The importance of microvascular inflammation in ageing and age-related diseases: a position paper from the ESH working group on small arteries, section of microvascular inflammation

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The importance of microvascular inflammation in ageing and age-related diseases: a position paper from the ESH working group on small arteries, section of microvascular inflammation

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Microcirculation is pervasive and orchestrates a profound regulatory cross-talk with the surrounding tissue and organs. Similarly, it is one of the earliest biological systems targeted by environmental stressors and consequently involved in the development and progression of ageing and age-related disease. Microvascular dysfunction, if not targeted, leads to a steady derangement of the phenotype, which cumulates comorbidities and eventually results in a nonrescuable, very high-cardiovascular risk. Along the broad spectrum of pathologies, both shared and distinct molecular pathways and pathophysiological alteration are involved in the disruption of microvascular homeostasis, all pointing to microvascular inflammation as the putative primary culprit. This position paper explores the presence and the detrimental contribution of microvascular inflammation across the whole spectrum of chronic age-related diseases, which characterise the 21st-century healthcare landscape. The manuscript aims to strongly affirm the centrality of microvascular inflammation by recapitulating the current evidence and providing a clear synoptic view of the whole cardiometabolic derangement. Indeed, there is an urgent need for further mechanistic exploration to identify clear, very early or disease-specific molecular targets to provide an effective therapeutic strategy against the otherwise unstoppable rising prevalence of age-related diseases.

Keywords: ageing, age-related disease, cardiometabolism, inflammation, microcirculation

Abbreviations: AD, Alzheimer's disease; AGEs, advanced glycation end products; AGO-1, argonaute 1; AngII, angiotensin II; ARD, autoimmune rheumatologic diseases; AS, ankylosing spondylitis; AVR, arteriovenous ratio; BBB, blood–brain barrier; BET, bromodomain and extraterminal

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domain; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CFR, coronary flow reserve; cGAS-STING, DNA-sensing enzyme cyclic GMP-AMP synthase stimulator of interferon genes; CV, cardiovascular; DM, diabetes mellitus; DPP-4i, dipeptidyl peptidase-4 inhibitors; ECs, endothelial cells; EF, endothelial function; Endo-PAT, non-invasive peripheral arterial tonometry; eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; ETA, endothelin-1 receptor A; FFA, free fatty acids; FMD, flow-mediated dilation; GLP-1RA, glucagon-like peptide-1 receptor agonists; HFpEF, heart failure with preserved ejection fraction; HHb, deoxygenated haemoglobin; HIF-1α, hypoxia-inducible factor 1α; ICAM-1, intercellular adhesion molecule-1; IFN-γ, interferon-γ; IL, interleukin; JNK, c-Jun N-terminal kinase; LDF, laser Doppler flowmetry; LSCI, laser speckle contrast imaging; M/L, media-to-lumen; MAPK, mitogen-activated protein kinase; MD, microcirculatory dysfunction; MHT, masked hypertension; MTHFR, methylene-tetrahydrofolate reductase; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor kappa-B; NK, natural killer cell; NLRP3, NOD-like receptor family pyrin domain containing 3; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; O2Hb, oxygenated haemoglobin; PA, psoriatic arthritis; PAT, pulse amplitude tonometry; PCs, pericytes; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PVAT, perivascular adipose tissue; RA, rheumatoid arthritis; RAGE, receptors for advanced glycation end products; RONS, reactive oxygen and nitrogen species; ROS, reactive oxygen species; SASP, senescent-associated secretory phenotype; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; Sirt1, mammalian silent information regulator 1; SLE, systemic lupus erythematosus; SPECT, single-photon emission tomography; Th, T helper lymphocytes; tHb, total haemoglobin; TLRs, toll-like receptors; TNF-α, tumour necrosis factor-α; Treg , T regulatory cells; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular epithelial growth factor; VSMCs, vascular smooth muscle cells; WCH, white coat hypertension; WMH, white matter hyperintensities

INTRODUCTION: MICROCIRCULATION IN CARDIOVASCULAR DISEASE

Microcirculation is the network of terminal vessels of the systemic circulation comprising arterioles, capillaries and venules less than 100 μm in diameter [1–3]. This network delivers oxygen and other nutrients to tissues while removing carbon dioxide, cellular waste products and toxins [1]. Importantly, microcirculation also regulates fluid homeostasis, temperature control and inflammatory response [1].

Contemporary evidence suggests that microcirculatory impairment may occur in adulthood and further deteriorate across the lifespan. Ageing progressively decreases blood flow and vessel density, ultimately reducing arterial compliance [1]. Beyond ageing, microcirculatory dysfunction (MD) characterises a multitude of conditions, including diabetes mellitus (DM), hypercholesterolemia, hypertension, peripheral arterial disease, chronic renal failure, menopause, obesity and chronic inflammatory autoimmune disorders [4–8]. Multiple mechanisms may contribute to microcirculatory impairment, including oxidative stress, enhanced leukocyte adhesion, activation of immune cells (both innate and adaptive [9]), endothelial dysfunction, vasoconstriction, attenuated angiogenesis, increased endothelial permeability, microcirculatory plugging and remodelling, lymphatic dysfunction as well as impaired autoregulation [5,10–16].

MD may develop in multiple tissue beds as an underlying systemic process preceding clinical symptoms long before their onset [17,18]. In this context, MD may reflect an early marker of vascular disease and predispose to the development of atherosclerosis [5]. Accordingly, several minimally or noninvasive techniques have been developed to provide useful MD biomarkers in different vascular beds (summarized in Table 1) [19]. However, although circulating biomarkers, including increased triglycerides, C-reactive protein (CRP), cystatin C, homocysteine, nitric oxide (NO), uric acid, interleukin (IL)-6, N-terminal pro-b-type natriuretic peptide, cardiac troponin, thrombomodulin, renalase, neuregulin-1, von Willebrand factor, serotonin and asymmetric dimethylarginine, are increased in patients with MD, their clinical use for this purpose is not yet validated [18,20–22].

MD is causally associated with the entire spectrum of ageing and age-related diseases, mainly through pro-inflammatory mechanisms (Fig. 1) [23] and may be the substrate for the further development of numerous cardiovascular (CV) diseases, such as coronary artery disease and heart failure with preserved ejection fraction (HFpEF). MD is also found in extra-cardiac tissues (i.e., brain, retina, and lungs) and clinically manifests as dementia, depression, anxiety, vision loss or pulmonary hypertension [14]. In the same context, MD has been implicated in rheumatic (e.g., skin MD) and oncologic diseases [24–32]. With respect to its prognostic value, MD is associated with an increased risk of short- and long-term adverse CV outcomes [33,34]. Both peripheral and coronary MD has been associated with adverse CV events and mortality [35–44]. Furthermore, MD has been linked with progression to kidney failure [18]. Notably, cerebral small vessel disease features are strongly associated with stroke, dementia- especially Alzheimer's disease (AD) and vascular dementias, depression and all-cause mortality [45]. Uterine and placental MD predispose to the onset of preeclampsia [46,47] and to early postnatal microvascular rarefaction and development of MD in offspring [48,49]. Finally, testicular MD and penile skin MD are linked to endocrine disturbances and the future development of hypertension and CV diseases [50,51]. Collectively, an integrative approach to understanding MD is needed to implement effective early diagnosis and treatment strategies.

THE LINK BETWEEN INFLAMMATION AND EARLY MICROVASCULAR AGEING

The microvasculature is pervasive, and its impairment influences every tissue in the human body [52]. Consequently,

TABLE 1. Currently available methods for assessment of microcirculatory function in humans.

