[238,513,657,687–689]	
Endothelial (dys)function generally		[616,690–696]	[342]
Fibromyalgia	Much more frequent use of LDI than of LSI	[90,93,697–699] (and for Complex Regional Pain Syndrome [700])	See [358], and for amyloid deposition in skeletal muscle [520]
General reviews		[402,524,663,701–704]	
Glaucoma		[705–707]	
Heart failure	Decreased microcirculation is seen as a risk factor (causative) for worse outcomes	[708–718]	
Hepatitis, viral		[719,720]	
Hypertension and hypertensives	As also seen with LSI, raised blood pressure correlates with lower flow rates (implying that the latter is a cause of the former)	[132,687,721–724]	
Inflammatory bowel disease	Measured as rectal blood flow	[725,726]	
Long COVID	Observable effects on the microcirculation well after the acute phase—surprisingly few studies.	[52,68]	[317–319,334–342]
Lupus (systemic lupus erythematosus, SLE)	Functional and morphological microvascular impairments in patients with SLE	[727–729]	
Migraine		[730]	[344]
Myalgic encephalopathy/chronic fatigue syndrome	Despite the fact that it is clearly an endotheliopathy associated with a deranged microcirculation, and with similarities to Long COVID [52,345,553] we have found only one relevant study	[52]	[279,346–348,359]
Obstructive sleep apnoea	Both improved with treatment	[154,731–733]	
Parkinson's disease	Very few studies	[734]	[327,349,350]
Peripheral artery disease	Often related to diabetes	[657,687,735–739]	
Polymyositis		[174,669]	
Port wine stain	Convenient non-invasive measurement/diagnostic	[557]	
Pre-eclampsia	Microcirculation impaired	[740–744]	
Psoriasis		[745–750]	
Raynaud's disease or Raynaud's phenomenon (a transient digital ischaemia, often related to systemic sclerosis)		[173,174,570,751–756]	
Rheumatoid arthritis		[757–764]	[351–353]
Sarcopenia		[73]	
Sepsis and septic shock	Microcirculation very important in sepsis. As with LSI, it can discriminate sepsis from septic shock, and lowered blood flow is a high predictor of mortality.	[765–773]	[300] and see [294]
Sjögren's syndrome		[174]	
Sickle cell disease	Microcirculation significantly impaired	[206,210,774–776]	
Stroke (ischaemic)	Very useful technique for monitoring and prediction	[777–779]	
Subarachnoid haemorrhage	Note that impaired blood flow (measured by ESR) was the only predictor of a subsequent stroke [226]	[780–784]	

Systemic sclerosis		[173,238–240,245,247,371,512,513,522,565,600,602,603,687–689,752,785–787]
Traumatic brain injury	Clear effects in decreasing microcirculation as a result of damage following the trauma	[248,249,788,789]
Urticaria		[790,791]

From the perspective of the role of fibrinaloid microclots in affecting the microcirculation, at least two features are of particular note. The first is that blood pressure is raised while flow is lower; this clearly speaks to either or both of capillary rarefaction (decreased density) [123] or to occlusion (or both), and that the raised blood pressure is the effect and not the cause of the change in flow rate. (One might comment that in this sense, blood pressure [792] corresponds to metabolic fluxes in general, as these tend to be regulated by demand and not by supply [793]). Secondly, many studies indicate—not least in diabetes—that changes in the microcirculation leading to hypoxia precede disease, again consistent with an aetiological role. This, of course, raises the significance of these phenomena considerably. In a similar vein, the fact that fibrinaloid microclots accompany so many of these diseases is again consistent with them having an aetiological role rather than being a simple side effect of whatever the core component of the diseases might be considered to be.

While the above table focused on disease, it is worth noting that LDI indicated that there are significant differences in local blood flow at acupuncture points relative to surrounding tissue [794–796], and that suitable treatments can affect the microcirculation as measured [797]. Given the significance of blood stasis in a variety of diseases [354], this is definitely noteworthy.

