Imaging Markers of Vascular Brain Health: Quantification, Clinical Implications, and Future Directions

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Abstract

Cerebrovascular disease (CVD) manifests through a broad spectrum of mechanisms that negatively impact brain and cognitive health. Oftentimes, CVD changes (excluding acute stroke) are insufficiently considered in aging and dementia studies which can lead to an incomplete picture of the etiologies contributing to the burden of cognitive impairment. Our goal with this focused review is three-fold. First, we provide a research update on the current magnetic resonance imaging (MRI) methods that can measure CVD lesions as well as early CVD related brain injury specifically related to small vessel disease. Second, we discuss the clinical implications and relevance of these CVD imaging markers for cognitive decline, incident dementia and disease progression in Alzheimer's disease, and Alzheimer's related dementias. Finally, we present our perspective on the outlook and challenges that remain in the field. With the increased research interest in this area, we believe that reliable CVD imaging biomarkers for aging and dementia studies are on the horizon.

Cerebrovascular disease (CVD) is a multi-factorial process negatively affecting the structure and function of the cerebral vasculature. While stroke is a clinical syndrome of CVD, a wide spectrum of CVD related disease processes that impact cognition include clinically asymptomatic cerebral infarctions, white matter hyperintensities (WMH), micro-infarctions, and microbleeds as well as more general brain changes such as blood brain barrier dysfunction, impaired interstitial fluid drainage, altered cerebral blood flow, and microstructural myelin injury[1, 2]. The potential impact of clinically asymptomatic CVD and the vascular etiology of these imaging findings were first identified by Hachinksi and colleagues[3, 4] who described the presence of attenuated white matter signals seen on

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cerebral x-ray computed tomography as "leuko-araiosis". Coincident to the discovery of leuko-araiosis, Awad and colleagues identified "incidental subcortical lesions" on MRI[5] (currently denoted as WMH) and suggested a possible vascular etiology to which they ascribed the state of "état criblé" based on pathology[6]. These coincident observations heralded a new era in medical research related to the risk and consequences of asymptomatic cerebrovascular brain injury as evaluated by various non-invasive neuroimaging methods. The advancements and versatility of magnetic resonance imaging (MRI) have made it an indispensable tool for capturing a variety of mechanisms through which CVD impacts the brain. The multiplicity of the markers and CVD related brain changes, however, has added confusion to the field as to which marker(s) should be considered as measures of CVD risk for cognitive impairment and dementia.

Our aim for this review is to focus on MRI which as a versatile imaging modality that aids in capturing a variety of mechanisms through which CVD can impact the brain[7]. We largely focus on the aspect of small vessel disease because it contributes to about 50% of dementias worldwide[1] and do not expand on acute stroke related changes. With this approach, we have three goals in mind. First, we present key imaging markers for measuring CVD starting with traditional lesion markers followed by methods available for measuring early CVD related brain injury. Next, we discuss clinical implications and relevance of these CVD imaging markers for cognitive decline, incident dementia and disease progression in Alzheimer's disease (AD), and Alzheimer's related dementias. Finally, and most importantly, we present our perspective on the outlook of research in this area.

CVD Imaging Features: Lesions

The most traditional markers of CVD related injury noted on MRI are WMH, microbleeds, microinfarcts, cortical superficial siderosis, and large infarcts (Figure 1). The population prevalence of these MRI findings are generally less than 10% at 50–59 years but increase to over 70% for those older than 80 years of age[8]. These changes are due to multiple different pathological processes. While genetics is a prominent driver of these changes in familial CVD, hypertension and cerebral amyloid angiopathy play a major mechanistic role in sporadic CVD that can be exacerbated by *APOE4* genotype.

T2/FLAIR MRI for measuring WMH and infarctions

Increasing WMH burden seen on T2 weighted or Fluid Attenuated Inversion Recovery (FLAIR) MRI is a common consequence of the aging process[9, 10], exacerbated by vascular risk factors, particularly hypertension[11] and generally increases over time[12, 13] as individuals age. This process, however, may evolve over decades as recent studies indicate white matter injury associated with emerging WMH can begin during middle life[14, 15]. Numerous observations support the clinical relevance of WMH[7]. Not only is WMH burden associated with cognitive impairment in cross-sectional studies[16], but evolution of WMH are associated with declines in both memory and executive function[17]. Furthermore, extensive WMH predicts incident MCI, stroke and dementia[7]. Consequently, the sum of existing evidence has led to WMH being recognized as the hallmark neuroimaging measure of small vessel

vascular disease and associated vascular contributions to cognitive impairment and dementia (VCID).