Technique	Tissue	Method of assessment	Advantages	Limitations
Peripheral arterial network				
Finger plethysmography	Arteries of fingers	Reactive hyperemia index in finger blood flow measured by using finger probes	-Safe and noninvasive -No need for specific training -Totally nonoperator-dependent -Prognostic value for adverse CV events	-More expensive -Environmental conditions and the autonomic nervous system may affect measurements
Antebrachial plethysmography	Brachial artery	Quantification of forearm blood flow by means of plethysmography during infusion of vasoactive drugs in the brachial artery immediately after cuff deflation and again at 1 and 5 min of reperfusion	-Safe, noninvasive -It allows the simultaneous study of large conduit vessels and small arteries	-Inexpensive -Small errors in the measurement of arterial diameter will result in large errors in the calculation of flow -Room temperature may affect measurements -Measures the local arterial extensibility
Transcutaneous oxygen tension	Skin	Quantity of oxygen molecules transferred to the skin microcirculation after heating skin>40°C	-Wide availability	-Time-consuming -Does not assess all ischemic regions
Flow mediated skin fluorescence	Skin	Assessment of microcirculation and metabolic regulation based on the measurements of NADH fluorescence intensity in epidermis	-Quick and simple -Good reproducibility -Flowmotion analysis -Correlated with endothelial biomarkers	- Lack of robust evidence on the prognostic value
Iontophoresis	Subpapillary plexus, nutritional capillaries, nerve-axon reflex	Delivery of vasodilators (acetylcholine/ SNP) subdermally and measurement of microcirculatory flow with laser Doppler fluxmetry or single-point probes	-Quick and simple -Small coefficients of variation -Correlated with other microvascular beds -Isolation of nerve-axon reflex	-Cannot distinguish subpapillary plexus from nutritional capillaries in glabrous skin
Skin pulp blood flow	Nutritional capillaries and AV shunts	Assessment of microcirculation of pulp skin of the toes with laser Doppler fluxmetry or heat and/or radioisotope washout methods	-Simple, can be performed on any area of skin quickly -Distinguishes nutritional capillaries and AV shunts in glabrous skin	-Not correlated with other tissue beds
Capillaroscopy	Subpapillary plexus, nutritional capillaries	Evaluation of morphology and blood flow by studying capillary changes with light microscopy or fluorescent dye dynamic capillaroscopy	-Distinguishes microvascular from the interstitial compartments, assesses transcapillary diffusion -Distinguishes subpapillary plexus from nutritional capillaries	-Cost and availability of the equipment -Patients need to be placed in the sitting position -Qualitative evaluation is largely dependent on the operator experience -Need for readily available software among different centers for quantitave evaluation of MD parameters
Hand-held vital-microscope device	Sublingual microcirculation, microvascular beds of different types of mucosa and solid organ surfaces	Video observation of the flowing RBCs of the microcirculation (3rd generation device – the newest technology – uses incident darkfield illumination for this purpose) and diffuse capacity	-Noninvasive monitoring of the microcirculation at the bedside -Alterations in sublingual microcirculation are highly sensitive and specific, predicting adverse outcomes *3rd generation device* -Computer-controlled image sensor -Better image quality -Evaluation of 30% more capillaries	- Microcirculation can be visualized only if the epithelial layer of the area of interest is thin - Presence of artefacts due to movement - Variability with the use of different generations of HVM
Micromyography	Subcutaneous tissues	Measurement of MLR or WLR of small subcutaneous vessels dissected from tissue biopsies by pressure or wire micromyography	-Gold-standard method -Precise and reliable -The most potent predictor of CV events in hypertensive patients	-Locally invasive
Laser speckle contrast imaging	Skin and subcutaneous tissues, Retinal and choroidal microcirculation	Mesurements of peripheral microcirculatory perfusion on a wide area of tissue LSCI coupled with vascular reactivity tests enables to assess endothelial function Complementary use of a fundus camera with a laser diode or a blue component argon laser for assessment of deep or superficial retinal flow, respectively	-Dynamic, real-time perfusion monitoring -Very good spatial and temporal resolution -Improved spatial and temporal reproducibility as compared to conventional laser Doppler flowmetry -Excellent reproducibility -Safe, noninvasive	-Cost and availability of the equipment -Lack of robust evidence on the prognostic value -Interference by movement artifacts -Limited interpatient comparability -Complexity of quantitative measurements

TABLE 1 (*Continued*)

Technique	Tissue	Method of assessment	Advantages	Limitations
Scanning laser Doppler flowmetry	Retinal vascular district	Quantification of the WLR of retinal arterioles using scanning laser Doppler flowmetry	-Easy repeatability and comfortable for patients -Good agreement with wire micromyography	-Lack of robust evidence on the prognostic value -Suboptimal variability in real-life situations due to the indirect nature of the measurement
Nears Infrared Spectroscopy	Muscle and brain microcirculation	Noninvasively assessment of (i) microvascular reactivity, (ii) skeletal muscle and brain oxygenation via continuous monitoring of functional changes in oxygenated hemoglobin dissociation	-Easy repeatability -Precise and reliable -Correlated with other microvascular beds	-Lack of prospectives and large epidemiological studies
Adaptive optics	Retinal vascular district	Direct measurement of WLR of retinal arterioles by an adaptive optics imaging system using a beam of light	-Better reproducibility than scanning laser Doppler flowmetry	-Lack of robust evidence on the prognostic value
Retinal Vessel Diameter	Retinal vascular district	Direct measurement of arteriolar and venular vessels diameter from fundus photographs	-Safe and noninvasive -Low cost and quick -Applicable in large populations -Implicated in large epidemiological studies predicting CV events -correlated with macro- and other microvascular beds	-Lack of normal values -Lack of studies investigating the changes after drug treatment
Coronary arterial network				
Coronary angiography-derived index of microcirculatory resistance	Coronary arteries	Physiological assessment of microvascular disease in coronary circulation from angiographic images	-May predict adverse CV outcome and extensive myocardial injury -Highly reproducible and excellent diagnostic accuracy, not affected by hemodynamic changes - Relatively independent of epicardial coronary disease	-Invasive method -Limited in clinical practice due to required additional procedural time, cost and technical complexity (in non-STEMI patients)
Coronary flow reserve	Coronary arteries	The ratio of the maximal or hyperemic flow down a coronary vessel to the resting flow	-Prognostic value for all-cause mortality and CV events -Quantitative and global physiological interrogation of the coronary circulation -Can be measured using noninvasive modalities, including echocardiography, PET and CMR	-Invasive method using a Doppler-tipped coronary guidewire -Difficulty in obtaining a suitable Doppler signal -Suboptimal repeatability of measurements - Lack of a clear cut-off between normal and abnormal CFR

AV, arteriovenous; CFR, coronary flow reserve; CMR, cardiac magnetic resonance; CV, cardiovascular; EndoPAT, noninvasive peripheral arterial tonometry.HVM, hand-held vital microscope; MLR, media thickness to internal lumen ratio of subcutaneous small resistance arteries; PET, positron emission tomography; RBCs, red blood cells; SNP, sodium nitroprusside; STEMI, ST-elevation myocardial infarction; WLR, wall–lumen ratio.

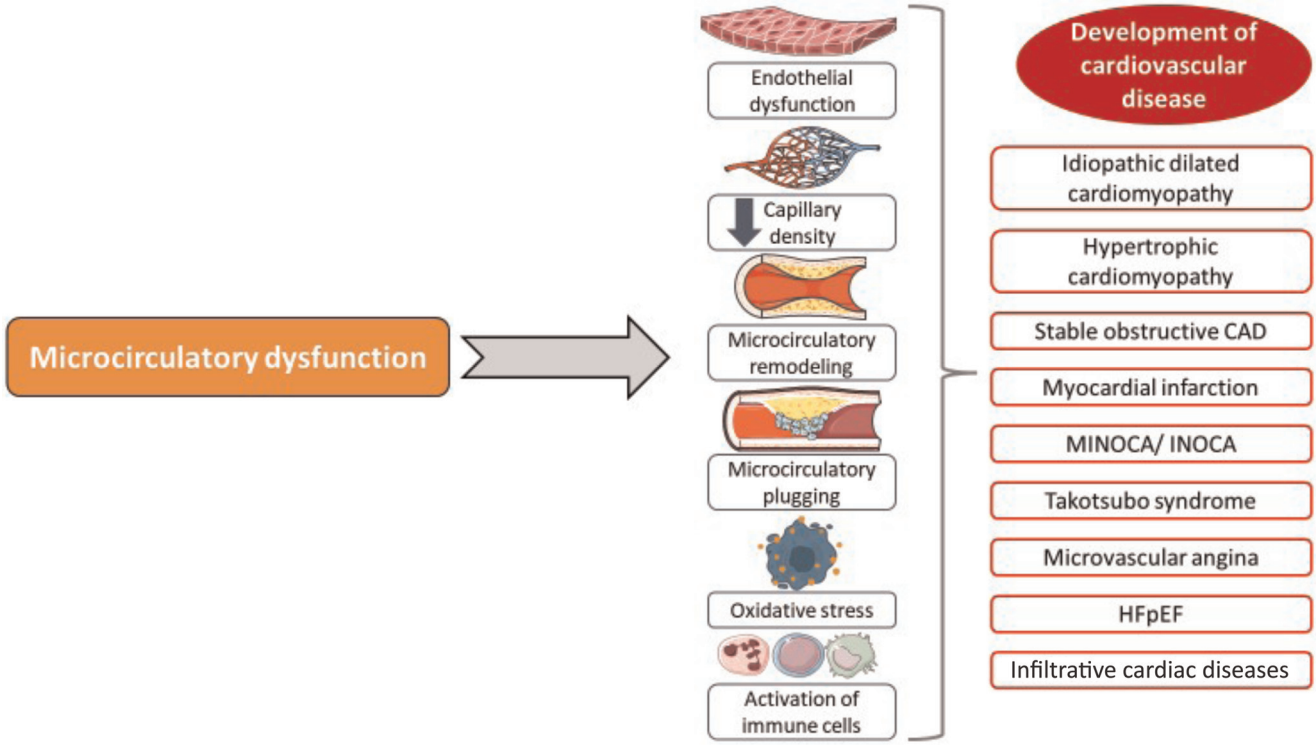

FIGURE 1 Mechanisms linking microcirculatory dysfunction with multiple manifestations of cardiovascular disease. CAD, coronary artery disease; HFpEF, heart failure with preserved ejection fraction; INOCA, ischemia with nonobstructive coronary arteries; MINOCA, myocardial infarction with nonobstructive coronary arteries.

vascular age is a reliable marker of biological age [53]. Microvascular ageing reflects a point at which MD becomes persistent and further deteriorates over time. The onset of MD marks a crucial point in the natural history of ageing.

