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Author(s): Paolo Camici, San Raffaele Hospital
Francesco Moroni, Università Vita-Salute San Raffaele
Enrico Ammirati, Niguarda Ca' Granda Hospital
Atticus Hainsworth, St Georges University of London

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Francesco Moroni[1], Enrico Ammirati[2], Atticus H Hainsworth[3], Paolo G Camici[1]

1. Cardiothoracic and Vascular Department, Vita-Salute University and San Raffaele Hospital, Milan, Italy
2. De Gasperis Cardio Center, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
3. Molecular and Clinical Sciences Research Institute, St George's, University of London, Cranmer Terrace, London, UK, SW17 0RE; Department of Neurology, St George's University Hospitals NHS Foundation Trust, Blackshaw Road, London, UK, SW17 0QT.

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Running title: WMH and cardiovascular disease

Address for correspondence: Professor Paolo G Camici, Cardiothoracic and Vascular Department, Vita-Salute San Raffaele University and San Raffaele Hospital, Via Olgettina 60, 20132, Milan, Italy.
E-mail: camici.paolo@hsr.it
Telephone: 0226436206

Abstract (230 words)

Cardiac and cerebrovascular diseases are currently the leading causes of mortality and disability worldwide. Both the heart and brain display similar vascular anatomy, with large conduit arteries running on the surface of the organ providing tissue perfusion through an intricate network of penetrating small vessels. Both organs rely on fine tuning of local blood flow to match metabolic demand. Blood flow regulation requires adequate functioning of the microcirculation in both organs, with loss of microvascular function, termed small vessel disease (SVD). SVD in the heart, known as coronary microvascular dysfunction (CMD), can cause chronic or acute myocardial ischemia and may lead to development of heart failure. In the brain, cerebral SVD (cSVD) can cause an acute stroke syndrome known as lacunar stroke, or more subtle pathological alterations of the brain parenchyma which may eventually lead to neurological deficits or cognitive decline in the long term. Coronary microcirculation cannot be visualized *in vivo* in humans and functional information can be deduced by measuring the coronary flow reserve (CFR). The diagnosis of cSVD is largely based on brain magnetic resonance imaging, with white matter hyperintensities, microbleeds and brain atrophy reflecting key structural changes. There is evidence that such structural changes reflect underlying cSVD. Here we review interactions between SVD and cardiovascular risk factors and we discuss the evidence linking cSVD with large vessel atheroma, atrial fibrillation, heart failure and heart valve disease.

1

Introduction

Cardiovascular and neurological diseases are currently the leading causes of mortality and disability worldwide(1,2), and notably affect more commonly the ageing population. Combined, cardiovascular and neurological disease make up over 350 million Disability-Adjusted Life Years, i.e. years lived in good health lost globally, per annum, and cause half of death due to non-communicable diseases around the world(2). A large proportion of death and disability attributable to these entities appears to be preventable(2). A thorough understanding of the pathophysiological bases, risk factors and eventually relation between cardiac and cerebral conditions is therefore of the outmost importance to reduce their yearly toll. Indeed, in spite of the different pathology and clinical manifestations, heart and brain disease appear to share, at least in part, some common pathophysiological features, mainly related to vascular function in both organ systems(3). The heart and brain display similarities in vascular anatomy, with large conduit arteries running on the surface of the organ providing tissue perfusion through an intricate network of penetrating small vessels. The public health burden of ischemic heart disease and cerebrovascular disease attributable to large artery pathology is well characterized(4). By contrast, the contribution of small vessel disease (SVD) is less well defined. SVD in the heart, known as coronary microvascular dysfunction (CMD), can cause chronic or acute myocardial ischemia and lead to development of heart failure(5,6). In the brain, SVD can cause an acute stroke syndrome known as lacunar stroke, or more subtle pathological alterations of the brain parenchyma including white matter hyperintensities, microbleeds and brain atrophy which may eventually lead to neurological deficits or cognitive decline in the long term(3,7). There is evidence that such structural changes reflect underlying cerebral SVD (cSVD). Among these subclinical cerebral alterations, white matter hyperintensities (WMH) are gaining increased attention due to their high prevalence in the general population and their prognostic implication(8). WMH appear as areas of signal hyperintensity in the deep or periventricular white matter, evident on brain magnetic resonance imaging (MRI) T2-weighted or Fluid-Attenuated Inversion Recovery images(9). WMH are broadly equivalent to leukoaraiosis within white matter, reported on CT scans(10). WMH appear to have a vascular origin and are associated with definite alterations in cerebral small vessels, and in some reports with blood-brain barrier abnormalities or with local inflammation(8). WMH are frequently reported in individuals at high cardiovascular risk(8). Indeed, also CMD is more commonly encountered in individuals with a high burden of cardiovascular risk factors, and recently was shown to have a strong inflammatory pathophysiology(11). The Aim of the present review is to discuss the evidence linking WMH and cSVD and their potential connection with cardiovascular disease and CMD.

Coronary and cerebral microcirculation

The coronary arterial system comprises three compartments, each with a different function, whose anatomic borders cannot be clearly delineated *in vivo* (Figure 1 Panel A). The large epicardial coronary

arteries have a diameter between 5 mm and 500 µm and act as conductance vessels, accumulating blood during systole and contributing through elastic recoil to myocardial perfusion in diastole. These arteries run on the surface of the heart before branching into the myocardium giving rise to intramural vessels(12). Pre-arterioles (diameter 100-500 µm) compose the intermediate compartment. Their main role is to maintain pressure at the origin of downstream arterioles within a narrow range, in response to changes in perfusion pressure or blood flow(11). Arterioles (10-100µm) are the third compartment, forming part of the microcirculation with capillaries and venules. Arterioles are the main site of myocardial blood flow regulation. They are responsible for matching myocardial oxygen demand to supply, by regulating their tone in response to signals produced by the surrounding cardiac myocytes(11,13). Coronary microcirculation cannot be visualized *in vivo* in humans. Functional information on the coronary microcirculation can be deduced by measuring the coronary flow reserve (CFR). This is defined as maximal myocardial blood flow (obtained during pharmacologically induced coronary vasodilation) divided by baseline myocardial blood flow. CFR reflects flow changes due to both the epicardial and microvascular compartments. In the absence of obstructive coronary artery disease, CFR is a marker of CMD. There is evidence that in the absence of obstructive coronary artery disease impairment of CFR is indicative of CMD(11).

