William M. Feinberg Award for Excellence in Clinical Stroke

Small Vessel Disease; a Big Problem, But Fixable

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Like much in stroke, this research journey started with a clot although this clot and this stroke were different.[1]

Small vessel disease (SVD) is now recognized to cause 20% to 25% of strokes, to be the second commonest cause of dementia, to cause cognitive decline, physical frailty, and late onset depression. In addition to acute small subcortical (lacunar) ischemic strokes, SVD includes lesions seen commonly on brain imaging: white matter hypertensities (WMH), lacunes, microbleeds, perivascular spaces (PVS), brain shrinkage,[2] and biomarkers in apparently normal areas (eg, increased tissue fluid volume and mobility).[3] However, when this research started, the strokes, cognitive presentations, and neuroimaging features of SVD were thought generally to be unrelated, silent, permanent, and lacunar stroke was a small version of large artery stroke.

How Did It Start?

In 2000 AD, a 70-year-old man presented to our hospital with a recent lacunar stroke. His computed tomographic scan showed a small, low attenuation area, consistent with a recent small subcortical (lacunar) infarct. There were 3 odd features.

1. In the center was a small white dot, like a mini version of the hyperattenuated middle cerebral artery commonly seen in patients with hyperacute cardio- or athero-thromboembolic ischemic stroke, an appearance not described previously.
2. Brain magnetic resonance imaging (MRI) immediately after the computed tomographic scan confirmed the recent lacunar infarct, including the odd central line/dot, except that there also appeared to be some blood in the arteriole wall. Although a few small cardiac or carotid atheromatous emboli can enter the basal perforating arterioles, ≈6% in experimental models,[4] and no more than 11% in patients,[5] an embolus would not explain the blood in the arteriole wall.
3. The infarct was around the affected arteriolar segment, not at the end of it, as would be expected in, for example, an infarct occurring secondary to an acute middle cerebral artery occlusion.

What Was Going on?

Most strokes are thought to result from blocked or bleeding vessels. The thrombus in the arteriole lumen, the wall abnormality, and the infarct location suggested some different process. Was the surrounding tissue change ischemic or another process? And what were the implications for other small subcortical lesions commonly seen in stroke, particularly in lacunar stroke,[2] such as WMH? Then, and now, WMH are commonly labeled ischemic and attributed to low cerebral blood flow (CBF). But, is every WMH at the end of a diseased arteriole?

We examined scans of all our patients with acute lacunar stroke in the previous 4 years and found a similar arteriole appearance in the symptomatic recent lacunar infarct in ≈10%.[1] Detailed examination of the few papers on lacunar stroke pathology was informative, particularly C Miller Fisher meticulous dissections of the perforating arterioles leading to lacunar strokes in the 1950s and 1960s.[6,7] Reading original observations is always valuable because subsequent interpretations may drift from the original over time. Fisher described the arterioles in and around lacunes in 4 patients with hypertension and small strokes in life as "segmental arteriolar disorganization" consisting of local dilatation and narrowing of the arteriole, thickened disintegrating wall, and leakage of fibrinoid material and blood into and around the wall. Others have called this process "fibrinoid necrosis" or "hyalinosis" among other names. Interestingly, some of his histological images of the arteriolar pathology looked similar to our macroscopic MRI (Figure 1).

Not Just Midlife Atheroma or Vascular Risk Factors

Much has been written about the causes of lacunar stroke and its distinct clinical syndromes pointing to an intrinsic process,[8] yet embolic processes and atheroma remain strong in stroke thinking. Fisher lesions were mostly not embolic, but they might have been a microatheroma and middle cerebral artery atheroma can obstruct the ostea of perforating arterioles. However, much research, from large epidemiological to small intensive studies, confirms a lack of direct

Received May 1, 2018; final revision received May 1, 2018; accepted May 15, 2018.

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(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.118.021184.)