1.7. Comparison of the Two Techniques

Both laser Doppler Imaging and Laser speckle imaging are capable of measuring the microcirculation effectively, are comparably priced, and in skilled hands generally reasonably reproducible [410,798–803] depending on the LSI exposure time (though seemingly not when assessed in boys [804]). They are significantly more expensive than nailfold capillaroscopy, but do offer real-time measurements. The general feeling is that LSI is more powerful but that LDI penetrates more deeply if that is important, although this depends on a variety of optical and geometric parameters [805–808]. In one study of dermal blood flow [809], LSI was considered more sensitive.

2. Discussion

2.1. Comparison of Technological Advantages and Innovative Breakthroughs

Laser speckle imaging (LSI) and laser Doppler imaging (LDI) quantify microvascular blood flow in a non-invasive manner, significantly enhancing the clinical value of microcirculation assessment. LSI captures real-time blood flow velocity and distribution with a high spatial resolution of 10 μm, suitable for dynamic monitoring of superficial organs. LDI is known for its ability to penetrate deeper tissues and locate low perfusion areas in deep regions such as the myocardium. The combined application of the two offers functional complementarity and provides a comprehensive analysis for complex microcirculatory disorders. The introduction of artificial intelligence algorithms has further improved the accuracy of blood flow parameter analysis, promoting the transfer of microcirculation imaging techniques and instrumentation from laboratory research to clinical practice.

2.2. Unity and Specificity of Cross-Disease Mechanisms

Fibrinaloid microthrombi, as the core pathological mediator of microcirculatory disorders, exhibit both mechanistic unity and significant specificity due to differences in precise phenotypes in various diseases. Its unity is reflected in the fact that, whether in acute infection (such as COVID-19), metabolic disorders (such as diabetes), or autoimmune diseases (such as systemic lupus erythematosus), the formation of microthrombosis involves three core links: endothelial cell injury, platelet activation, and a systemic imbalance between coagulation and fibrinolysis. The commonality of these pathological processes suggests that microthrombi may be a common hub for the transformation of various diseases into microcirculatory disorders and *vice versa*.

2.3. Opportunities and Challenges for Further Clinical Translation

Laser speckle imaging (LSI) and laser Doppler imaging (LDI) bring new opportunities for the diagnosis, treatment and prognosis of microcirculatory disorders: intraoperative blood flow imaging can optimize the effect of cardiovascular surgery, portable equipment can improve the early screening rate of chronic diseases such as diabetes and foot, and objective blood flow parameters may support the evaluation of the efficacy of traditional Chinese medicine. However, the promotion of the technology still faces obstacles: the blood flow calculation standards of different devices are not unified, imaging of deep organs (such as the myocardium) is limited, and high costs constrain grassroots applications.

2.4. Future Research Directions and Technological Innovation

Future research may be expected to focus on a number of major directions: precision imaging technology, developing targeted probes and super-resolution microscopes to achieve subcellular-level visualization of microthrombi; intelligent diagnostic systems, using AI algorithms to automatically analyze blood flow patterns and improve the efficiency of recognition of microthrombi and their effects; and multimodal integration, combining optical, ultrasound and other technologies to simultaneously obtain three-dimensional information such as blood flow and vascular elasticity. As examples of deep learning, Shang et al. [810] used convolutional neural networks to transform speckle dynamics into absolute blood flow rates in mm/s, Yosovich et al. [597] used deep learning to classify flow abnormalities directly from speckle images, Morales-Vargas and colleagues [811] used deep learning for vessel segmentation and depth estimation, Park and Ahn [812] used AI effectively to solve the inverse scattering problem, while Shi and colleagues [813] were able to apply these methods in an intraoperative setting. As to multimodal methods, Wang and colleagues [814] have successfully implemented combined hyperspectral and laser speckle imaging.

Together with biochemical analyses involving multiomics and the data mining thereof, this will greatly promote microcirculation research from “functional observation” to “molecular mechanism analysis”, providing new tools for the diagnosis and treatment of cardiovascular and cerebrovascular diseases.

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Declaration of Competing Interests

E.P. is a named inventor on a patent disclosing the use of fluorescence microscopy in Long COVID.

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