Watching Small Vessel Disease Grow

Frank M. Faraci

Cerebrovascular disease is a major contributor to loss of brain health, a leading medical, societal, and financial issue worldwide.[1] Although ischemic and hemorrhagic strokes are widely known end-organ effects, diseases of the cerebral circulation are important contributors to mild cognitive deficits, dementia, and an array of neurological and psychiatric disorders.[2,3] Of the risk factors for large and small vessel disease (SVD), aging, and hypertension lead the way, with genetic, metabolic, and behavioral contributors and modifiers (Figure). This Viewpoint briefly highlights features of SVD, its impact on brain health, emerging evidence SVD contributes to diseases not thought to have a cerebrovascular basis, and some suggestions as the field moves forward.

Brain Microcirculation and SVD

SVD is often defined based on clinical features (white matter abnormalities, microbleeds, etc). Here, SVD refers to changes in the microcirculation (small arteries, arterioles, capillaries, and venules), while highlighting select end-organ effects. The pial (brain surface) segment of the microcirculation has been studied widely and continues to provide insight into the biology and pathogenesis of SVD.[4] Interest in SVD has intensified recently because of growing appreciation for its impact on brain health, substantial knowledge gaps, and emerging tools and models to support such efforts. Despite these trends, our understanding of small vessel biology, the pathogenesis, and full impact of SVD is still modest. There are currently no specific therapies for SVD.

How Does Vascular Disease Affect Brain Health?

Mild SVD may be present (but undetected) in cognitively normal subjects. Silent strokes because of SVD are much more common than clinical strokes. As SVD progresses, however, its consequences and impact increase, reducing cognitive reserve, contributing to perhaps 25% of strokes and almost half of all dementia.[3,4] Its contribution to mild cognitive deficits and noncognitive abnormalities suggest SVD is more impactful than previously appreciated. Two patterns are common. The first relates to hemodynamics where changes in global or local cerebral blood flow (CBF) result from integrated structural, mechanical, and functional vascular changes. The second involves integrity and function of cellular barriers including the blood–brain barrier (BBB; Figure).

Cerebral Blood Flow

Vascular disease impacts genomics, proteomics, intracellular and intercellular signaling, vascular tone, structure, mechanics, as well as trophic effects on nonvascular cells (Figure). Endothelial cells are a determinant of resting CBF and mediator of communication between small and large vessels. Signaling pathways activated during neuronal excitation elicit changes in vascular resistance, adjusting delivery of O_2, and glucose with shifting energy requirements. Autoregulatory mechanisms maintain CBF relatively constant despite changes in perfusion pressures during daily activities and in the face of chronic hypertension. Chemoregulatory mechanisms adjust CBF during reductions in O_2 or increases in CO_2.

Reductions in vascular lumen diameter occur because of wall thickening or remodeling or changes in distensibility (because of collagen deposition, elastin fatigue, or fragmentation). Rarefaction of capillaries or other vascular segments can occur (Figure). Collectively, loss of adaptive functional mechanisms along with constraints imposed by structural and mechanical changes result in chronic hypoperfusion. White matter (regions critical for neural signaling) may be particularly sensitive to hypoperfusion and local hypoxia, an issue amplified by the lack of collateral branches in parenchymal arterioles that often supply these regions. Over time, SVD may evolve from endothelial dysfunction and increased wall thickening, to lacunar or microinfarcts, to wall thinning (wall degeneration) and microbleeds. Accumulating evidence suggests chronic hypoperfusion is a prelude and predictor of dementia.[2,5] The relative importance of each vascular change is difficult to quantify. For example, in relation to delivery of O_2 or glucose, is chronic hypoperfusion or impaired neurovascular coupling more important? Does inward vascular remodeling or impaired autoregulation have a greater impact? Last, it is not always clear whether SVD is the primary driver of reduced brain health or a secondary factor that nonetheless contributes to overall disease. Regardless, it is difficult to identify neurological abnormalities where the presence of SVD would not accelerate progression of the disease.

Brain Barriers

The site of the BBB is endothelial cells, anchored to each other via tight and adherens junctional proteins, whereas expressing an array of transporter molecules. BBB function is compromised in diverse forms of disease and injury. Such loss can result in molecular and cellular extravasation, changes in synaptic function and excitability, edema, and reduced clearance of β-amyloid. BBB dysfunction results from tight junctional changes, increased transcytosis, loss of trophic support from pericytes or

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Nonstandard Abbreviations and Acronyms	
BBB	blood–brain barrier
CBF	cerebral blood flow
SVD	small vessel disease

astrocytes, or altered hemodynamics. In the choroid plexus, the blood–cerebrospinal fluid barrier is at the level of the epithelium. In circumventricular organs, molecular and cellular movement is limited by specialized tanycytes and basement membranes.

Beyond Stroke and Cognition

Most forms of neurological and psychiatric disease exhibit vascular abnormalities. This includes migraine, epilepsy, multiple sclerosis, Parkinson disease, depression, autism, schizophrenia, social stress, and traumatic brain injury. SVD has been linked with deficits in gait and balance. Basic and clinical data suggest BBB dysfunction is sufficient to induce seizure. Experimentally deleting NF-κB essential modulator in endothelium causes hypoperfusion, loss of BBB integrity, edema, seizures, changes in social behavior, and anxiety.[6] Such data highlight the far-reaching consequences that can result from changes in a key signaling molecule within a single vascular cell type.