Evidence for silent cerebral infarction was first described by Case et al. in 1989[18] through a comprehensive survey of stroke patients in the Framingham Heart Study. Nearly 10 years later, however, Bryan et al. identified "stroke-like lesions" on MRI of asymptomatic individuals in the Cardiovascular Health[19] and the Atherosclerosis Risk in Communities studies[20] and showed strong age-related increase in prevalence reaching >30% amongst the oldest participants. Subsequent large community-based studies using multi-modal MRI imaging to more accurately detect MRI infarcts[21, 22] have found similar age-related differences[9, 22, 23]. Silent MRI infarctions share the same vascular risk factors as clinically apparent infarcts[24, 25] confirming the causal association. While diffusion weighted imaging is used for reliable detection of recent infarctions, T1 imaging and FLAIR MRI are typically used for detection and quantification of silent infarction in dementia related research studies[2]. Multiple studies show that the MRI infarction is associated with poorer cognitive performance[26–28] and predicts future MCI, dementia and death[29].

The location of infarctions and WMH on T2/FLAIR vary and have been linked to heterogeneity of the underlying etiology. While lacunar strokes are likely due to hypertensive arteriopathy, cortical strokes are due to large vessel disease. There is increasing understanding that the etiology of WMH as well as progression is complex (with also some evidence of WMH reversibility[30]). In addition, there is evidence that there are likely non-vascular contributions to WMH in addition to the primary CVD contribution to WMH[31]. Research in familial AD patients, where CVD contribution to WMH is much lower, and pathology studies have provided initial evidence for the role of cerebral amyloid angiopathy (CAA) markers and cortical tau deposition in the emergence of WMH[32–35]. While there is evidence for greater CAA and AD related posterior WMH, further studies are required to understand the dynamics of WMH evolution with concurrent measurement of vascular health, amyloid, and tau pathologies.

T2* GRE/SWI for measuring microbleeds and superficial siderosis

T2* Gradient Recalled Echo (GRE) or Susceptibility Weighted (SWI) MR pulse sequences are most useful for measuring hemorrhagic manifestations, i.e. microbleeds and cortical superficial siderosis. Microbleeds or microhemorrhages are microscopic (~200μm) areas of blood leakage from injured vessels. Following the leakage of blood from a damaged vessel, hemosiderin is deposited in macrophages and these deposits are visible as hypointense lesions <10mm in size on T2* GRE and SWI[36]. SWI offers greater reliability and sensitivity in detecting microbleeds in comparison to T2* GRE[37]. Microbleeds can occur in either subcortical or lobar cortical brain regions. Subcortical microbleeds are associated with small vessel disease pathologies and vascular risk factors[38], whereas lobar cortical microbleeds are associated mostly with cerebral amyloid angiopathy (CAA)[39] where amyloid deposits in the vessel wall lead to injury and subsequent blood leakage. Focal tracer uptake in the areas of cerebral microbleeds[40–43] as seen on amyloid PET support the causal relationship between amyloid and microbleeds. The presence of microbleeds are clinically relevant as meta-analyses consistently show associations with cognitive dysfunction[7, 44] but further

work is still warranted to understand the impact of the location of the microbleeds (lobar vs. deep) on cognitive performance (including specific domains impacted). It also remains unclear to what extent the association between microbleeds and cognition is independent of co-existing injuries such as microinfarcts or AD pathology.

Cortical superficial siderosis is a distinct pattern of iron deposits in superficial cortical layers, observed by a dark rim along the gyri on T2* GRE or SWI images[45]. This lesion is relatively rare in the general population and sporadic forms of small vessel disease, but more common among patients with CAA[46]. In CAA, cortical superficial siderosis is the strongest predictor for future intracerebral hemorrhage and poor functional outcome[47].