We need to address lifestyle and environmental stressors to look at the earliest perpetrators of microvascular damage. In addition to the genetic predisposition, each individual is constantly exposed to various noxious *stimuli* that can induce MD. A sedentary lifestyle can increase vascular nicotinamide adenine dinucleotide phosphate (NADPH)-derived reactive oxygen species (ROS) production that affect the endothelial function [54]; similarly, exaggerated exercise training induces mitochondrial dysfunction leading to MD [55]. Unhealthy dietary and eating patterns [56], as well as nutrient overload [57], cause an imbalance in the oxygen supply/demand ratio, activating hypoxia-inducible factor 1α (HIF-1α) and promoting impaired angiogenesis [58]. Additional environment determinants, including environment pollutants, temperature, seasonal changes, circadian rhythm and infections have demonstrated significant role in regulating microvascular inflammation and cardiovascular (CV) diseases [59–68]

The final effector through which all these stressors promote microvascular ageing [69–71] is the immune-inflammatory response [60]. Ultimately, they create a low-grade pro-oxidant pro-inflammatory environment [72] that leads to MD [73,74]. Inflammation disrupts microvascular function by increasing ROS generation, reducing NO bioavailability, and leading to vascular wall hyperpermeability and glycocalyx remodelling [75]. In the long term, this promotes the hyperactivation of compensatory pathways such as endothelial and vascular smooth muscle cells (VSMCs) proliferation, pathological angiogenesis [76–78] and, ultimately, permanent vessel wall remodelling. The lymphatic vasculature also plays a role in this detrimental interplay. While it generally regulates dietary lipid absorption and cholesterol efflux [79], it becomes dysfunctional when exposed to stressors, further compromising local homeostasis. Lymphatic dysfunction results in reduced immune cell clearance, increased insulin resistance [80] and reduced lymphangiogenic potential [79]. These maladaptive changes, which are common in ageing and age-related diseases, ultimately prolong the inflammatory response and microvascular remodelling [81]. The consequence of all these processes is that if the MD is not rapidly targeted and reversed, its alterations become permanent, characterised by epigenetic cues that are not easily targeted by current therapies [82] and predispose to more significant harm when a subsequent exposition to risk factors [83] occurs, even several years ahead. This marks the point when vascular age diverges from chronological age, and ageing diverges from his physiological trajectory.

An aged vasculature is characterised by a low-grade inflammatory state which originates directly from the vessel and the surrounding environment (i.e., perivascular adipose tissue (PVAT) [84], neural terminations [85], abnormal shear stress [86]), even after the removal of the *stimuli*. In this condition, the vessel is not only the target of the damage exerted by the CV risk factors [87] but also becomes the perpetrator by first-hand promoting the low-grade inflammatory response which characterizes chronic time-dependent disease [72]. This, in turn, further dampens microvascular homeostatic control mechanisms and aggravate MD [71]. This vicious cycle is characterised by a

profound cross-talk between nonimmune and immune cells, which is often present in the context of CV disease, for instance, in macrovascular atherosclerotic remodelling [88] and cardiac fibrosis [89]. However, a clear understanding of this dialogue between distinct cell types is still an unmet need, especially in MD setting.

This model accurately reflects cardiometabolic disease. First, environmental stressors significantly influence the natural history of obesity, type 2 diabetes, arterial hypertension, and HFpEF [60]. Second, they all present an early MD [38,90–92] and are characterised by accelerated microvascular ageing [58]. Third, these conditions are tightly connected [52]. Fourth, all of them are characterised by a persistent systemic low-grade inflammation which further deteriorates the cardiometabolic homeostasis and that it has in the microvascular bed one of its primary perpetrators [72,84,93].

Inflammageing [72,94] and immunometabolism [95] are thus fundamental integrated approaches to explore the connections and the cross-talks between environment, metabolic disease, vascular health, and CV risk. Although this conceptual framework is generally related to cardiometabolic disease, it might be easily translated to other chronic and time-dependent conditions such as neurodegenerative pathologies, autoimmune diseases, and cancer. As indirect evidence, epigenetic pan-deactivators of vascular inflammation as the inhibitors of bromodomain and extraterminal domain (BET) proteins [96] have recently been proposed for all these disease settings [97–103]. Similarly, anti-inflammatory drugs are attracting substantial attention in the context of CV diseases [104]. But the link between inflammation and microvascular ageing is multidirectional. As environmental stressors link inflammation with microvascular ageing, inflammation also becomes the link between aged vasculature and systemic metabolic diseases, which further promotes microvascular inflammation. The onset of this vicious cycle is at the base of age-related diseases. It is clear that only by an accurate understanding of the pathophysiologic and molecular mechanisms underpinning this connection we will be able to develop therapeutic strategies to challenge the steadily increasing prevalence of chronic diseases [105,106] (Fig. 2).

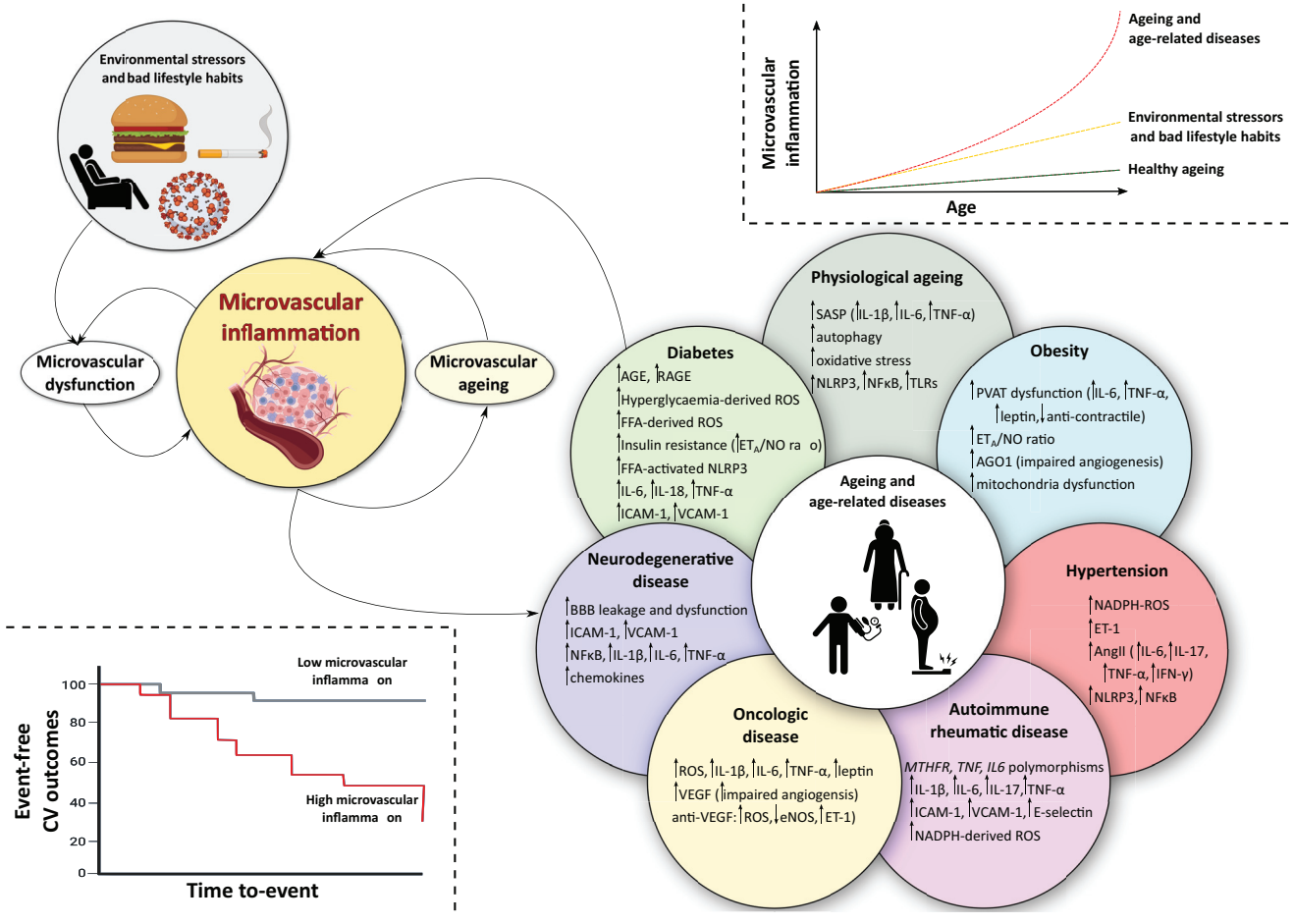

FIGURE 2 Graphical abstract. Microvascular inflammation links environmental stressors to microvascular ageing. Environmental stressors induce microvascular dysfunction, which in turn promotes microvascular inflammation. When microvascular inflammation causes permanent changes in vascular structure and function, microvascular age and biological age diverge. The vessel becomes the architect of microvascular inflammation, exposing the microcirculation to further damage from environmental stressors and thus promoting the onset of cardiometabolic disease, exponentially increasing the degree of microvascular inflammation and the individual cardiovascular risk. The major common and distinct molecular-, cell- and tissue-level mechanisms involved in microvascular inflammation are summarized. AGE, advanced glycation end products; AGO1, argonaute 1; BBB, blood–brain barrier; eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; ET_A, endothelin-1 receptor A; FFA, free fatty acids; ICAM, intercellular adhesion molecule-1; IFN, interferon-γ; IL, interleukin; MTHFR, methylene-tetrahydrofolate reductase; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor kappa-B; NLRP3, NOD-like receptor family pyrin domain containing 3; NO, nitric oxide; PVAT, perivascular adipose tissue; ROS, reactive oxygen species; SASP, senescent-associated secretory phenotype; TLR, toll-like receptors; TNF-α, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular epithelial growth factor.

Statement: Environmental stressors predispose to unhealthy ageing and age-related disease by promoting MD. If MD is not prevented or rapidly treated, the microvascular environment in turn becomes the perpetrator of microvascular inflammation through detrimental cross-talk between nonimmune and immune elements, leading to the low-grade inflammatory response that characterises unhealthy ageing and age-related disease.