CMD can result from structural or functional alterations of the coronary microvasculature resulting in altered myocardial perfusion which manifests clinically as anginal pain and dyspnea(5). Specifically, adverse remodeling of intramural arterioles, with medial wall thickening due to increased collagen deposition and smooth muscle hypertrophy as well as some degree of intimal thickening, has been documented in patients with reduced CFR(12). Functional abnormalities leading to CMD include impaired dilatation or excessive coronary microvascular constriction, which may be due to abnormalities in endothelium-dependent as well as to endothelium-independent mechanisms(11). Aside from the obvious impact of symptoms on quality of life, CMD carries an increased risk of adverse events, including nonfatal myocardial infarction, nonfatal stroke and hospitalization for heart failure, or death(14).

The cerebral circulation can be subdivided similarly into three different anatomical and functional compartments (Figure 1 Panel B). 1) cerebral arteries entering the neurocranium, acting as conductance vessels; 2) the pial circulation, which lies within the leptomeninges, and, the resistance vessels; 3) smaller penetrating arteries, arterioles and capillaries which compose the cerebral microcirculation(15). Just as for the heart, the brain lacks substantial energy reserves and therefore relies upon adequate minute-by-minute perfusion to meet its metabolic requirements. The regulation of microcirculatory resistance therefore is a key in maintaining an adequate local blood flow in the brain. On the one hand, cerebral circulation is characterized by autoregulation, the ability to maintain a broadly stable blood flow over a wide range of perfusion pressures(16). On the one hand, cerebral blood flow can selectively increase in areas of increased neuron activity through direct and metabolic regulation, a process known as “neurovascular coupling”(17).

Unique to cerebral microcirculation is the presence of the blood-brain barrier (BBB), which is the functional element constituted by endothelial cells, pericytes and astrocytes connected by tight junctions, with additional contribution of endothelial transporters(18). The BBB acts as a key regulator of trafficking of metabolites and waste products between blood and brain extracellular fluid(18). Similar to microvessels in the heart, the cerebral microcirculation cannot be imaged in human *in vivo*. Therefore, brain parenchyma lesions caused by SVD have been adopted as the marker for microvessel alteration(19).

Cerebral SVD has been associated to a variety of brain parenchyma structural alterations, including WMH, micro- hemorrhages, disruption of myelin, lacunae, dilated perivascular spaces, reduced glial and neuronal density(19). Pathological analysis of the small arteries associated with these alterations has showed loss of smooth muscle cells from the tunica media, with thickening of the vessel wall due fibro-hyalinosis, similar to what is encountered in CMD(19,20). Microatheroma has been reported in earlier pathological reports though now is not common. There is little evidence for small vessel thrombosis. In analogy to reduced CFR in CMD, reduction of cerebrovascular reactivity, i.e. the ratio of maximal blood flow after a maximal vasodilation to basal cerebral blood flow, has been described, using various techniques, in cerebral SVD(21).

Figure 2 (panel A and B) shows two non-diseased arterioles of the coronary (panel A) and cerebral (panel B) circulation.

White matter hyperintensities prevalence, pathophysiology and clinical relevance

WMH are amongst the most prominent and commonly encountered features in cerebral MRI. As described above, they appear as areas of signal hyperintensity scattered in the deep or periventricular white T2-weighted or FLAIR images(22). WMH can be found in MRI scans of asymptomatic individuals, and their prevalence increases with age. Indeed, while 11-21% of otherwise healthy subjects with a mean age of 64 have WMH, these alterations are encountered in approximately 64-94% of otherwise healthy octogenarians(23,24). Their prevalence, is even higher in subjects with a history of cardiovascular risk factors, established cardiovascular disease or renal impairment(8,25). Compared to the frequency of WMH on imaging studies, surprisingly few pathological studies are available to date(26). Furthermore, the reliability of these studies is hampered by difficulties of matching MRI images with anatomical counterpart in post mortem evaluation and tissue-processing artifacts(26). Therefore, the neuropathological substrate of WMH is not yet defined. Earlier reports proposed demyelination and axonal loss as cardinal features of WMH(27). Diffuse vacuolation, with glial rarefaction was also described to be present in WMH(28). reduction of myelin content in WMH, therefore causing white matter “pallor”, has been described(29,30). Whether the observed pallor is due to loss of myelin sheath or to myelin content reduction secondary to neuronal loss, is still a matter of debate(31). Other studies focused on the presence of blood-brain barrier (BBB) dysfunction, causing plasma protein leakage and chronic edema, a key feature of WMH(32).

However, these findings are not universally supported by neuropathological studies, and some evidence exists that BBB alterations may in fact be an independent phenomenon with respect to WMH(33). Reduced blood vessel density alongside increased arteriolar wall thickening and tortuosity have been described in WMH(34). In addition to these changes on the arterial side, venular fibrosis and stenosis have been demonstrated(35). An ischemic pathogenesis of WMH has been supported by immuno-histochemistry and gene expression profiling, which suggest a role of hypo-perfusion in the genesis of these changes(36). It is probable that reduced cerebral perfusion can cause BBB leakage and fluid extravasation that, in turn, can contribute to altered local tissue perfusion(37). Therefore, the two putative pathogenic elements are likely to be inter-dependent. A report on 3248 participants in the Framingham Heart Study, whole blood gene expression profile demonstrated a more prominent expression of inflammation-related genes in subjects with WMH, pointing at inflammation as a potential pathogenic element(38).