T1 and T2 images for detection of Microinfarcts

With the emergence of increased imaging resolution of 7 Tesla ultra-high field MRI, small cortical lesions (small cavitation's) termed as cortical microinfarcts[48] can now be detected, although most microinfarcts detected on histopathological examination are even smaller, and escape high-resolution scans[49]. High-quality 3 T MRI can also be applied to detect small cortical lesions using standardized rating procedures, but rating is labor-intense and rater reliability is typically modest[48]. Cortical microinfarcts have an independent effect on cognitive impairment and dementia after accounting for traditional CVD markers such as WMH, microbleeds, and infarctions[50]. Small cortical lesions can also be seen with diffusion-weighted imaging, presumably resembling small acute or subacute cortical ischemia[51]. These cortical lesions on diffusion-weighted imaging mostly disappear without any trace on follow-up scanning,[52], suggesting that the remnants of most acute cortical infarcts are too small to be detected by MRI. This is a clear limitation to current technology, but an area of future research as this technology continues to evolve.

CVD Imaging Features: Early brain changes

While lesions are traditionally used to indicate vascular brain injury, vascular risk factors specifically hypertension, causes both functional and structural alterations to the brain prior to evidence of the typical lesions noted above. New MRI measures of brain microstructural and functional changes now enable identification of more subtle brain injury due to CVD. There are four recognized methods for measuring the spectrum of early CVD changes: 1) Diffusion MRI for measuring white matter microstructural injury, 2) Arterial spin labeling and cerebrovascular reactivity for measuring cerebral blood flow, 3) T2 images for measuring dilated perivascular spaces, and 4) Volumetric methods for measuring regional brain atrophy. An image with several of these early CVD related changes is shown in Figure 2. We have placed greater focus on diffusion MRI due to the extensive evidence available in the literature indicating that it may be a specific and a sensitive biomarker to CVD.

Diffusion MRI for measuring microstructural changes

Diffusion MRI has emerged as a key method for quantifying cerebrovascular burden[53–56]. It has been found to be more sensitive than conventional, lesion-based markers in detecting disease-related white matter alterations, even in regions appearing normal on conventional MRI[53, 57]. Diffusion MRI assesses brain microstructure indirectly by characterizing water

mobility in the tissue. Quantification is achieved by fitting models on top of raw diffusion weighted data with multiple diffusion-encoding directions. The most used model is diffusing tensor imaging. Various metrics can be derived from the tensor including Fractional Anisotropy (FA) that specifies the directedness of diffusion (decreased with pathology) and Mean Diffusivity (MD) which summarizes the extent of diffusion (increased with pathology). Since the imaging method is based on water motion, two important sources need to be considered and controlled: patients head motion and contamination by freely diffusing water in CSF space through partial volume effects, especially in brains with atrophy.

Diffusion MRI-based metrics have shown strong associations with CVD-related clinical deficits, such as cognitive and gait impairment, typically outperforming conventional lesion markers in this regard[53, 58–60]. Furthermore, longitudinal diffusion MRI measures can track small vessel disease progression with high accuracy[61, 62]. Beyond small vessel disease, diffusion MRI can also be used to measure secondary degeneration of white matter microstructure after stroke[63, 64]. While other etiologies, developmental differences, and abnormalities due to inflammation, oxidative stress can cause diffusion changes, the effect of CVD has been suggested to be the most dominant effect[65]. Regional analysis further suggests that AD pathology causes mostly posterior white matter injury, whereas CVD is periventricular, consistent with the differing pathophysiology of these processes[66, 67].

In addition to various diffusion MRI metrics, there are multiple analytical approaches, such as whole-brain or region-of-interest-based analysis of diffusion metrics, voxel-wise analysis, or structural connectomics using tractography, brain parcellations and graph theory network metrics[68]. By restricting analyses to the center of major white matter tracts to avoid CSF contamination, peak width of skeletonized mean diffusivity (www.psmd-marker.com) has been proposed and validated in multiple CVD samples[53, 69]. As more diffusion methods are proposed and more accurate biophysical models can now be applied based on newer acquisition technologies[70], there is a need to thoroughly validate and compare across various approaches.