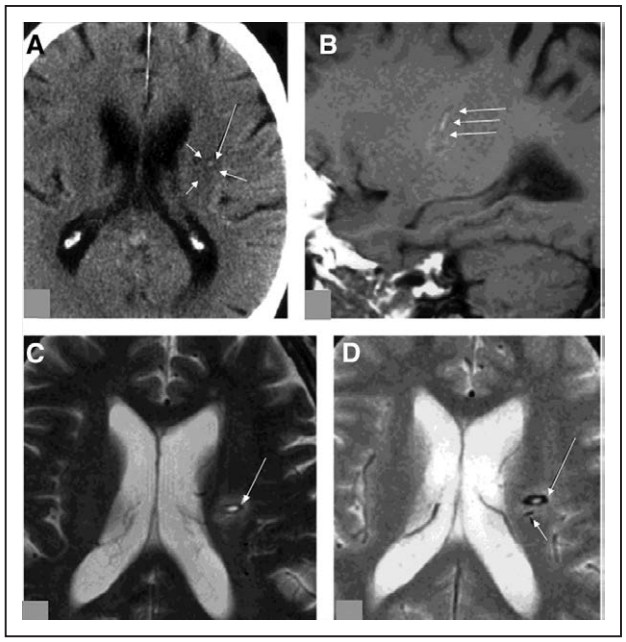

Figure 1. Computed tomography (**A**) and magnetic resonance (**B** sagittal T1, **C** axial T2, **D** axial T2*) images from a 70-year-old man who presented shortly after a left hemisphere lacunar syndrome (adapted from Wardlaw et al[1] with permission; Figure 1, publ. John Wyllie and Sons, with permission, license number 4351401429541). Note the infarct (**arrows**, **A**) with the central hyperattenuated dot in cross-section like a mini hyperattenuated artery sign; this seems linear on the sagittal T1 (**B**) consistent with the orientation of the perforating arteriole. The arteriole wall seems thickened with blood signal within it (**C** and **D**) particularly striking on the T2* blood-sensitive sequence (**D**). The infarct is around about the mid arteriole, not at its end. A tiny side branch is visible in **D** (short arrow). Reprinted from Wardlaw et al[1] with permission. Copyright © 2001, Wiley-Liss, Inc.

association between embolic sources or atheroma and most small subcortical infarcts[5,9] or WMH.[10–13] Consistent with this, long-term intensive versus single antiplatelet agents not only did not prevent recurrent lacunar stroke in the 3000+ patient SPS3 (Secondary Prevention of Small Subcortical Stroke) trial but found that long-term dual antiplatelet drugs were hazardous.[14]

Furthermore, although hypertension is a major risk factor for stroke, including lacunar stroke,[9] it and other common vascular risk factors are not the only cause. For example, in ≈750 community-dwelling subjects aged 72 years, and separately in ≈150 patients with nondisabling ischemic stroke, all common vascular risk factors combined (hypertension, smoking, diabetes mellitus, hypercholesterolemia, measured blood pressure, cholesterol, hemoglobin A1c), accounted for <2% of the variance in WMH burden.[12] Of this 2%, hypertension and smoking were the strongest risk factors. The unavoidable conclusion is that 98%, that is, most, of the variance in WMH is not explained by common vascular risk factors, also consistent with the SPS3 trial in which intensive (versus guideline) blood pressure reduction did not prevent recurrent stroke, WMH progression, or cognitive decline, in >3000 patients with lacunar stroke.[15]

These results do not mean that common vascular risk factor avoidance is not important. On the contrary, it is important. However, it does mean that the search for modifiable risk factors should extend beyond conventional concurrent vascular risk factors, the main message being that lacunar stroke and SVD are not simply a small version of large artery cardio-athero-thrombo-embolic stroke.

SVD Risk Occurs Across the Life Span

What might account for this unexplained 98% of SVD variance? The high heritability of at least 2 common SVD features, WMH[16] and PVS,[17] indicate that genes are important, yet genetic studies have to date identified relatively few SVD-related genes. However, their detailed discussion is beyond the scope of this short article which focuses on unraveling SVD pathophysiological pathways through direct human studies.