Prognostic relevance of WMH

WMH have been associated to an overall decline of superior functions, as well as with an increased risk of stroke, dementia and death(39). A high burden of WMH has been associated with gait disturbance and the risk of falls(40,41), as well as urinary symptoms(42), which contribute to increased overall disability and dependency. WMH have been shown to confer a higher risk of incident stroke (hazard ratio 3.1, 95% confidence interval 2.3-4.1) in a metanalysis comprising more than 12.500 individuals(39). The burden of WMH was also shown to be associated with stroke outcomes including all-cause mortality, functional and cognitive outcomes as well as recurrent stroke(43). WMH have been associated with a 2.15 times greater risk of developing depression in late life(44). Brain parenchymal alterations are specifically encountered in elderly subjects with low mood and in individuals with reduced interests and motivation(45). The connection between WMH and cognitive decline and dementia has been well established: a large meta-analysis, including over 7500 subjects, was able to detect a 3-fold risk of incident dementia in subjects free of cognitive impairment at baseline, but with evidence of WMH on MRI(39). Other prospective studies have shown that the risk of both dementia and mild cognitive impairment is increased in the presence of WMH(46). WMH lower the onset of overt dementia in a variety of neurodegenerative diseases(47). coexistence of neurodegenerative forms of dementia, in particular Alzheimer's Disease (AD), with cerebrovascular disease and vascular forms of cognitive impairment is well described(48). recent work has shown that younger individuals carrying an AD-causing autosomal dominant mutation exhibit WMH, and these are evident well before onset of AD symptoms(49).

Cardiovascular diseases, WMH and CMD

An ever-growing amount of data is building inking cardiovascular disease with dysfunction in the microvasculature of both the heart and the brain. The following sections discuss currently available data on the complex association between cardiovascular diseases, WMH and CMD, while Figure 3 provides a model

for their relationship and Tables 1 and 2 provide a summary of the most relevant studies.

Cardiovascular risk factors and SVD

Cardiovascular risk factors are well known to negatively impact on vascular function throughout the body. Their contribution to overall cardiovascular disease is high, and strategies aimed at the reduction of cardiovascular risk factor burden are effective in reducing cardiovascular morbidity and mortality.(50) Not surprisingly, microvascular dysfunction in the coronary and cerebral circulation are sensitive to cardiovascular risk factors, itemised below.

Hypertension

Hypertension is the risk factor which has been shown to have the strongest association with WMH. In an early report by Wisemann et al. on approximately 150 subjects, hypertension was associated with a higher overall burden of periventricular and subcortical WMH(51). In 1352 subjects free of dementia included in the Framingham Offspring Study, the presence of arterial hypertension in midlife, was associated with accelerated WMH progression on follow up(52). In another, larger cohort from the same study, (n=1814), hypertension and increased left ventricular mass, a marker for hypertension-related damage in the cardiovascular system, were associated with WMH burden(53).

Just as signs of cerebral SVD are more frequently encountered in hypertensive subjects, individuals with high blood pressure were shown to have impaired CFR. In their seminal study, Gimelli and colleagues elegantly showed that untreated hypertensive individuals have significantly reduced maximal coronary blood flow and CFR when compared with normotensive subjects(54). Subsequent work showed that the reduction of CFR is due to a transmural impairment of maximal blood flow and is directly proportional to systolic blood pressure values(55). Further, CMD due to adverse structural remodeling of intramyocardial arterioles contributed to the observed impairment of CFR(11). Initiation of anti-hypertensive treatment improved CFR in these subjects(56). Figure 2 (panel C and D) shows arteriolar remodeling of the coronary (panel C) and cerebral (panel D) arterioles in patients with arterial hypertension.

Hypercholesterolemia

The role of blood cholesterol on the development of WMH is less well defined when compared to hypertension. In a large cohort comprising 1135 subjects with a history of ischemic stroke, Jimenez-Conde and colleagues showed an association between hyperlipidemia, defined as hypercholesterolemia, hypertriglyceridemia or current lipid-lowering treatment, and lower levels of WMH(57). By contrast, in a Chinese cohort of 4683 hospitalized subjects plasma low density lipoprotein (LDL) cholesterol was associated with an increased burden of WMH(58). This is consistent with the recent finding that subjects affected by familial hypercholesterolemia have an increased burden of WMH when compared to healthy controls(59). A recent trial on 732 hypertensive individuals has shown a significant reduction in WMH progression in subjects assigned to treatment with Rosuvastatin(60). The effect of Rosuvastatin was

178 additive with that of blood pressure lowering medications(60).

179 In their seminal paper, Yokoyama and colleagues first reported reduced CFR in hypercholesterolemic
180 individuals with normal epicardial coronary arteries(61). Subsequent evidence showed that plasma LDL
181 cholesterol concentration was indeed the subfraction more strongly associated with reduced CFR, an effect
182 which was shown to be, at least partially, reversed by lipid-lowering medications, suggesting a causal
183 relationship(62,63).

184 *Insulin Resistance and Diabetes*

185 There appears to be a relation between WMH and altered insulin sensitivity, though this is incompletely
186 characterized. A large study of 1232 subjects with manifest arterial disease has shown that individuals
187 (n=451) with evidence of metabolic syndrome did not have increased burden of WMH, despite being at
188 higher risk for cognitive impairment when compared to healthy controls(64). At variance, a significant
189 association between hyperglycemia or diabetes and WMH burden was found in a larger cohort consisting of
190 1597 young adults (mean age 40 years)(65). On the other hand, insulin resistance did not predict WMH
191 progression at 10 years of follow up in a cohort of 932 individuals from the Atherosclerosis Risk in
192 Community (ARIC) study(66). Similarly, glycemic control was not significantly associated with WMH in type
193 2 diabetic patients enrolled in the Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes
194 (ACCORD MIND) trial at 40 months of follow up(67).

195 Hyperglycemia impairs endothelial function, even in healthy individuals(68). Indeed, diabetes mellitus and
196 hyperglycemia have been consistently associated with reduced CFR, measured with various techniques and
197 with the use of different vasodilators(69,70). the few available data on glucose-lowering drugs have been
198 inconsistent in reporting an improvement in CFR(71,72).

199 Cigarette *Smoking*

200 Smoking was associated with accelerated WMH progression on long term follow up in the Framingham
201 Offspring Study(52). In a subsequent report on 972 subjects from the ARIC Study, the risk of WMH
202 progression was proportional to the lifetime exposure to cigarette smoking, measured in pack-years(73).
203 Smoking was shown to substantially contribute to altered coronary microvascular function, with
204 detrimental effects on CFR detectable after the first few cigarettes(74,75). As shown by Kaufmann and
205 colleagues, high doses of antioxidants rapidly reversed coronary blood flow impairment in smokers,
206 suggesting increased oxidative stress as the cause of smoking-induced microvascular dysfunction(74).