Arterial Spin Labeling and Cerebrovascular reactivity for measuring Cerebral Blood Flow

Arterial Spin Labeling (ASL) was developed in the 1990's[71] based on the idea of using water in the arterial blood as an endogenous tracer. The signal relies on blood flow and the time it takes for the labeled spins to travel from the labeling plane to the imaged voxel in the capillary bed where there is exchange of water and nutrients in the tissue. Altered perfusion is of particular interest in CVD where there is compromise of blood flow in cerebral vasculature and of the neurovascular unit is suspected[72]. Though ASL is considered a quantitative measure of CVD, three sources of variability reduce the utility of ASL as a marker of CVD: 1) low signal to noise of the image acquisition modality; 2) in populations with vascular pathology, prolonged arterial transit time to tissue can cause artifacts, i.e. increased signal in vascular regions, and spuriously reduced perfusion in tissue[73]; and 3) reduced perfusion due to neurodegeneration unrelated to CVD[72]. In a systematic review by Shi et. al.[74], the association between cerebral blood flow and WMH was significantly attenuated when demented individuals were excluded suggesting that the effect sizes of

perfusion deficits in relationship to small vessel disease especially in early disease may be small.

Cerebrovascular reactivity, CVR as is generally referred to as, measures the change in relative blood flow due to vasodilation-- most commonly after CO_2 inhalation. Altered cerebrovascular reactivity is highly predictive of stroke[75] but also occurs with dementia[76]. While cerebrovascular reactivity is an attractive methodology to measure inefficient cerebrovascular function, further systematic validation across large populations is needed.

T2 images for measuring perivascular spaces

Space surrounding the vasculature is important for the clearance of fluid and metabolic waste[77]. Enlarged perivascular spaces (PVS) or Virchow-Robin spaces are visible on high resolution MR imaging (hyperintensity on T2-weighted images in conjunction with hypointensity on T1-weighted images) and are identified as dilated spaces along the blood vessels. PVS are very common with aging, neurodegenerative diseases, and vascular risk factors[78]. Due to the importance of increased PVS in mechanisms involving several aging related disorders[78] and the potential to significantly impact cognition[79], there is tremendous interest in measuring these changes. The location of PVS's are likely related to different etiologies. So far, the literature on PVS has not been consistent and there is a need for robust and reliable PVS measurements to test their clinical usefulness consistently across studies.

Volumetric MRI for measuring atrophy

While the impact of CVD is generally assumed to be associated with MRI measures such as WMH and infarctions, multiple studies show that CVD can cause cerebral and hippocampal atrophy[9, 67, 80]. The etiology of gray matter loss associated with CVD has received limited attention, despite studies suggesting that it may result from metabolic dysregulation[81, 82], inflammation associated with atherosclerosis[83] or secondary neurodegeneration[63]. The non-specific nature of MRI volumetric changes due to CVD, however, does not make for wide use as a CVD marker.

Clinical Implications of CVD features for Dementia

Recognizing that vascular brain injury can lead to cognitive decline and incident dementia, prompts discussion regarding the impact of CVD on dementia incidence within the general population, where AD pathology is common and co-occurrence of these two pathologies is likely[84]. In this section, we discuss potential mechanisms by which these two processes combine to result in incident dementia.

CVD as an essential Dementia Risk Factor

Two widely recognized AD risk factor scales include common vascular risk factors[85, 86] supporting the role of vascular disease in dementia incidence even when the clinical phenotype is AD dementia. In this regard, CVD—due to increased prevalence earlier in life[87] and known subtle brain injury in middle age[15, 88]—would lead to increased risk for late-life dementia[89].

CVD and AD as additive pathologies

Pathological studies of individuals with dementia as well as combined MRI and PET imaging studies of non-demented individuals indicate an additive effect of CVD and AD pathologies[90–93]. This evidence is particularly strong for neuroimaging studies that find no significant association between amyloid deposition and MRI vascular makers[92, 94]. Moreover, in each of these studies, individuals show faster decline with both AD and CVD pathologies[95, 96] as compared to either in isolation.

Synergistic effects of CVD and AD and common features

Several synergistic mechanistic hypotheses have been proposed in the literature but to date have been inconclusive and need further validation. One hypothesis proposes changes in blood flow and blood brain barrier dysfunction as an earliest marker of all neurodegenerative disorders[97]. Another suggests that hypoperfusion and hypoxia caused by atherosclerosis of cerebral vessels may enhance the production of Aβ, which in turn, may promote formation of atherosclerotic lesions through vascular oxidative stress and endothelial dysfunction leading to additional vascular damage[38]. A third hypothesizes CVD leads to poor clearance of extracellular Aβ through the glymphatic system[98]. Finally, there is evidence that CVD may interact with the AD process (ATN biomarker cascade[99]) through worsening systemic vascular health that exacerbates both amyloid[100] and tau deposition[101, 102]. In addition, some of the CVD features are a direct consequence of AD pathophysiology. For example, it has been suggested that some of the WMH are seen due to Wallerian degeneration triggered by AD pathology[103 104]. However, there is no clear consensus on the mechanisms and evolution of these proposed inter-relationships.