MICROVASCULAR INFLAMMATION ACROSS THE AGE-RELATED DISEASES CONTINUUM

Physiological ageing

Physiological ageing is a natural phenomenon driven by a variety of complex, and yet loosely understood mechanisms that strongly interact with each other. In addition to these, initial emergence of genomic instability, which includes dysregulated DNA damage repair pathways and telomere shortening, other key mechanisms are involved. These include the stimulation of senescence and impairment of autophagy at a cellular level and the consequential development of oxidative stress and microvascular inflammation at the tissue level. Ultimately, these mechanisms contribute to the ageing-related phenotype characterized by endothelial, vascular and consecutively tissue dysfunction (Fig. 3a) [107,108]. Notably, these mechanisms are often bidirectional, ultimately establishing a vicious cycle.

Senescence

Cellular senescence is a stress-induced, durable, cell cycle arrest of previously replication-competent cells and is considered a central hallmark of ageing [109]. Senescence contributes to ageing process through multiple mechanisms, among which the propagation of inflammation prevails. Pertinent to this, it has been shown that senescent cells secrete a plethora of potent pro-inflammatory factors termed the senescent-associated secretory phenotype (SASP), which drive an intense inflammatory response [110,111]. SASP also contributes to the spread of inflammation and oxidative stress from senescent to healthy nonsenescent cells via paracrine fashion, which leads to a pro-inflammatory and pro-oxidant phenotype at a microvascular level [107]. Consistent with its inflammatory potential, several in vitro and preclinical data have documented the role of senescence in promoting oxidative stress and endothelial dysfunction [112,113]. In healthy ageing humans, markers of endothelial senescence have been correlated with significantly impaired endothelial function [114].

Autophagy

Autophagy is a highly selective clearance pathway that degrades several defective cellular components through lysosomal activation. Therefore it is tightly associated with the maintenance of cellular and tissue homeostasis and, in the long term, longevity [115]. Altered autophagy has been proposed as a prominent feature of physiological ageing, with increasing evidence suggesting an impaired autophagic activity across ageing in different organisms [116]. In humans, it has been demonstrated that the expression of autophagy-related genes (i.e., ATG5, BECN1) and the proteolytic function of lysosomes decline with age [117]. Consequently, compromised autophagy leads to cellular and vascular dysfunction and enhanced inflammation, as evidenced by the promotion of oxidative-induced senescence, the production of endothelial reactive oxygen species (ROS) and the development of endothelial dysfunction in both aged mice and human subjects [117–119]. In addition, autophagy has been recognized as a significant inhibitor of inflammasome which is a potent mediator of microvascular inflammation [120].

Oxidative stress

Oxidative stress is a consequence of the imbalance between the production and detoxification of reactive oxygen and nitrogen species (RONS) [121]. Ageing process is associated with reduced activity of the antioxidant transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) [122]. Hence, accumulation of oxidative damage by RONS produced by NADPH oxidases and mitochondria is considered one of the core pathophysiologic pathways driving physiological ageing and age-associated diseases [123]. Particularly in the context of ageing and age-related diseases, mitochondrial dysfunction and mitochondria-derived ROS are key drivers of the inflammatory response leading to pathogenetic processes [124,125]. The oxidative environment further stresses mitochondrial pathways, leading to the detrimental escape of mitochondrial DNA from organelles and cells [126,127]. Mitochondrial-free mitochondrial DNA and the pro-oxidant environment, in turn, transduce a pro-inflammatory signal within and between cells, leading to the activation of multiple signalling pathways: nucleotide-binding oligomerization domain (NOD)-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation, DNA-sensing enzyme cyclic GMP-AMP synthase stimulator of interferon genes (cGAS-STING) and toll-like receptor (TLR). It also leads to induction of senescence and SASP production with consequent nuclear factor kappa-B (NF-κB) activation, as well as hyperactivation of the pro-oxidant mediator p66Shc [82,125], consumption of NAD+ and consequent mammalian silent information regulator 1 (Sirt1) dysregulation [52,128]. Furthermore, oxidative stress exerts a detrimental effect on endothelial function by quenching the bioavailable, endothelium-derived NO and reducing both NO availability and endothelial NO synthase (eNOS) expression. Therefore, oxidative stress is strongly linked to the development of endothelial and microvascular dysfunction with ageing in humans [129,130].

Inflammation

The inflammageing state, a sterile, subclinical, low-grade inflammation increasing with age and promoting the development of age-associated diseases, has been well recognized in the elderly [72]. Indeed, in older adults are frequently reported persistently elevated circulating levels of SASP factors, including IL-1β, IL-6 and tumour necrosis factor (TNF)-α [131–133]. In elderly, inflammageing is largely considered an aftermath of immunosenescence, a significant immune system dysregulation observed with

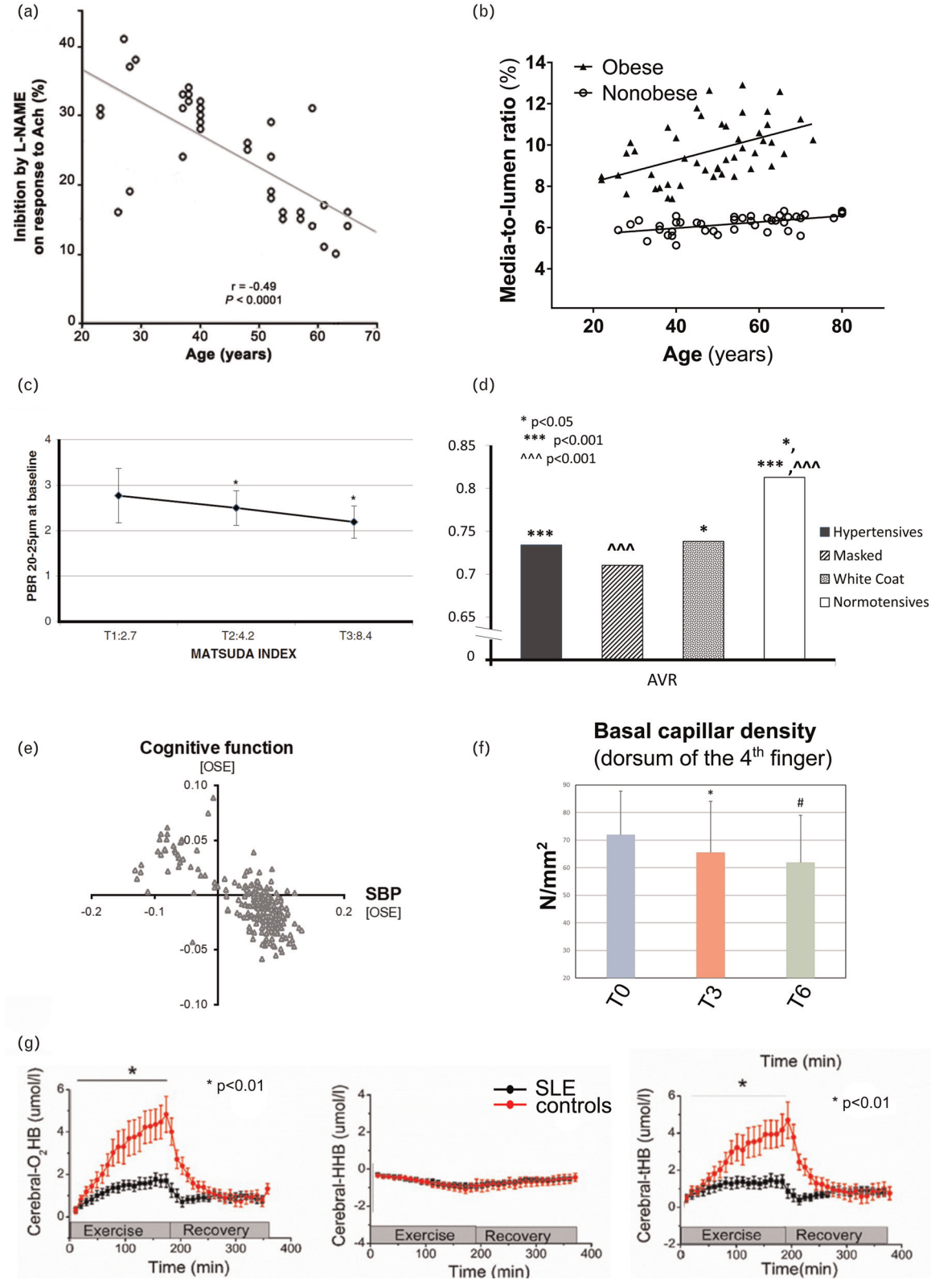

FIGURE 3 Microvascular inflammation and its impact on microvascular dysfunction across ageing and age-related disease. (a) Relationship between age (x-axis) and the inhibition by *N*-nitro-l-arginine methylester (L-NAME) on maximal response to acetylcholine (y-axis) in normotensive subjects ($n = 41$). Adapted from [108]. (b) Increased media-to-lumen (M/L) ratio per year of age in healthy nonobese (white circle; $n = 42$) and obese with no other comorbidities (black triangle; $n = 47$) subjects. Regression lines for each group are shown. The M/L ratio is expressed as a percentage (%). Age and M/L are tightly related in both groups (obese: $r = 0.487$, $P < 0.01$; nonobese: $r = 0.555$, $P = 0.001$). The slope is five-fold steeper in the obese group. Figure and captions adapted from [125]. (c) Association of tertiles (T1–T2–T3) of Matsuda index with perfused boundary region (PBR) measured in the microvessels ranged from 20 to 25 µm indicating an association between insulin resistance and damaged glycocalyx ($F = 4.8$, $P = 0.03$) in $n = 100$ subjects with different degrees of insulin resistance ($n = 40$ first-degree relatives of type-2 diabetes patients, $n = 40$ subjects with abnormal oral glucose tolerance test and 20 subjects with normal oral glucose tolerance test without parental history of diabetes). Adapted from [182]. (d) Comparison of the retinal