207 **Carotid Atherosclerosis and SVD**

208 Carotid atherosclerosis is common in the general population, with an estimated prevalence reaching up to
209 40% in otherwise healthy middle-age adults in some series(76). In addition to being a known etiologic factor
210 for around 20% of ischemic strokes(77), carotid atherosclerosis is associated with cSVD and with WMH and
211 it has been hypothesized that carotid plaques may be a source of microemboli(78). A meta-analysis of cross

sectional studies comprising 5306 subjects showed a significant association between the presence of carotid artery plaques and WMH(79). The potential atheroembolic etiology of WMH has been suggested by small studies showing an association between the presence of WMH and an ipsilateral vulnerable carotid artery plaque(80). However, vascular risk factors may be the confounding variables underlying the observed associations(8). In a recent publication by our group, carotid plaque features were not associated to WMH progression in asymptomatic subjects at intermediate-high cardiovascular risk with non-critical carotid stenosis at 20 month follow up(81). The relationship between CMD and carotid atherosclerosis has been less investigated. Indeed reports of reduced CFR in individuals with different stages of carotid atherosclerosis exist in the literature(82,83). Considering that, in the case of CMD, no direct pathogenic role for carotid plaque may be hypothesized, it is likely that cardiovascular risk factors mediate the link between carotid atherosclerosis and reduced CFR. Figure 4 shows FLAIR images on MRI scans for the identification of WMH of two subjects at baseline and at 20 months.

Atrial fibrillation and SVD

Atrial fibrillation (AFib) is the most common disorder of the heart rhythm(84). It contributes to a substantial proportion of ischemic strokes in the general population, and has been associated with the development of cognitive impairment(85,86). A growing body of evidence is building linking AFib and WMH. Kobayashi et al first reported increased WMH in AFib patients when compared to age and sex matched controls in a cohort of 142 subjects(87). Gaita and colleagues reported an increased risk of WMH in subjects with AFib when compared to controls (odds ratio 11, 95% confidence interval 6 to 21)(88). Patients with paroxysmal AFib had less WMH when compared to those with persistent AFib(88). This is consistent with the higher risk of thromboembolic events observed in persistent versus paroxysmal AFib, and supports the hypothesis that part of the observed WMH could be related to subclinical embolism(89). However, in another observational study on 234 stroke patients, an increased burden of WMH was found in AFib subjects specifically localised in the anterior subcortical white matter(90). Due to the specificity of the WMH pattern and the lack of relation with embolic distribution, Mayasi and colleagues put forward the hypothesis that the link between AFib and WMH may extend beyond thromboembolism, and in fact may be due to a more global cardio-vasculopathy(90).

Few data currently exist on CMD and AFib. Currently available reports have consistently shown a reduction in maximal coronary blood flow with increased microvascular resistance, both parameters being markers of CMD(91,92). These alterations persisted after conversion to sinus rhythm, and therefore appeared not to be strictly arrhythmia-related, but possibly the expression of underlying endothelial dysfunction(91).

Heart failure and SVD

Heart failure (HF) has been consistently associated with cognitive impairment and dementia, possibly due to the high comorbidity burden that is generally encountered in HF patients, and possibly to impaired cerebral perfusion resulting from a failing heart(8).

In an early report by Vogels and colleagues, HF patients had a higher burden of WMH when compared to individuals with established cardiovascular disease(93). Left ventricular ejection fraction was shown to be an independent predictor of WMH burden in HF subjects(93). A subsequent report on 69 HF patients confirmed the association between reduced cerebral perfusion and WMH burden(94).

As extensively reviewed elsewhere(6), CMD is an hallmark of HF, both HF with preserved and with reduced ejection fraction. Indeed, the synergistic effect of multiple cardiovascular risk factors and the low-grade inflammatory milieu often found in subjects with cardiac conditions, was shown to impair the function of coronary microcirculation. Ischemia secondary to CMD is a major contributor to structural and functional myocardial impairment in HF with preserved ejection fraction, but also to contribute to myocardial dysfunction in HF with reduced ejection fraction(11,95).

Heart valve disease and SVD

Substantial evidence on the association between heart valve disease an SVD is lacking. In 232 subjects with significant chronic valve disease, Lee and colleagues report an association between WMH burden and right atrial pressure(96). Therefore, they postulate a reduced perfusion pressure and increased capillary hydrostatic pressure, secondary to increased venular pressure in the context of high right atrial pressure, as a potential mechanism for WMH genesis in heart valve disease(96). As for what concerns CMD, severe calcification causing aortic stenosis has been associated with reduced CFR(11). A possible reason for that could be the increased left ventricular wall tension in the setting of increased afterload, with both reduced coronary perfusion pressure and increased microvascular resistance due to extrinsic compression of the microvasculature(6,11).

Congenital heart disease and SVD

Congenital heart disease may be associated with major cardiac dysfunction and potentially with impaired systemic blood oxygenation. Patients with Eisenmenger syndrome were shown to have increase WMH, possibly again attributable to impaired cerebral oxygenation(97).

Interestingly, to date no study has investigated CMD selectively in congenital heart disease. However, evidence exists that the stressors of hypoxia and cardiopulmonary bypass do alter endothelia and microvascular function systemically(98).

Treating microvascular dysfunction

There is relatively little high-quality data from randomized controlled trials on the treatment of microvascular dysfunction and on the prevention of further accumulation of WMH. Based on the observations reported above, approaches aimed at reducing the overall burden of cardiovascular risk factors could be advocated. Adopting a healthy lifestyle incorporating a diet rich in fruits and wholegrains, limiting high salt foods, sugary drinks and alcohol consumption, avoiding cigarettes smoking and incorporating daily exercise has proven efficacy on reducing blood pressure and cholesterol concentrations, as well as for improving glycemic control(50). While no formal data exist on the effectiveness of this

approach in preventing SVD, the observation that overall cardiovascular risk factors burden in early adulthood is associated to WMH development justifies advocating a lifestyle that limits risk factors exposure(99). Angiotensin Converting Enzyme inhibitors (ACE-i) and statins were shown to improve endothelial function and to significantly improve microvascular function in CMD(100). While less evidence is available for cSVD, modulation of the renin-angiotensin-aldosterone axis and statin use has proven efficacy in limiting WMH progression(60). Antiplatelet medications may be indicated in particular if large-vessels atherosclerosis is detected. Indeed, inhibition of thromboxane A_2 pathway by low-dose aspirin has shown to reduce microvascular constriction and local thrombosis(100). The use of phosphodiesterase type 3 inhibitor cilostazol, an antiplatelet medication with vasodilating properties, was shown to improve CFR(100). Preliminary data on animal models suggest that cilostazol may improve cerebral microvascular and BBB(101). Other approaches have been proposed, targeting hyperglycemia, inducing vasodilation or modulating inflammation, but so far they remain experimental(100).