Open Questions and Exciting Research on the Horizon

While tremendous progress towards improving the acquisition protocols, measuring these CVD changes, understanding risk factors, prevalence, and the impact of these changes on cognition has been made, biological questions remain, and exciting research avenues are on the horizon. Some of the current impediments are related to measuring the reliability of the markers across studies, need for greater precision in measurements, better acquisition and quantification of CVD changes, and lack of understanding of the pathological underpinnings and are discussed here.

1. Repeatable and reproducible marker(s) across different populations

A wide variety of measures of CVD exist including several discussed in this review. Reliability, however, is a crucial aspect for widespread application of an MRI marker in research as well as clinical care. To be reliable, MRI markers should be both repeatable (when scanning a patient twice) and reproducible (when scanning a patient on two different MRI scanners)[105, 106]. Unfortunately, there have been few technical validation studies, which assess the reliability of CVD measures in the target populations. Among more advanced measures, reliability is best assessed for diffusion MRI. In cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephaly or CADASIL patients, reproducibility of diffusion measures across two scanners without harmonized MRI protocol was improved by using histogram analysis[53]. Another study with a harmonized acquisition

protocol found almost perfect reproducibility of tensor and kurtosis metrics and excellent repeatability using high-frequency serial imaging data[70, 107].

Biological/clinical validity is another important issue. For example, evidence suggests that diffusion MRI has greater predictive value in comparison to traditional WMH measures[70 108]. There has also been literature on the need to combine several measures to create a composite CVD measure for use in clinical and research studies[109–111]. Yet, none of these metrics have widely been validated.

Recently, the Mark VCID consortium, supported by the National Institute on Neurological Disorders and Stroke, an institute within the NIH, was created to develop and validate methods to identify and longitudinally assess VCID (https://markvcid.partners.org/). This consortium consists of five sites and a coordinating center that has developed a series of novel "kits" using various imaging tools, blood and CSF based biomarkers to further refine methods developed for use in clinical trials specifically aimed at treatment of VCID. While this study is still ongoing, near future expectations for reliable, validated biomarkers of CVD are high.

Generalizability is another limitation of current work in CVD neuroimaging. There is a compelling need for expanding demographic diversity in studies of CVD cognitive decline. Dementia[112] and vascular disease prevalence[87] are both increased among diverse individuals and it is hypothesized that vascular disease may have a greater impact on the cognitive health of these individuals. Evidence for this comes from epidemiologic studies showing that *APOE4* genotype conveys less risk for dementia among non-white populations[113] and that vascular risk factors are associated with cognitive decline in both Black and Hispanic populations[114–118]. These studies are consistent with neuropathological findings that CVD is more prevalent among demented Black and Hispanic individuals[119]. To be relevant to the changing demographics of our aging population[120], therefore, these markers need to be assessed and validated in diverse populations.

2. Development of Quantitative Imaging based measures

In a lesion-centric approach, tissue is typically labelled in a binary fashion as either being pathological or normal appearing. However, especially studies using diffusion tensor imaging have already shown that CVD causes gradual damage, which established the concept of the WMH penumbra[57]. Binarization is therefore artificial. Further, it can be regarded as ill-posed to quantify disease burden based on image contrast developed for visual rating, not for quantification. It is not straightforward to simply quantify arbitrary values on T1 weighted or T2 weighted scans, which do not correspond to a physical measure. Quantitative relaxometry, on the other hand, determines relaxation times (measured in ms) as a physical property of tissue, providing the basis for quantifying gradual signal alterations using quantitative T1, T2 and T2* maps[121]. These techniques are not new, but – except for T2* – rarely applied in patients because of long acquisition times. Recent developments in acquisition acceleration, e.g. using k-space under sampling, might propel a renaissance of quantitative MRI[122]. Of particular interest is magnetic resonance fingerprinting, a dictionary-based technique to obtain multi-parametric quantitative MRI data from unique patterns of signal evolution during a single, short image acquisition[123].