Because SVD develops in the brain for many years, long before the lacunar stroke or cognitive decline starts, what about risk factors earlier in adulthood? Long-term adult lifestyle habits, such as taking less exercise[18] and more dietary salt,[19,20] are associated independently with more WMH and lacunar (versus nonlacunar) ischemic stroke. The overall health benefits of exercise, and detrimental effects of dietary salt, are well established, but their specific effects on brain microvascular health are less appreciated. These invite public health approaches to preventing SVD because that will help prevent dementia, as well as stroke.

What about factors occurring even earlier in life? Interestingly, a large published literature indicates that lower childhood intelligence, socioeconomic status, and educational attainment each predict increased lifetime risk of all types of SVD lesions,[21] as well as stroke,[22] independent of adult risk factors. Because these 3 factors are inter-related, and few studies which examined all 3 simultaneously, their independent contribution to SVD or stroke risk is unclear. However, the magnitude of effect of any one of them is similar and important on a population basis. For example, expect 3.5/1000 more strokes in those who completed full-time education to high school level versus those with university education,[22] or 17% relative increase in SVD lesions[21] for the same education difference, moving responsibility for stroke and SVD prevention from purely medical or public health onto Government policies.

Consider the Blood-Brain Barrier

Sporadic SVD is a complex disorder that develops for many years. Although genetics, childhood factors, and adult lifestyle may raise the SVD risk, they do not explain what actually goes wrong. The pathology described by Miller Fisher and others tends to reflect late stage features,[7] but preventing development or progression requires consideration of the earliest disease stages. A possible unifying hypothesis to explain all 3 odd features observed in our original case was dysfunction of the endothelium and subtle blood-brain barrier (BBB) leakage.[23] If there was leakage, then it would have to be subtle, otherwise it would have been obvious given the widespread clinical use of contrast-enhanced brain imaging.

In studies including ≈3000 subjects up to the mid-2000s, BBB leak, mostly detected using the cerebrospinal

fluid:plasma albumin ratio, increased with age, was worse in any dementia versus healthy controls, in vascular versus Alzheimer disease, and in patients with more WMH.[24] However, the cerebrospinal fluid:plasma albumin ratio could not locate or quantify the leakage.

We developed methods to image subtle BBB leakage using dynamic contrast-enhanced MRI with intravenous gadolinium and sequential T1 MRI seeking increased tissue and cerebrospinal fluid signal.[25,26] Gradually, as MRI and image processing improved, scan times shortened and methods to calculate permeability improved.[27] The details are beyond the scope of the present article, but suffice to note that the methods are complex, involving correction for several factors (precontrast tissue T1,[28] hematocrit,[27] repeated measures to overcome background noise, a reliable estimate of vascular input function[27]) and detailed image processing that avoids tissue cross-contamination especially by large vessels.[28] Despite this, all current permeability calculations rely on several assumptions, including that microvessel density and surface area do not change with age, disease, or tissue type (clearly untrue). Thus, careful between-group comparisons of signal change to assess leak may be safer.

Accumulating human cross-sectional analyses indicate that BBB leakage increases with age, in lacunar versus nonlacunar stroke, with increasing visibility of PVS,[25] in WMH versus apparently normal tissue,[29,30] close to WMH in normal appearing tissue,[3,30] with increasing WMH in normal appearing white matter,[3,31] in the hippocampus with cognitive impairment,[32] in white matter in Alzheimer disease,[33] and vascular dementia.[29,34,35] Furthermore, in longitudinal studies, BBB leakage predicts recurrent stroke, worsening of WMH,[36] and cognitive decline in patients with lacunar stroke.[30]

Might a leaky arteriole and increased periarteriolar interstitial fluid also explain the location of the infarct around, rather than at the end of, the arteriole in our patient with acute lacunar stroke? Perhaps, the infarct is increased extracellular fluid, not just ischemia, a speculation that needs more research. Unfortunately, the chances of scanning someone just before they develop a lacunar stroke are remote although there is 1 example: a patient had gadolinium-enhanced MRI the day before presenting with a lacunar stroke; examination showed gadolinium enhancement in the thalamus where the stroke developed.[37]

Further evidence for BBB leak comes from sensitive MRI methods that show that increased interstitial fluid present in WMH, before demyelination and axonal loss, typically seen pathologically.[3,38–40] This observation is further strengthened by other recent work showing raised tissue water, for example, in skeletonized white matter mean diffusivity, to be the most sensitive marker of cognitive impairment in patients with white matter disease.[39]

Why the discrepancy between MRI and pathology? They are sensitive to different factors: conventional MRI relies on hydrogen, a major component of water, so is sensitive to shifting water content; pathology generally removes water from the specimen during processing leaving rarefied axons visible, in part explaining why WMH until recently were conventionally thought to indicate demyelination and axonal loss.