Future perspectives

The complex interplay between cardiovascular and nervous systems is gaining increasing attention, and the central role of the microcirculation is currently an area of active investigation. Several studies are underway to define strategies to abate SVD burden. These include lifestyle modification including aerobic exercise to prevent WMH and improve cognitive function across different age categories (see ClinicalTrials.gov NCT02729428). Pharmacological approaches with the use of cilostazol to improve blood vessel health are being tested in randomized controlled trials (see ClinicalTrials.org NCT01932203). in both CMD and cSVD, vasodilator drugs are being tested, including PDE3 and PDE5 inhibitors and ETA antagonists (ClinicalTrials.org NCT03855332, NCT04097314 and NCT02450253). Furthermore, studies are being carried out to directly evaluate the relationship between coronary and cerebral microcirculation (see ClinicalTrials.go NCT04131075).

Conclusions

The heart and the brain both rely on fine tuning of blood flow to match rapid changes in metabolic demand. Blood flow regulation requires adequate functioning of the microcirculation in both organs, with loss of adequate small vessel function leading to clinical manifestations including chest pain, dyspnea, heart failure, lacunar ischemia, WMH, cognitive impairment and dementia. Small vessel disease in the heart and in the brain appear to share some common pathophysiological aspects, as can be inferred from the presence of common risk factors and common morphological features of the diseased vessels. Further studies are needed to elucidate the relation between cerebral and cardiac microvessels and to evaluate effective therapeutic strategies for small vessel disease.

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Figure Legends

Figure 1. Structural and spatial organization of cardiac and cerebral circulations

Panel A. Resin cast of the coronary circulation, showing large epicardial conductance arteries branching down to penetrating small vessels (reproduced with permission from Camici PG, and Rimoldi OE J Nucl Med 2009;50:1076-1087)

Panel 2. Resin cast of the cerebral circulation Large, superficial cerebral arteries give origin to pial and penetrating vessel, providing blood flow to brain parenchyma (reproduced with permission from Zlovovich BV et al, Neurosurgey 1998;43:877-878).

Figure 2. Small arteries of the heart and brain

Panel A. Small artery, healthy human myocardium. Male aged 27 y. Hematoxylin and eosin stained section, kindly provided by Mary Sheppard & Joe Westaby, St George's Cardiac Pathology group.

Panel B. Small artery, healthy human brain subcortical white matter. Male aged 56 y. Hematoxylin and eosin stained section, tissue kindly provided by Margaret Esiri, Oxford Brain Collection. Bar=20 microns.

Panel C. Adverse remodelling of intramural coronary arteriole in a patient with arterial hypertension resulting in medial wall thickening, mainly due to smooth muscle hypertrophy and increased collagen deposition, with variable degrees of intimal thickening. This is the anatomical substrate underlying the abnormal coronary physiology and blood flow in these patients. Masson trichrome stained section. Bar=100 microns. (Courtesy of Prof Giulia D'Amati, Sapienza University, Rome).

Panel C. Small penetrating arteries exhibiting cerebral small vessel disease, human brain subcortical white matter. Green: fibrous connective tissue, Masson trichrome stained section. Bar=100 microns. Tissue kindly provided by Margaret Esiri, Oxford Brain Collection.

Figure 3. Proposed model for the relationship between cardiovascular disease, white matter hyperintensities and coronary microvascular dysfunction.

Cardiovascular risk factors all contribute to endothelial dysfunction which in turn causes microvessels alterations, in terms of functional impairment or adverse vascular remodeling. Altered structure and function of the microcirculation is the basis of coronary microvascular disease (CMD) and cerebral small vessels disease (cSVD). Carotid atherosclerosis is associated to cSVD, to which it may contribute through microembolization. On the other hand, atherosclerosis and carotid plaque development share the same risk factors. Atrial fibrillation is associated to cSVD, and again microembolization has been put forward as a potential pathogenetic mechanism. Valvular heart disease alters hemodynamics across microcirculation,

and possibly reduces perfusion pressure both in the coronary and cerebral arteries. Finally, congenital heart disease was shown to be associated to cSVD, possibly due to cerebral hypoperfusion and due to the effects of heart and lung machine in early heart surgery. Cardiopulmonary bypass was shown to alter endothelial function systemically.

CMD is commonly found in heart failure, and it appears to contribute to its pathogenesis and progression. Heart failure per se may afterwards contribute to cSVD through reduced cerebral perfusion.

Figure 4. Fluid attenuated inversion recovery images (FLAIR) of two subjects affected by non-critical carotid atherosclerosis

Subject A had a minimal white matter hyperintensities (WMH) burden, with no progression after 20 months. Subject B had a higher burden of WMH (note the hyperintense, patchy areas of the deep white matter, more prominent around the posterior horns of the lateral ventricles), with evidence of progression (red region of interest) after follow up. Both individuals had non-critical carotid atherosclerosis, no plaque related parameter was found to predict WMH progressors. (Reproduced from Ref 80, with permission).

Table 1. Summary of selected publications concerned with the relationship between white matter hyperintensities and cardiovascular diseases

Abbreviations. AFib= atrial fibrillation; BP= blood pressure; FH= familial hypercholesterolemia; HR= hazard ratio; HTN=hypertension; LVEF= left ventricular ejection fraction; OR=odds ratio; SBP= systolic blood pressure; WMH= white matter hyperintensities.