ageing, which substantially propagates the inflammatory milieu and consists in overall aberrant activation of innate and adaptive immune response [134]. In this context, microvascular inflammation can be exacerbated by an age-associated inappropriate activation of TLRs and the NLRP3 inflammasome complex, both representing crucial activators of the innate immune inflammatory response which leads to increased expression of NF-κB and the production of several proinflammatory mediators [135–137]. Activation of the ROS-sensitive, proinflammatory effector NF-κB holds a central role in the ageing-associated inflammatory response. Endothelial cells (ECs) from older humans actively express NF-κB, which is directly implicated in endothelial dysfunction [132,138] as well as in exacerbating inflammageing and oxidative stress, thus corroborating an intricate relationship between senescence, oxidative stress and inflammation across ageing and extending the vicious cycle [139–141]. Finally, mammalian sirtuins represent another significant ageing-associated mechanism implicated in microvascular inflammation. They are a family of nicotinamide adenine dinucleotide-dependent deacetylases involved in several processes that regulate metabolic homeostasis and modulate the benefits of calorie restriction and exercise. They control mitochondrial function, cell survival, attenuation of inflammatory responses and circadian rhythm. Because of their contribution to many protective pathways and their central involvement in longevity mechanisms, they have attracted increasing attention as potential therapeutic targets [142]. In particular, Sirt1, a deacetylase implicated in many critical physiological responses to altered energy metabolism and stress, has multiple anti-inflammatory, antioxidant and anti-ageing properties [143–145]. Reduced expression of Sirt1 has been observed in ECs and VSMCs obtained from older adults, associated with a senescent phenotype and the development of endothelial dysfunction [125,146,147]. Furthermore, data has shown that persistently reduced levels of Sirt1 lead to upregulation of NF-κB and NLRP3 inflammasome, hence significantly amplifying the inflammatory response [145,148].

Statement: In physiological ageing, stimulation of senescence, impairment of autophagy, and increased oxidative stress lead to microvascular inflammation at the tissue level. This culminates in the ageing-related phenotype characterized by MD and increased susceptibility to the onset of age-related diseases.

Obesity

Obesity, given its high and steadily increasing prevalence [105], probably represents the closest human model to exploring the contribution of environmental stressors to microvascular inflammation and accelerated ageing. Its relevance in the global landscape is sadly acknowledged: obesity ranks first in terms of mortality related to metabolic diseases, with no trend towards reduction [149]. The impact of obesity on MD starts very early: in patients with obesity, the slope of the media-to-lumen (M/L) ratio plotted against age diverges from the healthy controls before the age of 20, being five times steeper (Fig. 3b) [125,150]. The increased nutrient supply ultimately overburdens the metabolic pathways, promoting hypoxia with consequent HIF-1α activation [151]. The resultant pro-oxidant and pro-inflammatory environment promotes the local low-grade inflammatory response, which eventually turns systemic and characterises the generalized MD observed in obesity [91].

Although multiple pathways contribute to its clinical phenotype, obesity is characterised by a prominent role of the PVAT. PVAT is a key member of the microvascular unit [91], with a brown-like and anticontractile phenotype in the healthy [152], which loses its thermogenic capacity and turns pro-contractile in the condition of diseases such as obesity [153]. The deep cross-talk between PVAT and the small vessels is directly responsible for both the inflammatory damage and response characterising obesity [154]. PVAT phenotype shift leads to increased secretion of several adipokines and cytokines, including chemerin, leptin, IL-6 and TNF-α [155]. While experimental studies in mice have reported how leptin leads to MD by first targeting the hypothalamic microvasculature [156], *ex-vivo* observations in humans have demonstrated how PVAT dysfunction, promoted by macrophage activation [157], results in an increase in PVAT-derived cytokines secretion [84,93]. This fuels the vessel-specific inflammatory response [93], induces endothelial dysfunction and further imbalance the homeostatic response from the vasculature by increasing the expression of endothelin-1 (ET-1) and its receptor A (ET_A). The altered ET_A/NO ratio upregulates c-Jun N-terminal kinase (JNK) signalling, increasing NAPDH-derived and mitochondria-derived ROS [84]. The bidirectional cross-talk further aggravates PVAT dysfunction, as the endothelium also secretes inflammatory cytokines and angiogenetic factors. Indeed, to match the increased nutrient flow, PVAT develops a pro-angiogenetic phenotype trying to compensate with an adequate oxygen supply. However, this neoangiogenetic process [76] ultimately proves detrimental and further promotes an overt dysfunctional phenotype for both the PVAT and the ECs. Recently, an elegant exploration in vivo has shown that, in high-fat diet mice, the ECs-specific deletion of argonaute 1 (AGO1), a pivotal

Figure 3 (Continued).
arteriovenous ratio (AVR) in $n = 201$ newly diagnosed individuals with hypertension of different phenotypes and normotension. Intergroup comparisons were made with analysis of variance ANOVA with Bonferroni correction after adjustment for age, sex, body mass index (BMI). Individuals with sustained hypertension ($n = 103$), masked hypertension (MHT; $n = 28$) and white coat hypertension (WCH; $n = 20$) had significantly lower AVR than normotensive subjects ($n = 50$; $P < 0.05$). Adapted from [206]. (e) Observational, standardised coefficients concerning 242 brain imaging-derived phenotypes genetically affected by SBP corresponding to their association with cognitive function or SBP at the imaging visit. Hypertension was used as a model associated with microvascular inflammation. Figure and caption adapted form [257]. (f) Altered capillaroscopy in oncologic disease. Basal capillary density in the dorsum of the fourth finger (Dpre_basal) in patients ($n = 20$) with cancer and treated with either a tyrosine kinase inhibitor or a vascular epithelial growth factor inhibitor at the different time points (T0, T3, T6). * T3 vs. T0 $P = 0.03$; # T6 vs. T0 $P = 0.02$. Data are expressed as mean+standard deviation. Adapted from [338]. (g) Accumulative data of near-infrared-spectroscopy cerebral responses during exercise in systemic lupus erythematosus (SLE; $n = 26$) vs. control ($n = 27$) group. Oxygenated haemoglobin (O_2Hb), deoxygenated haemoglobin (HHb) and total haemoglobin (tHb) levels were measured. Cerebral O_2Hb continuously increased during exercise in the control group, whereas the SLE group exhibited a plateau in O_2Hb after the first minute of exercise ($P < 0.01$). During exercise, the SLE group exhibited significantly lower average-O_2Hb (1.20 ± 0.89 vs. 2.69 ± 2.46, $P = 0.001$), and a lower peak-O_2Hb) response (2.89 ± 1.56 vs. 5.83 ± 4.59, $P = 0.004$) compared with the control group. No differences were detected in the average HHb responses between groups. Adapted from [299].

contributor to the ECs response to hypoxia, arrests impaired angiogenesis and reverts the PVAT to a browning phenotype, rescuing the MD and the whole-body metabolic homeostasis [158].

Finally, the overload of the metabolic processes leads to mitochondrial dysfunction in obesity, which in turn promotes microvascular inflammatory response by increasing mitochondria-derived ROS levels [125] and activating NLRP3 [159] and cGAS-STING pathways [160]. Evidence supports sirtuins [125] (main elements in nutrient balance/imbalance signalling [161]) as crucial regulators of this process. In ECs, lower levels of Sirt1 induce MD and are associated with an increase of pro-inflammatory and pro-ageing factors p66shc [82] and Arginase II [150], an increase in mitochondria-derived ROS, and a downregulation of several genes involved in the mitochondria electron transport chain.

The documented MD confirms this experimental evidence in patients with obesity. An increased vascular remodelling in visceral fat arteries [125], an impairment in finger microcirculation detected by dynamic nailfold microcapillaroscopy [162], a thin sublingual microvasculature glycocalyx assessed by sidestream darkfield imaging [163], an increased retinal arteriolar narrowing [164] and a decreased retinal microvasculature response to flicker light [165] all characterise the microvascular damage found in patients with obesity. Remarkably, bariatric surgery, the gold standard treatment for treating severe obesity, showed a remarkable effect in terms of MD rescuing in patients with severe obesity, as shown by an improvement in skin microcirculation [166] and in subcutaneous arteries reactivity, which appears even more robust when including PVAT [167].

Statement: Obesity-related microvascular inflammation is characterised by accelerated ageing starting from adolescence/early adulthood, defined by a derangement in the PVAT phenotype, a hyperactivation of inflammatory pathways (mainly TNF-α and IL-6), an impaired angiogenesis and an early mitochondrial dysfunction.

Diabetes

It is well recognized that low-grade inflammation plays an essential role in the pathogenesis of DM, as well as in the development of diabetic microvascular complications. Studies have demonstrated that inflammatory mediators, such as CRP, TNF-α, IL-6 and IL-18, have elevated expression in DM [168,169]. Hyperglycaemia acutely increases circulating cytokine levels through an oxidative mechanism among subjects both with features of insulin resistance and with clinically overt DM [170,171]. In subjects with type 2 DM, a correlation was observed between high-sensitive CRP and IL-6 with HbA1c independent of the presence of coronary heart disease [172,173]. Furthermore, serum levels of TNF-α were associated with the level of insulin resistance and with HbA1c in diabetic subjects [174].