What About Ischemia?

If WMH are areas of increased fluid, what role does CBF play? In upwards of 10 cross-sectional studies to date, in ≈400 subjects, resting CBF is lower in people with more versus less WMH (standardized mean difference: −0.73; 95% confidence interval,−1.16, −0.31).[41] However, many studies did not have age-matched controls or included patients with Alzheimer disease. Excluding patients with Alzheimer dementia renders the CBF-WMH association nonsignificant (standardized mean difference: −0.32; 95% confidence interval, −0.67, 0.02); focusing on studies with age-matched controls removes any residual CBF-WMH association (standardized mean difference: −0.78; 95% confidence interval, −2.04, 0.49).[41] What does this mean? Are WMH ischemic or not, or might the falling CBF reflect having less brain to supply, perhaps explaining the association with Alzheimer disease a classic feature of which is brain atrophy? The 6 longitudinal studies of WMH and CBF to date overall show that low baseline CBF does not lead to increasing WMH burden; instead, a high WMH burden at baseline leads to falling CBF at follow-up,[41,42] suggesting the reduction in CBF reflects having less brain to supply.

Resting CBF may not reflect CBF during brain activity. The brain has a highly responsive vascular system designed to match the complex, rapid demands for increased oxygen, glucose, and removal of metabolic waste, the failure of which results rapidly in neurological dysfunction. Cerebrovascular vasoreactivity, measured with Doppler ultrasound in the middle cerebral artery, falls with age and is worse in patients with stroke, and in lacunar versus nonlacunar stroke, or with more WMH.[43] To measure individual tissue-level vasoreactivity requires techniques, such as blood oxygen level–dependent MRI,[44] although results of most studies to date are limited by not adjusting for age or hypertension.[45] In 60 patients with varied severities of WMH, cerebrovascular vasoreactivity fell independently with increasing WMH and basal ganglia PVS visibility,[46] and cerebrovascular vasoreactivity was not related to resting CBF but was related to increased intracranial vascular pulsatility. Increased intracranial pulsatility was also related to increased WMH and PVS visibility. These findings concur with the established relationship between systemic arterial pulse pressure, which is strongly associated longitudinally with increased WMH and PVS, independent of blood pressure,[47] and implicates impaired cerebrovascular vasoreactivity and vessel stiffness in the endothelial dysfunction contributing to SVD pathogenesis (Figure 2).

PVS deserve further mention. Visible on MRI as thin linear or round cerebrospinal fluid-intensity structures parallel with perforating microvessels, they are important conduits for brain interstitial fluid balance, waste management, and immune competence. Their enlargement (best seen on T2 or T1 MRI) is associated with hypertension, inflammation, BBB leakage, increased WMH, and lacunar stroke. Close inspection of T2 and fluid attenuated inversion recovery MRI shows deep WMH forming around PVS, consistent with growing evidence above on BBB leak[25] and implying impaired interstitial fluid drainage in SVD pathogenesis (Figure 2).

Rodent studies suggest that tissue clearance and drainage via PVS may increase during sleep[48] although the results are controversial. However, increased clearance of