Condition	Study	n	Main findings	Ref
Hypertension	Debette et al, 2011	1352	HTN, i.e. SBP>140 mHg or current BP lowering medications, at a mean age of 54 years old were associated with WMH progression during 7 year follow up ($\beta \pm SE = 0.23 \pm 0.06$, $p < 0.001$).	51
	Jeerakatil et al, 2004	1814	HTN (R= 0.473, p<0.0001) is associated with WMH load. Cigarette smoking (avg daily cigarettes 5.2±11.2 vs 3.1±8.7, p<0.001) are associated with the presence of large WMH.	52
Dyslipidemia	Todate et al, 2019	63	WMH were more common in subjects with familial hypercholesterolemia than in healthy controls (controls, 0% vs. FH, 14.2%, p=0.02) at a mean age of 49.	58
	Zhang et al, 2019	732	Low-dose Rosuvastatin significantly reduced new WMH and cognitive impairment with respect to placebo at 59.8 months of follow up in a cohort of hypertensive elderly (HR=0.500; 95% CI: 0.34-0.74, p<0.001 and HR=0.54; 95% CI: 0.36-0.80, p=0.002, respectively).	59
Diabetes	Weinstein et al, 2015	1597	Diabetes was associated to increased WMH volume in subjects with mean age of 40 years ($\beta \pm SE = 0.22 \pm 0.09$, p=0.015).	64
	De Havenon et al, 2019	816	Effective intensive glycemic control (lower HbA1C) was not associated with reduced WMH progression over 40 months (p=0.916).	66
Smoking	Power et al, 2015	972	Active cigarette smoking was associated with WMH progression at 6 years follow up (OR 1.52; 95% CI 1.01-2.30). Probability of WMH progression increased with pack/year (OR 1.21; 95% CI 1.04-1.41).	72
Carotid atherosclerosis	Moroni et al, 2016	5306	Carotid atherosclerosis was associated with the presence of WMH in a meta-analysis of cross-sectional studies (OR 1.42, 95% CI 1.22-1.66, p<0.0001).	78
	Ammirati et al, 2019	51	No association between carotid plaque features of vulnerability (including plaque density, plaque neovascularization, microcalcification or remodeling) and WMH progression at 20 months of follow up (all p>0.05).	80
Atrial Fibrillation	Gaita et al, 2013	270	WMH were more common in AFib subjects when compared to healthy age, sex-matched controls (OR 11, 95% CI 6-21; p<0.001). Persistent AFib patients had a higher WMH burden with respect to paroxysmal AFib (WMH number 41.1 ± 28.0 vs. 33.2 ± 22.8, p = 0.04).	87
	Mayasi et al, 2018	234	Among stroke patients, AFib is associated to increased burden of WMH selectively in	89

			anterior subcortical WMH (OR 3.647, 95% CI 1.681 to 7.911, p=0.001).	
Heart failure	Vogels et al, 2007	148	Heart failure is significantly associated with an increased burden of WMH compared to controls (p<0.001). LVEF correlated significantly with WMH burden (R=-0.495, 0<0.001).	92
	Alosco et al 2013	69	Reduced cerebral perfusion, measured as peak flow velocity of the middle cerebral artery, was associated to increased WMH burden in subjects with heart failure (β=-0.34, p=0.02)	93
Valvular heart disease	Lee et al, 2018	232	Among patients with significant heart valve disease, right atrial pressure was linearly associated with WMH volume (beta= 0.702; 95% CI, 0.373-1.031; p = 0.001)	95

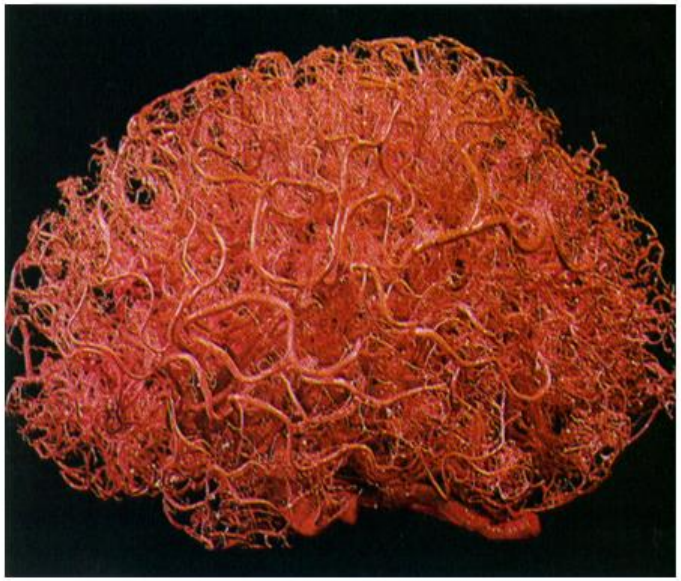
Table 2. Summary of selected publications concerned with the relationship between coronary microvascular dysfunction and other cardiovascular diseases