Diabetic hyperglycaemia increases oxidative stress by excessive intracellular ROS generation, which in turn leads to activation of the NF-κB pathway resulting in the production of major pro-inflammatory cytokines. Hyperglycaemia-induced oxidative stress increases the formation of advanced glycation end products (AGEs), which results in increased insulin resistance. Moreover, receptors for advanced glycation end products (RAGE) are involved directly in inflammatory cell recruitment [175,176]. Insulin resistance is associated with endothelial dysfunction. In particular, the endothelial balance between NO-mediated vasodilator actions and ET-1-mediated vasoconstrictor effects of insulin are regulated via phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways, respectively. In states of insulin resistance, dysregulation of PI3K-dependent signalling may cause an imbalance between the NO production and secretion of ET-1 [177]. Thus, insulin resistance induces vasoconstriction and VSMCs proliferation and plays a significant role in the occurrence of endothelial dysfunction [178]. Indeed, markers of insulin resistance are associated with abnormal arterial elastic properties and impaired coronary microvascular function not only in dysglycaemic subjects but also in first-degree relatives of diabetic subjects before the development of impaired glucose tolerance or DM [179].

Furthermore, oxidative stress is characterized by the production of peroxynitrite that down-regulates NO bioavailability and leads to vasoconstriction. Also, the accumulation of ROS promotes the apoptosis of ECs and augment the expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin resulting in microvascular inflammation and hypercoagulability [180]. Chronic inflammation inhibits the production of endothelial eNOS and promotes the expression of ICAM-1, VCAM-1 and ET-1, further damaging endothelial integrity [181].

Acute and long-term hyperglycaemia have a detrimental effect on endothelial glycocalyx integrity [182–184]. The glycocalyx is a gel-like layer composed of sulphated proteoglycans and glycoproteins that prevents the direct contact of circulating inflammatory cells to the luminal surface of the endothelium [185]. Intriguingly, HbA1c is associated with the impaired perfused boundary region, a marker of the microvascular glycocalyx thickness, while intensified glycaemic control ameliorates glycocalyx integrity in diabetic subjects at the 1-year follow-up [186]. The impaired glycocalyx is an independent predictor of adverse outcomes in subjects without established CV disease [43].

Besides hyperglycaemia, high free fatty acid levels (FFA) may stimulate ROS production via protein kinase C (PKC)-dependent activation of NADPH oxidase in both VSMCs and ECs. This finding may explain the excessive acceleration of atherosclerosis and microcirculation damage in diabetic subjects [187]. In addition, hyperglycaemia and lipotoxicity lead to hyperactivation of NLRP3 inflammasome, which mediates caspase-1 activation and the secretion of pro-inflammatory cytokines IL-1β and IL-18. Thus, NLRP3 inflammasome activation in DM leads to chronic inflammation and increased vascular permeability [188].

The most common microvascular complication of DM is diabetic retinopathy. Ocular microcirculatory damage on the grounds of hyperglycaemia causes capillary occlusion leading to retinal ischemia and neovascularization [189]. Interestingly, experimental data show that microcirculatory changes, including adherence of neutrophils and leukostasis, in nonocular tissues of diabetic mice appear to be related and reflect retinal microvascular lesions in the

context of diabetic retinopathy [190]. Underlying retinal microvascular dysfunction seems to precede the clinical manifestation of DM-associated CV disease [191]. New advances in retinal vessel analysis provide useful diagnostic tools to improve the prediction and risk stratification of CV disease [192]. However, there is also evidence of nonretinal MD in diabetes: diabetic subjects have impaired dermal microvascular hyperaemia response to local skin heating [193], reduced glycocalyx thickness (Fig. 3C) [194]. Similarly, digital pulse amplitude tonometry (PAT) is impaired in type 2 diabetes and influenced by glucose level fluctuations [195].

Finally, it should be mentioned that several of the novel antidiabetic agents, namely dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium-glucose cotransporter-2 inhibitors (SGLT-2i), have potential anti-inflammatory properties and improve endothelial function and presumably microcirculation [194,196–200], and this might be – at least partially - responsible of the significant benefit observed in terms of reduction of CV risk [201].

Statement: Hyperglycaemia and FFA-derived ROS produce a substantial increase in oxidative stress, directly affecting microvascular inflammation and promoting an AGE/RAGE and lipotoxic environment, which determines peripheral insulin resistance, further worsening the low-grade inflammatory response.

Arterial hypertension

Arterial hypertension is characterised by diffuse microvascular damage (Fig. 3d, Figure 1, Supplemental Digital Content, http://links.lww.com/HJH/C223) [202–206]. Hypertension and inflammation have a bidirectional physiological and pathophysiological background [207,208]. Several human studies have evaluated the relationship between inflammation and essential hypertension. In a meta-analysis ($n = 21\,458$ patients), higher levels of circulating CRP, high-sensitivity CRP (hs-CRP), and IL-6, but not IL-1β, were associated with the risk of developing hypertension [209]. Studies have also reported correlative links between arterial stiffness and inflammatory markers in essential hypertension [210].

A hallmark of inflammation is the release of inflammatory cytokines such as IL-6, IL-17A, interferon-γ (IFN-γ), and TNF-α by T $CD4^+$ cells, and more specifically by subsets of T helper (Th) cells, Th1 and Th17 [9,207,208]. Involvement of IL-6 has been shown in mice, where *Il6* knock-out mice showed reduced hypertension severity in response to angiotensin II (AngII) infusion [211]. Further, in human renal proximal tubular cells, IL-6 increased angiotensinogen expression [212]. IL-17A affects renal sodium handling [213] and inhibits eNOS, causing impaired vasodilatation and increased peripheral vascular resistance [214]. Long-term effects of IL-17A include the promotion of vascular fibrosis, leading to arterial stiffening [214]. In addition, in mice lacking IL-17A, the number of T cells and macrophages in blood vessels was reduced, illustrating the effect many of these cytokines have in attracting more immune cells, further amplifying the immune response [207]. They induce oxidative stress [215] through enhanced NADPH oxidase subunit expression. Increased oxidative stress affects sodium retention by decreasing the glomerular filtration rate [216]. This, as many of the classical pathophysiological factors in hypertension (ET-1, aldosterone, and AngII), activates the NLRP3 inflammasome through NF-κB. NLPR3 activation leads to increased levels of proinflammatory cytokines IL-1β and IL-18, activating immune and vascular cells as T cells (mainly $CD4^+$), monocytes, ECs and VSMCs [217].

The contribution of innate and adaptive immune cells to the development of MD leading to hypertension is substantial [218]. Regarding immune cells, in animal models of genetic hypertension, vascular ageing is associated with increased PVAT infiltration of macrophages, neutrophils and natural killer cells (NKs), which promote NADPH oxidase 4-driven microvascular remodelling [9,219,220]. Macrophages, as a major source of ROS, are considered important in this process, although the precise mechanisms by which they are involved remain unclear [9]. Similarly, NKs are found to increase before the development of hypertension in spontaneously hypertensive rats [219]. Neutrophils from the plasma of untreated patients with essential hypertension generate neutrophil extracellular traps that lead to collagen production and consequent microvascular remodelling [221]. In adaptive immunity, T cells are considered to play a predominant role. Following antigen recognition, CD4+ T cells are activated and differentiate into T effectors (Th1, Th2 and Th17) or T regulatory cells (T_{reg}), the balance of which influences the inflammatory response [9]. In experimental models of hypertension, as well as in hypertensive patients, the inflammatory response generated by the ratio of T helper lymphocytes (Th) 1/17 (Th1/Th17) is not adequately balanced by the pool of regulatory T lymphocytes (Treg), thus contributing to structural damage of the microcirculation [9]. Recently, it was discovered that the T cell mir214 partially recapitulates and transduces the fibrotic effects of the immune system to the microvasculature, leading to vascular fibrosis, vascular stiffening and remodelling. In particular, cytokines released from PVAT mediate these effects [220]. It is thus clear that the immune system is one of the leading mechanisms supporting the cross-talk between vascular inflammation and hypertension. However, it should be noted that most of the evidence comes from in vivo studies, as further investigations in patients are needed [9].

However, over the last years, evidence has been accumulated showing that this dialogue also involves the sympathetic nervous system [222,223]: an increase in sympathetic activity elicits T-lymphocytes activation and vascular inflammation [224]; significant correlations have been found between circulating plasma norepinephrine, and IL-6 produced by T-lymphocytes as well as TNF-α produced by macrophages and monocytes [225]; chronic sympathetic activation in patients with a peculiar form of high blood pressure desensitizes lymphocyte β_2-adrenoceptors and thereby alters immune function [225]. On the other hand, inflammation and T-lymphocytes activation, which are both triggered by oxidative stress [226], may favour sympathetic activation, as already shown in other diseases characterized by an adrenergic overdrive, including essential hypertension

[222]. In any case, pro-inflammatory substances and mediators may trigger signals to the central nervous system activating the sympathetic neural component [222].

Statement: arterial hypertension is characterised by increased sodium retention and higher levels of ET-1, aldosterone and AngII, which disrupt the microvascular environment by promoting NAPDH-derived endothelial dysfunction and IL-6, IL-17 and TNF-α-driven inflammatory responses. The innate and adaptive immune systems play a central role. In particular, a balance between effectors (Th1, Th17) and regulators (Treg) T cells orchestrates microvascular inflammation and consequent microvascular remodelling.