3. Advanced diffusion models and their application to CVD

While the tensor model has frequently been used to study white matter microstructure alterations in CVD, there are other, more advanced diffusion models which potentially allow better characterization of the complex brain microstructure and thus additional insight. Free water imaging is a bi-tensor model that allows separating the contribution of extracellular free water and tissue microstructure on the diffusion signal. Studies using free water imaging have shown that diffusion alterations in CVD are largely driven by alterations in free water content.[124] Free water itself has been used as a sensitive marker for clinical deficits,[107, 125] and strong predictor of cognitive and functional trajectories among older individuals, as well as for unraveling pathophysiological cascades of events triggered by elevated blood pressure[126]. These findings led to the hypothesis that increased extracellular water due to blood brain barrier dysfunction may precede microstructural white matter changes and WMH development[127].

Even more advanced models, such as diffusion kurtosis imaging or biophysical models, e.g. neurite orientation dispersion and density imaging, typically require a more elaborate diffusion acquisition scheme, with multiple and stronger diffusion weighting (multi-shell acquisition)[128, 129]. This leads to a prolonged acquisition time and comes with higher requirements regarding scanner hardware. So far, only one study systematically assessed the added benefit of these advanced, more demanding models and found a benefit of diffusion kurtosis imaging in assessing associations with cognitive deficits in early-stage small vessel disease[70].

4. Pathological and multimodal imaging studies to understand early CVD changes

There is paucity in the number of antemortem imaging and postmortem validation studies for confirming the pathologic basis of early CVD markers. For example, diffusion alterations have been suggested to be largely driven by increased free water[130] not by the degeneration of white matter tracts[124], indicating a perturbed blood-brain barrier mechanism due to vascular pathology. On the other hand, Colgan et. al. showed greater sensitivity of neurite density measures from advanced diffusion models to histological measures of tau pathology[131]. However, unless there are systematic histopathological studies mapping the CVD features to pathological changes (e.g. leaky vessels, demyelination), we will be unable to discern the source of variability in our biomarkers.

5. Newer imaging techniques for detecting small vessel function and pathology

To date, most CVD MRI markers do not measure the small vessels, but downstream tissue alterations because of vessel pathology. MRI metrics of vessel function or integrity can be obtained, e.g. cerebrovascular reactivity using blood oxygenation level dependent-based MRI after CO_2 stimulus or blood-brain-barrier function using dynamic contrast enhanced MRI[132, 133]. Neither of these methods are generally preferred across common dementia studies, since they are time-consuming, suffer from low signal-to-noise ratio, and require additional equipment or contrast agent application.

Instead, there is a need to develop robust methods to measure small vessel function/ pathology, impaired blood-brain barrier, and endothelial dysfunction to test the mechanistic

hypothesis by which CVD impacts cognitive aging and dementia. Examples of this type in development include 7 Tesla ultra-high field MRI can image single perforating arteries *in vivo*[134] and also measure flow characteristics, such as vessel stiffness measured by pulsatility[135]. Similarly, non-contrast mapping of water exchange across the blood-brain barrier by diffusion-prepared perfusion also has been proposed for measuring impaired blood-brain barrier dysfunction in CVD patients imaging[136]. As newer methodologies emerge, however, there will be need for rapid validation and clinical translation of the techniques.

6. Better lesion detection and quantification tools

MRI acquisitions now allow for high resolution 3D acquisitions that offer better delineation and detection of CVD lesions. While manual or semi-manual detection and editing of CVD lesions have been the most common initial approaches, they are extremely labor intensive to implement given the much higher frequency of CVD lesions detected through the current acquisition strategies. There is a need, therefore, for robust computational methodologies that are widely available and can be employed to efficiently measure obvious CVD lesions as well as early brain injury for the general population.

Conclusions

MRI enables detection of a broad spectrum of CVD changes that significantly impact brain and cognitive health and newer technologies are beginning to explore causal mechanisms at the level of small vessel and BBB integrity. Moreover, newer concepts of dementia pathophysiology that encompass disease heterogeneity has led to tremendous progress in understanding the clinical implications of CVD on the burden of dementia. While several open questions and challenges remain, ongoing work on development and validation of reliable CVD imaging markers will bring us closer to identification and implementation of CVD imaging biomarkers for use in observational and interventional studies of aging and dementia.