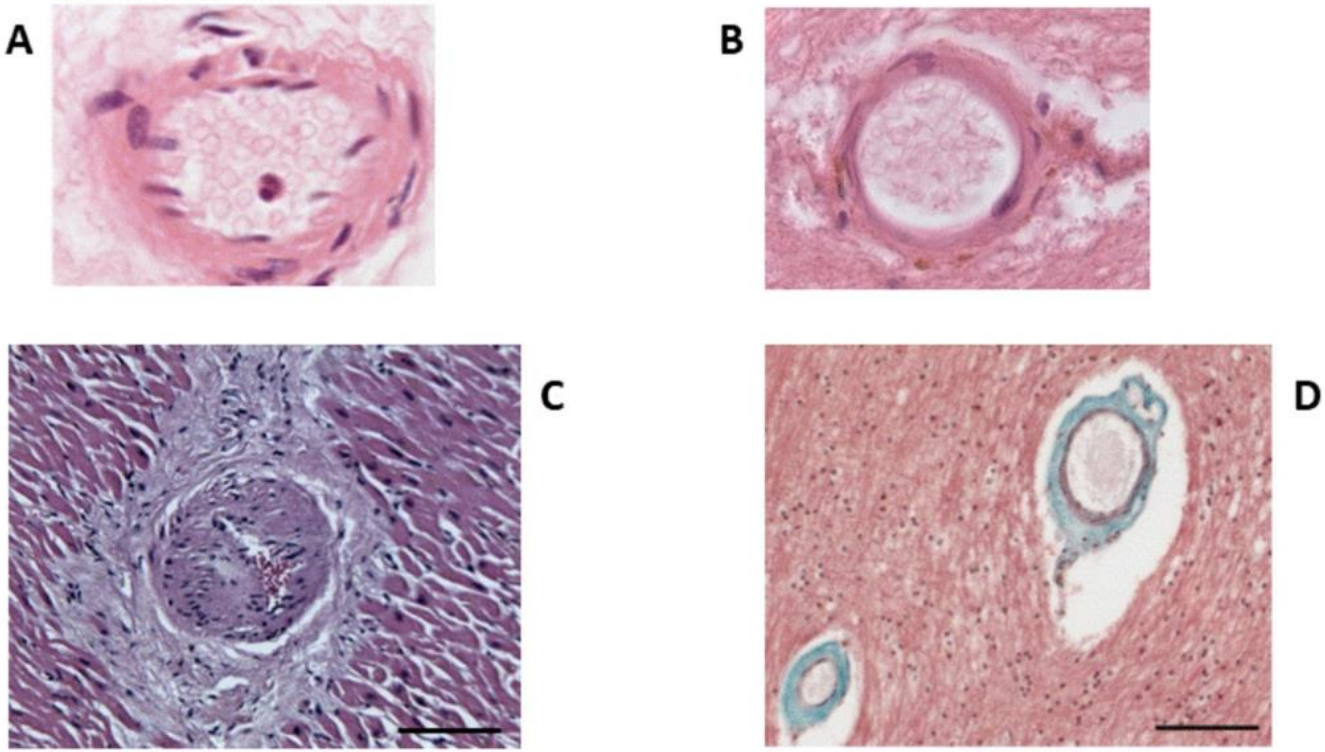
ACEi= angiotensin converting enzyme inhibitor; AFib=atrial fibrillation; CC-IMT= common carotid intima-media thickness; CFR= coronary flow reserve; HTN=hypertension; LDL= low density lipoprotein cholesterol; LVH= left ventricular hypertrophy; MBF= maximal blood flow; For an updated and in-depth review of coronary microvascular dysfunction in Heart Failure see ref 94.

Condition	Study	n	Main findings	Ref
Hypertension	Rimoldi et al, 2014	40	CFR was reduced in subjects with HTN and LVH when compared to healthy controls. CFR reduction was mainly due to MBF impairment (subepicardial MBF 3.07 ml/min per g vs 1.76 ml/min per g, p<0.001, subendocardial MBF 3.18 ml/min per g vs 1.91 ml/min per g, p<0.001)	54
	Masuda et al, 2000	12	ACEi initiation increases MBF in subjects with hypertension after 12 weeks of treatment (1.77 vs 1.70; p non significant). Coronary resistance was shown to significantly decrease p<0.003.	55
Dyslipidemia	Kaufmann et al, 2000	80	LDL was shown to negatively correlate with CFR in hypercholesterolemic subjects (r=-0.61, p<0.05)	61
Diabetes	Yokoyama et al, 1997	37	CFR is significantly reduced in subjects with non-insulin dependent diabetes mellitus (2.77±0.85 vs 3.8±1.0, p<0.01).	67
Smoking	Kaufmann et al, 2000	19	CFR was reduced in 3 (21%) of the 11 smokers and none of the 8 controls (p<0.05). High dose of vitamin C normalized CFR in smokers (p<0.05).	73
Carotid atherosclerosis	Sen et al, 2009	60	CC-IMT was higher in subjects with microvascular angina compared to control subjects (0.71 ± 0.11 vs 0.60 ± 0.16 <0.01). Subjects with microvascular angina were also more likely to have carotid artery plaques (33% vs 10%, p=0.03)	82
Atrial Fibrillation	Wijesurendra et al, 2018	74	MBF was reduced in AFib patients both under resting and stress conditions (p=0.044 and p<0.001 respectively). Rest and stress MBF did not change 6 to 9 months after successful catheter ablation	90