Neurodegenerative diseases

The cerebral vasculature is unique in its anatomy and physiology. It constructs a highly specialized blood–brain barrier (BBB) that controls the admission of solvents and ions into the brain and clearance into the blood metabolic end products or endogenous neurotoxin produced by the brain [227,228]. The BBB, therefore, play a critical role in maintaining brain homeostasis. It comprises endothelial cells, basement membrane, pericytes and VSMCs, astrocytes, microglia and neurons [229,230]. Vascular ECs are known to secrete vasoactive substances implicated in regulating cerebral flow, intravascular blood coagulation, and preserving the integrity of the BBB. Their atheroprotective role and homeostasis are controlled by releasing vasoactive factors, especially NO. This leads to cGMP-mediated cerebral vessel relaxation and proper blood supply to the brain tissue and autophagy [231]. Pericytes (PCs) directly encircle endothelial cells and VSMCs and are considered vascular mural cells. ECs and PCs have direct contact through gap junctions and contribute to blood vessel formation and BBB function maintenance by regulating immune cells' entry ($CD4^+$ and $CD8^+$ T cells, peripheral macrophages and neutrophils) to the central nervous system [232–234].

Similar to the peripheral circulation, impairment in NO production, inflammation and enhanced ROS production [235,236] are vital in promoting ECs dysfunction manifested by increased expression of leukocyte adhesion molecules such as ICAM-1, VCAM-1 and E-selectin. These molecules promote higher immune-endothelial cell interaction and accumulation of inflammatory cells in the vascular and perivascular niches. The higher expression of ICAM-1 and VCAM-1 is observed in cerebral endothelial cells in animal models of cerebral hypoperfusion, while their inhibition protects against cognitive impairment [237,238]. Furthermore, soluble adhesion molecules like sE-selectin, sP-selectin, sICAM-1 and sVCAM-1, considered endothelial dysfunction markers, are elevated in patients with small vessel brain diseases [239].

The chemotactic process is strictly controlled by numerous chemokines secreted by the vascular cells [240], pericytes [233], microglia [241], and astrocytes [242] in a concentration-directed gradient. Recent studies have implicated the importance of CCL2, CCL3, CCL5 and CXCL8 in many vascular and neurogenerative diseases, including cognitive impairment, stroke and neuroinflammation [243].

Microcerebrovascular endothelial cell activation and BBB leakage promote the migration and accumulation of proinflammatory macrophages [244] and T cells [245,246] in perivascular space (Figure 2, Supplemental Digital Content, http://links.lww.com/HJH/C223). The role of various immune cells in the pathogenesis of endothelial dysfunction and vascular inflammation in CV diseases has been well established [220,247]. Activated immune cells release diverse pro-inflammatory mediators, which propagate microvascular inflammation and may provoke microhemorrhages, further escalating the inflammatory process. Co-involvement of IL-1β, IL-6 and TNF-α, in microvascular brain injury and inflammation has been widely reported [248,249]. IL-1β is considered the main proinflammatory cytokine that increases the astrocytic production of CCL2, CCL20 and CXCl2 [250]. In addition, IL-1β impairs microvascular ECs by disturbing tight and adherent junctional proteins and increasing adhesion molecules expression, prompting vascular leakage and the parenchymal infiltration of leukocytes. In contrast, anti-IL-1β treatment blunts cerebrovascular inflammation and improve outcome in a mouse model of acute ischaemic stroke [251]. IL-6 is a pleiotropic inflammatory cytokine produced by infliltrating leukocytes, ECs, activated microglia and astrocytes. Its expression affects many neuroinflammatory and neurodegenerative conditions [252–254]. IL-6 mediates the elevation of superoxide production and endothelial impairment by affecting NO–cGMP signalling pathway [255]. In addition, it may enhance CRP released by brain cells [256]. Similarly to IL-6, TNF-α affects proper endothelial function by decreasing eNOS levels by destabilising its mRNA expression. Furthermore, TNF-α activates NF-κB, a major regulatory transcription factor, playing a pivotal role in regulating various inflammation-related genes, including key inflammatory cytokines (along with IL-1β and IL-6), chemokines and adhesion molecules.

Cognitive impairment is a hallmark of numerous CV diseases [257]. In hypertension, white matter hyperintensities (WMH) are a critical imaging biomarker linked to this process (Fig. 3E). Indeed, neurovascular inflammation is involved in the aetiology of WMH [258]. Similarly, cerebral small vessel disease has been identified as a key hallmark of a broad range of neurodegenerative conditions. Human neuroimaging and genetic studies show that it is characterised by microvascular endothelial dysfunction impacting cell-cell interactions and leading to brain damage [259]. One broadly studied model of cerebral small vessel disease caused by NOTCH3 mutations, CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) [260], is characterised by accelerated cognitive decline and dementia, recurrent stroke without vascular risk factors, and mood disturbances. This hereditary disorder provides a unique opportunity to understand some of the molecular mechanisms of small vessel disease [261].

Elevation of proinflammatory mediators such as IL-1β, IL-6, TNFα and CRP has been linked with cognitive impairment in humans [262,263]. Furthermore, proinflammatory cytokines secreted by immune and vascular cells have direct neurotoxic and apoptotic properties [264], which could perpetuate local neuroinflammation and neurodegradation. Interestingly, neuroinflammatory changes found in the

brains of coronavirus disease 2019 (COVID-19) patients were accompanied by the presence of macrophages and T cells in the perivascular space [265], suggesting higher microvascular inflammation caused by a cytokine storm which might affect the proper BBB function [266]. Furthermore, cerebral microvascular inflammation enhances the prevalence of cognitive impairment even in mild symptomatic COVID-19 subjects [267]. Similarly, experimental and epidemiological studies indicate a relationship between cognitive decline and CV diseases [228,268–270], associated with chronic low-grade inflammation and dysregulation of the immune system [271,272]. In particular AngII is at the crossroad, acting as cardiovascular and immune systems modulator, initiating inflammation by indirect promotion of vascular permeability and the recruitment of peripheral macrophages and $CD4^+$ and $CD8^+$ T cells [273,274]. In turn, augmented permeability leads to further inflammation and secondary damage to the BBB, with the entry of plasma proteins and neurotoxic substances [275].

The most prevalent form of dementia, AD, is marked by a steady decline in cognitive function and neurodegeneration. The vascular hypothesis suggests that cerebral microvascular alterations are central to the pathogenesis of AD, providing a link with CV disease [276]. Possible mechanisms include neurovascular coupling imbalances and BBB disruption [276]. Impaired removal of beta-amyloid may be a consequence of these neurovascular changes: vascular changes may precede the development of tau pathology [277]. A two-hit hypothesis has been developed in which classical risk factors leading to the development of microvascular dysfunction facilitate AD-specific pathology. This is linked with the development of a vicious cycle between microvascular damage and beta-amyloid aggregates that contribute to AD development. Brain imaging supports these observations, as well as chronic cerebral hypoperfusion, microvascular dysfunction, and perivascular space enlargement – hallmarks of small vessel disease – precede cognitive decline and changes in conventional biomarkers [276]. These mechanisms of small vessel disease are shared between vascular dementia and AD: assessment of retinal microvasculature has shown apparent microvascular dysfunction and remodelling in neurodegenerative diseases [278,279].

Statement: In neurodegenerative disease, MD favours the increased BBB dysfunction and leakage paired with higher NF-κB activation and consequent microvascular levels of IL-1β, IL-6, TNF-α, which promotes the onset of a vicious cycle leading to progressive cognitive impairment and increased predisposition to tau pathology.

Autoimmune rheumatic diseases

Autoimmune rheumatic diseases (ARD) are distinct heterogeneous disorders with common immune responses against self-antigens arising from genetic predisposition, dysregulation of the immune system and environmental factors. Among them, chronic inflammatory rheumatic conditions, mainly represented by rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and spondyloarthritis (ankylosing spondylitis (AS) and psoriatic arthritis (PA)) are those further characterized by increased and premature CV morbidity and mortality [280]. Atheromatosis is a chronic inflammatory process in which the immune system, blood and vascular cells, and several hormonal systems are primarily involved in the structural and functional damage of the small vessels [281]. Microangiopathy has been used as an important subclinical CV risk indicator, and ARD patients [282,283] have an increased prevalence of CV diseases which cannot be fully explained by the classical CV risk factors [284].

In ARD, a combination of elements is able to contribute specifically to MD and microvascular inflammation: genetic predisposition due to the polymorphism in *MTHFR*, *TNF*, *IL6* loci and the *HLA-DRB1* status [285]; activation of IL-1β, IL-6, IL-17 and TNF-α pathways [285]; enhanced ECs activation with the expression of ICAM-1, VCAM-1, E-selectin [286]; the increase in NAPDH-derived ROS production, leading to eNOS uncoupling and formation of 3-nitrotyrosine.

RA is the most prevalent autoimmune inflammatory rheumatic disease [287], characterized by a 50% excess in CV mortality compared to the general population [288]. RA has been associated with diffuse microvascular injury (Fig. 3g) [24] documented by decreased myocardial perfusion (Figure 3, Supplemental Digital Content, http://links.lww.com/HJH/C223) [289], altered retinal arteriolar diameters [290,291], and dermal capillary density assessed with nailfold capillaroscopy [292], as well as impaired coronary microcirculation evaluated by coronary flow reserve (CFR) [293] and impaired endothelial glycocalyx integrity [294] even in the absence of overt CV disease. This is paired with an attenuated microvascular response to different stimuli, assessed with venous occlusion plethysmography [295,296], and an increased hyperaemic vasodilatory response [297] in RA patients compared to healthy controls. Pronounced impairment of microcirculatory blood flow responses assessed by laser speckle contrast imaging (LSCI) and decreased coronary microvascular perfusion has also been found in RA individuals free from CV disease [298] (Figure 4, Supplemental Digital Content, http://links.lww.com/HJH/C223).