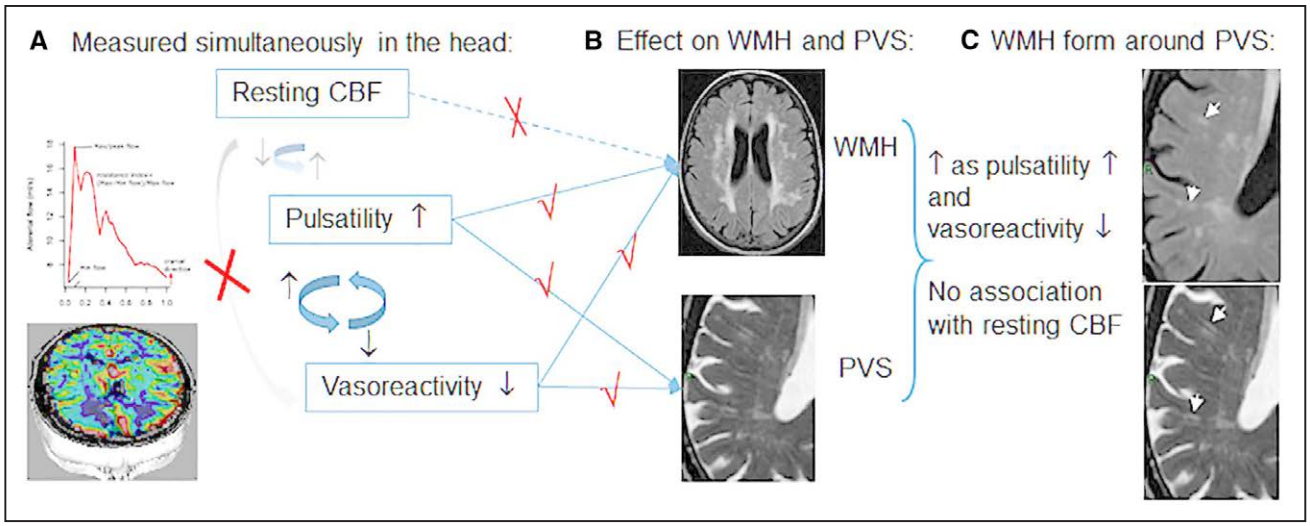

Figure 2. Diagram illustrating dynamic relationships between small vessel function and small vessel disease lesions. **A**, Resting cerebral blood flow (CBF) is weakly related to intracranial vascular pulsatility but not to cerebrovascular reactivity while increasing pulsatility is strongly related to declining cerebrovascular reactivity. **B**, falling CBF is not related to white matter hypertensities (WMH) or perivascular spaces (PVS) severity, but both increasing pulsatility and falling cerebrovascular reactivity are associated with increased WMH and PVS. **C**, Close inspection of fluid attenuated inversion recovery (**top**) and T2-weighted (**bottom**) magnetic resonance imaging shows that WMH form around PVS.

metabolites would perhaps explaining the importance of sleep to brain health.

Small Vessel Brain Damage Is Permanent?

The assumption that SVD features are because of ischemia and demyelination implies that the lesions represent end-stage, permanent damage. However, 2 recent studies demonstrate that WMH can shrink, and even lacunes and microbleeds can disappear.[49,50] We followed 200 subjects to 1 year after nondisabling ischemic stroke and found that WMH volume clearly decreased in ≈20%, increased in ≈20%, and either did not change at all or only by a small amount in the remainder.[49] Reduction in WMH volume was associated with fewer recurrent neurological events and contemporaneous reduction in brain water content on MRI, supporting that the WMH change was real, not measurement error. The RUN DMC study (Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort) during 10 years of follow-up found lacunes, microbleeds, and WMH forming and disappearing.[50] It seems that the pathology underlying SVD is not permanent and lesions are much more dynamic than previously thought.

What to Do?

What can be done to prevent or correct subtle BBB leakage, stiff vessels, and poor vasoreactivity? Might any current therapies, licenced for other purposes but with relevant modes of action, be helpful? There are many established cardiovascular drugs with relevant effects, which might also help mitigate the cognitive effects of SVD, thereby addressing a huge unmet societal burden of dementia and stroke, buying time for more specific novel agents to be developed.

A detailed literature search identified several agents with potentially relevant modes of action, of which 2 oral agents had the most encouraging human data: isosorbide mononitrate and cilostazol.[51] The animal literature supported the same conclusion.[52] Why these 2 drugs? Most importantly, they are both widely used, have known safety profiles, and limited but encouraging data in lacunar stroke.