A

B




A
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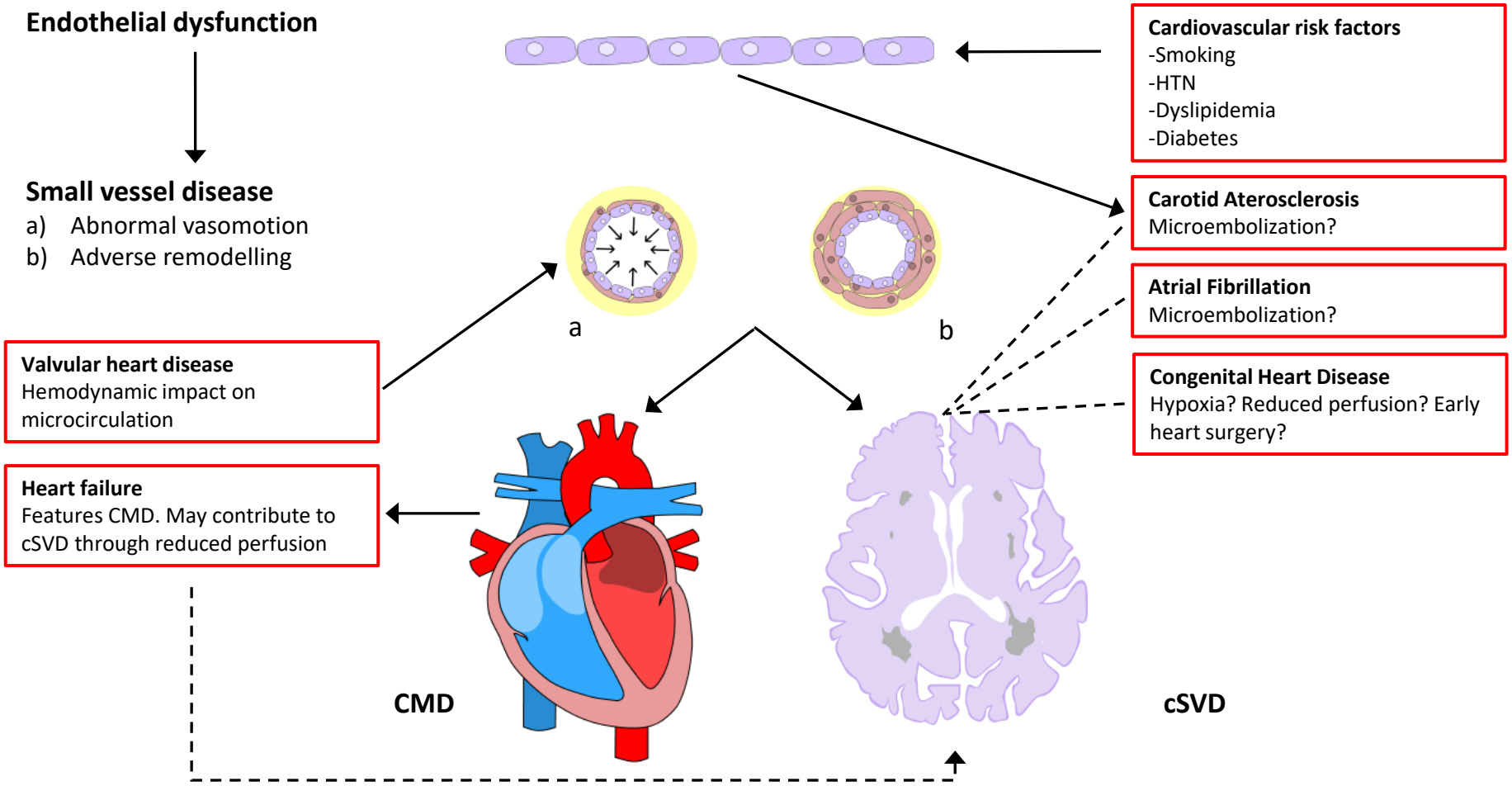
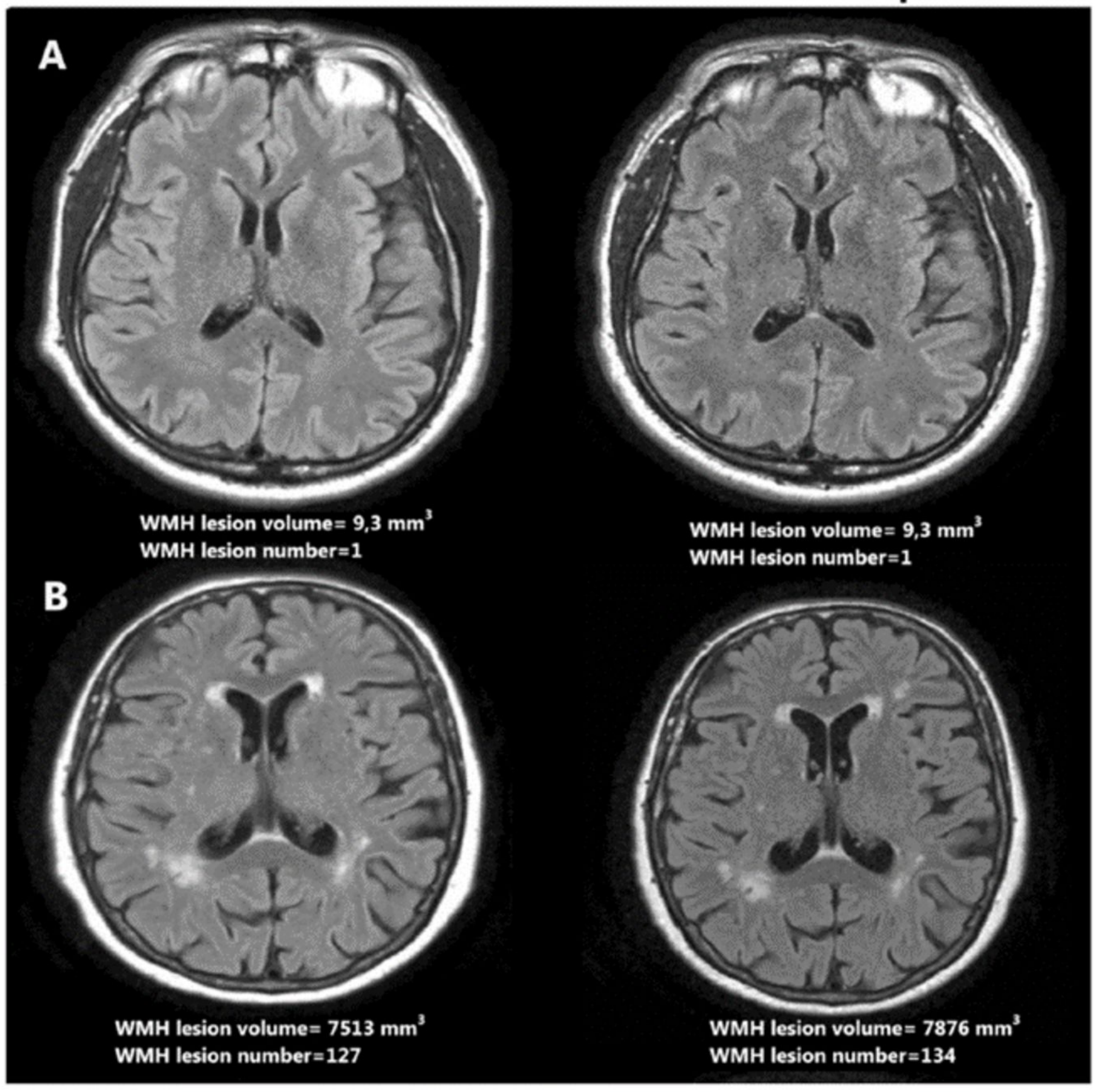

Endothelial dysfunction
Small vessel disease
a) Abnormal vasomotion
b) Adverse remodelling
Cardiovascular risk factors
-Smoking
-HTN
-Dyslipidemia
-Diabetes
Carotid Aterosclerosis
Microembolization?
Atrial Fibrillation
Microembolization?
Congenital Heart Disease
Hypoxia? Reduced perfusion? Early heart surgery?
a
b
Valvular heart disease
Hemodynamic impact on microcirculation
Heart failure
Features CMD. May contribute to cSVD through reduced perfusion
CMD
cSVD


Baseline
Follow-up
A
WMH lesion volume= 9,3 mm3
WMH lesion number=1
WMH lesion volume= 9,3 mm3
WMH lesion number=1
B
WMH lesion volume= 7513 mm3
WMH lesion number=127
WMH lesion volume= 7876 mm3
WMH lesion number=134