In SLE, prevalent in about 0.1% of the general population, apart from the widespread inflammation and tissue damage in the affected organs, the blood vessels, especially the brain and kidneys, could also be severely impaired. Since vascular involvement, presenting as noninflammatory necrotic vasculopathy, thrombotic microangiopathy, and lupus vasculitis, is considered the leading cause of death in patients with SLE, interest has been focused on identifying the presence and role of early, subclinical microcirculation alterations, potentially anticipated before the establishment of CV events [25]. In addition to the classical subclinical structural changes (cortical atrophy and white matter hyperintensities), identified mostly by conventional MRI in patients with SLE regardless of the presence of neuropsychiatric manifestations, functional changes such as a blunted increase in cerebral oxygenation during exercise assessed with near infra-red spectroscopy [299] and hypoperfusion lesions with single-photon emission tomography (SPECT) in comparison to controls [300] are present. They often precede the permanent changes identified by conventional imaging [301] and are also found in sites

different from the classical one targeted by lupus vasculopathy (e.g., SLE nephritis): the fundus [26,302,303], the skin, with capillaroscopic alterations concerning density, dimensions, morphology and haemorrhages, and the myocardium, presenting coronary microvascular dysfunction [304–306]. Functional microcirculation studies with digital PAT [307,308], Portable Oxygen Transmitter [309] and LSCI [310,311] document reduced peripheral perfusion and impaired microvascular reactivity in SLE patients (Figure 4, Supplemental Digital Content, http://links.lww.com/HJH/C223).

Subclinical microvascular alterations in psoriatic disease, inflammatory bowel disease, vasculitis and AS have also been studied [312–314]. Psoriatic patients and patients with inflammatory bowel disease present coronary microcirculatory dysfunction, as assessed by CFR, reduced endothelial glycocalyx thickness and microvascular perfusion impairment leading to impaired cardiac function (Figure 4, Supplemental Digital Content, http://links.lww.com/HJH/C223) [27,28,315–318].

Remarkably, biological anti-inflammatory therapies and statins in autoimmune diseases improve endothelial glycocalyx and function, as well as coronary and peripheral microcirculation and thus, have beneficial effects on CV function [28,317,319,320], providing indirect evidence of the beneficial impact of targeting microvascular inflammation. Nonetheless, the precise role of MD and microvascular inflammation, in terms of risk prediction and therapeutic target, needs to be addressed appropriately by rigorous prospective studies.

Statement: ARD are a heterogeneous group of diseases characterised by MD and microvascular inflammation, driven by the combination of genetic predisposition and innate immunity hyperactivation via IL-1β, IL-6, IL-17 and TNF-α pathways. The beneficial effects of anti-inflammatory drugs in terms of CV risk reduction provide indirect evidence of the centrality of microvascular inflammation in ARD.

Oncologic disease

As previously mentioned, systemic and local inflammation have a major role in the development and maintenance of microvascular structural alterations [9]. Oncologic diseases may cause or be associated with systemic inflammation, possibly contributing to the development of hypertension and CV diseases, thus reducing overall survival in these patients [321]. However, due to many clinical reasons, including relatively short follow-up periods, few data are available about microvascular alterations in cancer patients *per se*.

Cancer primarily shares with CV disease several pathophysiological mechanisms and similar risk factors. In this respect, chronic inflammation is a crucial feature in the pathogenesis and progression of both CV disease and cancer. It may be directly involved in the induction of some cancer types (e.g. H-pylori and stomach cancer) or indirectly promote local carcinogenesis and its progression by releasing inflammatory mediators and recruiting immune cells within the tumour microenvironment [29]. Other mechanisms such as oxidative stress, cytokines, hormones (e.g. leptin), growth and metabolic factors have also been proposed to connect both diseases. However, a clear pathogenetic understanding is still lacking: although T cells appear to be involved, which specific subtype and by which mechanism they induce MD requires further investigation. [29]. The concomitant presence of CV risk factors or conditions such as physical inactivity, smoking, obesity, and diabetes may further induce inflammation worsening the prognosis of cancer and cancer survivor patients [30]. Cancer cells secrete VEGF to stimulate tumour vascularization, which increases vascular permeability and may contribute to microcirculation structural remodelling and perivascular fibrosis [31,32].

Particularly relevant is that several cancer treatments present CV toxicity and may cause MD, microvascular inflammation, hypertension and thus, an increase in CV events [321,322]. While anthracyclines have been mostly related to specific cardiotoxicity [323], VEGF and other tyrosine kinase inhibitors are the most frequently associated anticancer drugs with a dose-dependent increase in blood pressure both in hypertensive patients and in normotensive subjects [322,324,325]. These drugs enormously improve the prognosis for several solid tumours [326], targeting specific pro-angiogenic VEGF signalling involved in the neovascularization of tumours in vivo [327]. A consequent increase in blood pressure has been suggested as a pharmacodynamic biomarker and predictor of therapeutic efficacy [328,329]. However, this was not confirmed by other studies [330], and, what is more, poorly controlled hypertension leads to an increase in CV events, causing the discontinuation of anticancer therapy and thus hindering its clinical benefit.

The mechanism underlying vascular toxicity and hypertension induced by VEGF inhibitors is still debated. VEGF-A, the most important isoform of VEGF, may promote the proliferation, differentiation, and migration of endothelial cells by interacting with the VEGF-A receptor, as well as NO production [331]. Accordingly, VEGF inhibition is associated with reduced NO bioavailability because of the inhibition of eNOS and concomitant increase in vascular ROS [324,332], resulting in MD [31]. Activation of the ET-1 system with increased concentrations of ET-1, nephrotoxicity and impaired natriuresis induces hypertension along with the inhibition of other growth factors, including platelet-derived or fibroblast growth factor, c-Kit and FMS-like tyrosine kinase 3 [333]. Recently, a novel molecular mechanism involving the interplay between endothelial microparticles, the endothelin system and endothelial cell pro-inflammatory and redox signalling have been described; such interactions could be important in CV toxicity and hypertension associated with VEGF inhibitors [334]. All these events would favour an increase in peripheral resistance, further increasing MD.

Another consequence of antiangiogenic drugs leading to vascular resistance increase and elevated blood pressure is microvascular rarefaction. A reduction of capillary density during antiangiogenic treatment, reversible with cancer drug discontinuation [335], was observed in some [336–339] but not in other studies [340]. In one of these studies [338], the effect of antiangiogenic drugs on the structure of

retinal arterioles and capillary density was investigated in 20 patients with cancer. No change in systolic or diastolic blood pressure values during treatment was observed [338]; however, during the study, antihypertensive treatment was optimized in most patients. Although no difference was observed in the retinal arteriole wall-to-lumen ratio [19], capillary density was reduced by antiangiogenic drugs after three or six months (Fig. 3f) [338]. These findings might imply that an up-titration antihypertensive treatment is necessary for patients treated with tyrosine kinase inhibitors or a VEGF inhibitor. Indeed, under adequate blood pressure control, microvasculature seems preserved [338]. Since the efficacy of these drugs could be related to the extent of the antiangiogenic effect, the noninvasive evaluation of capillary density should be evaluated by further studies as a predictive parameter of drug efficacy. The better identification of the mechanisms underlying adverse cardiac and vascular effects of anticancer therapies may allow to develop novel vasculoprotective strategies. Only by doing so will patients achieve optimal cancer treatment at the minimum cost to cardiac and vascular health [323].

Statement: In oncological disease, the pan-activation of inflammatory response concurs to induce MD and microvascular inflammation. Even more relevant is that anticancer drugs, particularly anti-VEGF, might cause detrimental derangement in microvascular function and inflammation, thus attenuating their medium/long-term beneficial effects in terms of survival. An adequate increase in treatment to achieve a stronger control of age-related disease (in particular, hypertension) is thus required.

CONCLUSIONS

Ageing and age-related diseases are all characterised by different degrees of MD, leading to high-CV morbidity and mortality. As microvascular inflammation is both the consequence of environmental stressors and the perpetrator of age-related damage, its centrality in CV risk is apparent. However, though damage pathways have been extensively studied over the last decades, a clear understanding of their involvement's temporal and spatial sequence across the age-related disease spectrum is missing. In particular, although the interaction between immune and nonimmune cells is receiving increasing attention, a precise definition of their cross-talk in the context of MD is lacking. Preventing their detrimental dialogue may be crucial to stopping the disease at a very early stage. This gap of knowledge substantially limits the translation in terms of clinical strategies. Targeting microvascular inflammation is still a difficult road to travel: as the microvascular damage leverage epigenetic remodelling [52], early or intensive treatment is required to revert it. However, even as some interventions have demonstrated a potential benefit in terms of rescuing MD (e.g., physical activity, weight loss [166,167], SGLT-2i [200]) and inflammation [104], translational studies addressing microvascular inflammation to identify either early common or disease-specific targets are required. At the same time, we need to clearly understand the strengths and limitations of each technique used to assess MD, as well as the ability to distinguish between microvascular and macrovascular. Efforts towards standardisation are needed to obtain interpretable results from studies.

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Conflicts of interest

The authors have no relevant conflict of interest to disclose.

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