Isosorbide mononitrate is a nitric oxide donor. Nitric oxide is reduced in acute, chronic, and possibly lacunar stroke; given acutely after stroke, nitric oxide donors improved cognitive test scores at 90 days in the 4000-patient ENOS trial (Efficacy of Nitric Oxide in Stroke).[53] Nitric oxide has multiple potentially beneficial effects for SVD, including improved BBB integrity, vasodilation, reducing inflammation, and neuroprotection,[51,54] although data on isosorbide mononitrate in lacunar stroke are sparse because ischemic heart disease (its main therapeutic indication) is uncommon in these patients.[9]

Cilostazol, a phosphodiesterase 3′ inhibitor, has multiple potential relevant beneficial effects, including that in humans, it improved BBB integrity and vasodilation, reduced vessel stiffness[55] and inflammation[51]; in models, it improved motor/cognitive function, reduced infarct volume, increased myelin repair via improved oligodendrocyte precursor cell maturation, and astrocyte-to-neuronal energy transfer.[56] Cilostazol trials include >6000 patients in Japan, Korea, and China, many with lacunar stroke, but cilostazol is little used in Europe or North America.

Because both isosorbide mononitrate and cilostazol combined may be synergistic, they are being tested factorially in the LACI (LACunar Intervention) trials: LACI-1 (ISRCTN12580546), recruited 57 patients in 2 centers to test short-term tolerability, safety, intermediary end points, and trial feasibility[57]; LACI-2 (ISRCTN14911850), planned n=400 in 20 centers, now ongoing, tests longer-term tolerability, trial feasibility, safety, and efficacy on patient relevant outcomes preparatory to large phase III trials.

More generally, hypertension is common in lacunar stroke. Some antihypertensive drugs may have more relevant endothelial effects, and blood pressure targets remain unclear especially in frailer older people, providing ongoing justification for trials (eg, PRESERVE, TREAT@SVDs [Effects

of Amlodipin and Other Blood Pressure Lowering Agents on Microvascular Function in Small Vessel Diseases]) testing specific antihypertensive strategies in specific patient populations. Other agents, such as allopurinol, also have relevant vascular effects and are being tested (eg, XYLOFIST).

Meanwhile, general advice to patients should include common sense: stop smoking, take regular exercise, eat a well-balanced diet, avoid excess dietary salt, and adhere to prescribed treatment for hypertension, hypercholesterolemia, and diabetes mellitus where relevant.

The Future

SVD is not silent, permanent, or untreatable. Importantly, advances made in recent years open new insights, offering new therapeutic targets. SVD is a common cause of stroke and worsens all stroke outcomes. As Hachinksi has said, the commonest form of cerebrovascular disease is dementia not stroke, vascular dementia is the second commonest dementia with SVD as the commonest cause, vascular dysfunction occurs early in Alzheimer disease, and dementia prevention and treatment are currently limited, yet many drugs with known vascular effects might prevent or delay progression of dementia. Stroke, dementia, and cardiovascular experts should combine their strengths because a united approach offers hope not just for stroke but also for dementia.

Acknowledgments

I am grateful to the many mentors, clinical and science colleagues, and early stage researchers with whom I have been fortunate to work for many years, whose collective thoughts have contributed to this work. I was privileged to receive the William M. Feinberg award in the company of many of them and the wider stroke community that continues to work tirelessly toward mitigating the personal and societal global burden of cerebrovascular disease.

Sources of Funding

The work described was funded by the Chief Scientist Office (CZB/4/281), Wellcome Trust (WT088134/Z/09/A), the Row Fogo Charitable Trust (BRO-D.FID3668413), Chest Heart Stroke Scotland (Res14/A157), Medical Research Council (G0701120, G1001245, MR/M013111/1, MR/K026992/1), AgeUK, Alzheimer Society (AS-PG-14–033), European Union Horizon 2020 (PHC-03-15, No 666881), and Fondation Leducq (16 CVD 05).

Disclosures

None.

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KEY WORDS: blood-brain barrier ■ cerebral infarction ■ cerebral small vessel diseases ■ lacunar stroke ■ middle cerebral artery ■ stroke ■ white matter hyperintensities

Stroke
Journal of the American Heart Association

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Stroke. published online June 12, 2018;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628