Sources of Funding

Non-standard Abbreviations and Acronyms:

CVD	Cerebrovascular disease
MRI	Magnetic resonance imaging
WMH	White matter hyperintensities
AD	Alzheimer's disease
FLAIR	Fluid Attenuated Inversion Recovery
GRE	Gradient Recalled Echo

SWI	Susceptibility Weighted Imaging
CAA	Cerebral amyloid angiopathy
PVS	Perivascular spaces

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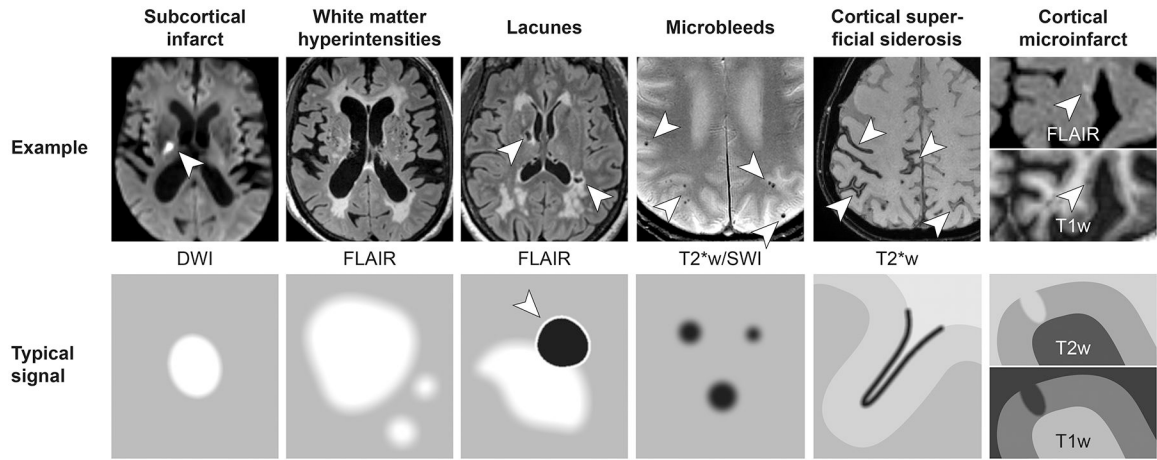
Figure 1:

Common CVD lesions and the contrast seen on MRI. DWI=diffusion weighted imaging; FLAIR= Fluid Attenuated Inversion Recovery; SWI=Susceptibility weighted imaging.
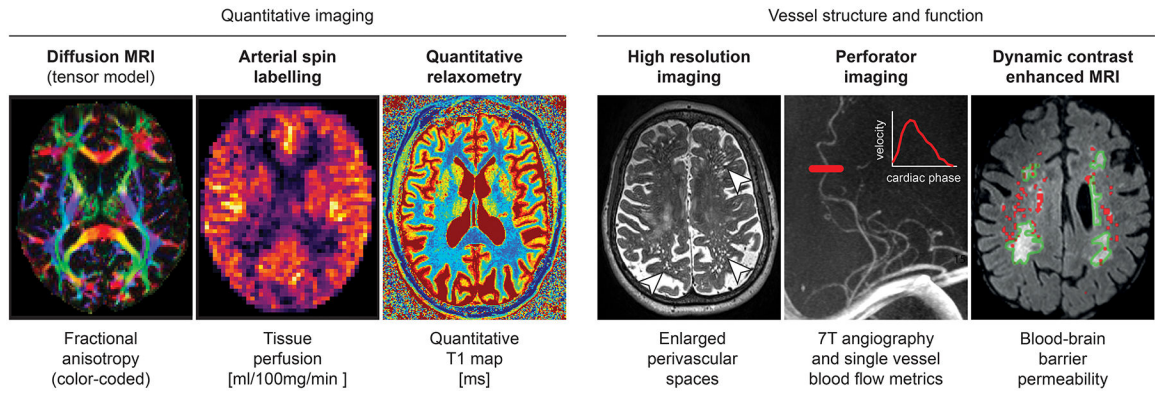
Figure 2:

More novel MRI markers used to capture early and subtle CVD related changes through quantitative imaging or by more directly probing vessel structure and function. Perforator image was unpublished and included courtesy of Tine Arts, Jaco Zwannenburg and Geert Jan Biessels. Permeability map was adapted from Huisa et. al. 2015 with permission. Copyright 2015, the American Heart Association.