Does the impact of cerebral SVD extend beyond the brain? Increasingly, the answer is yes. For example, the majority of hypertension is because of unknown causes although the renin–angiotensin system and sympathetic nerves are major contributors. BBB integrity is compromised during hypertension, including in the hypothalamus, a key region for autonomic control.[7] Changes in CBF or BBB in regions of the hypothalamus, circumventricular organs, or brain stem may promote hypertension via local effects on microvascular pressure, Po_2, glucose delivery, synaptic activity, or inflammation. Such mechanisms may contribute to neurohumoral, metabolic, and noncognitive changes during diseases such as heart failure. Similar changes in hypothalamic subregions may affect nutritional and leptin regulation and control of body weight and obesity. Dysfunction of choroid plexus or circumventricular organs may affect immune cell trafficking, disrupting glial, and neuronal homeostasis. Thus, depending on the regions involved, brain SVD may be a contributor to hypertension, metabolic, and other systemic disorders.

Moving Forward

Targeted Approaches

The link between SVD and cognition is based predominately on temporal relationships. For both stroke and cognition, there has been a general lack of vascular-specific study and treatment. One exception has been studies of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, a disease caused by mutations in the Notch3 receptor, expressed primarily in vascular muscle in adults.[8] Such work has provided proof of principle in both mice and men that vascular cell–specific changes have a major impact on brain integrity and function. Increased focus on vascular protection may yield results that exceed what can be achieved by neuroprotective strategies.

Better Models

Established and emerging risk factors for SVD are often not incorporated into preclinical models. The lack of

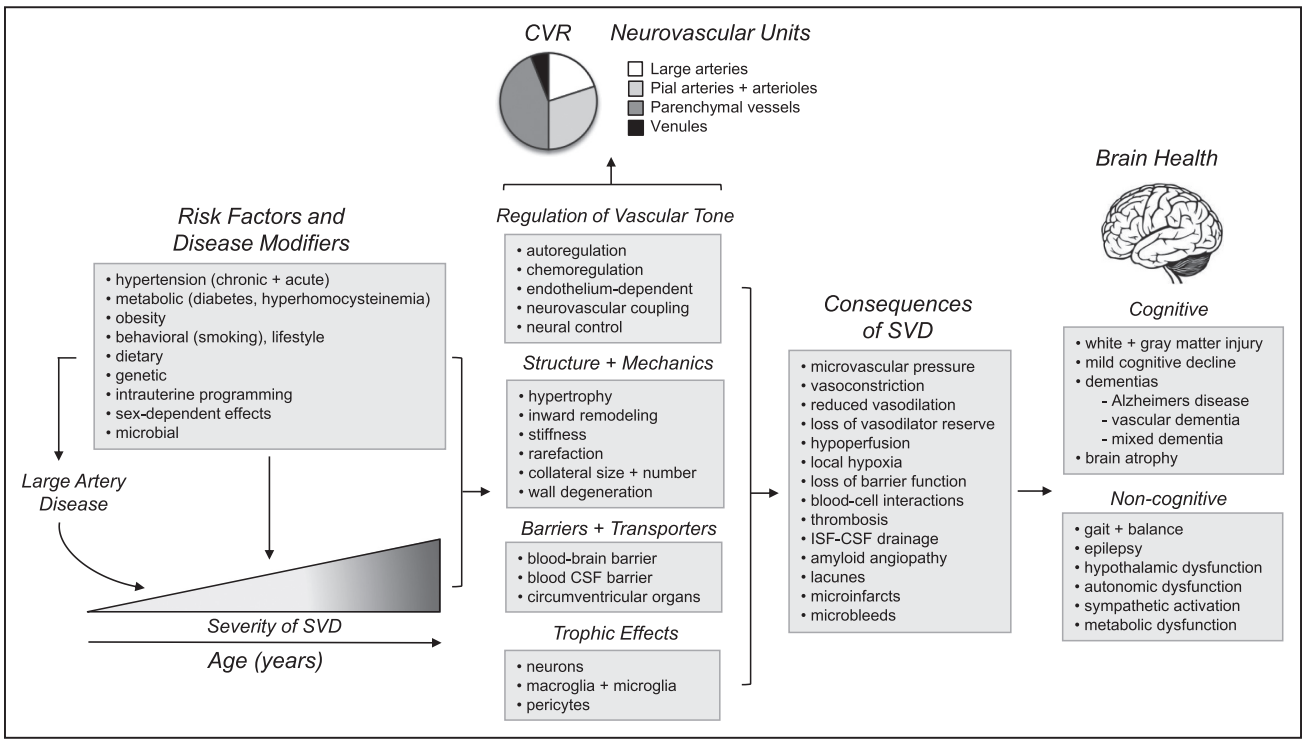

Figure. Schematic of risk factors and modifiers for small vessel disease (SVD), changes in the vasculature, along with consequences of SVD for the microcirculation, as well as brain health and function. The pie graph illustrates the normal distribution of vascular resistance in brain. CSF indicates cerebrospinal fluid; CVR, cerebrovascular resistance; and ISF, interstitial fluid.

incorporation of aging is a key issue. Even with diseases like cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, it is the combination of a genetic mutation and time that is essential for the pathogenesis. Although hypertension is a leading risk factor for SVD, the most appropriate preclinical models are not clear because the mechanistic basis is unknown for most hypertensive humans. A very common hypertensive model involves chronic systemic infusion of angiotensin II. Because of the importance of the renin–angiotensin system as a therapeutic target, such models have relevance. However, models that mimic a greater percentage of patients with essential hypertension (eg, models with normal or low circulating renin), models of resistant hypertension, or models that activate the renin–angiotensin system within specific organs (eg, brain) may have additional or greater relevance.

Twenty-First Century Hemodynamics

Although hemodynamics dictate global and local CBF, these relationships are sometimes ignored or lost in a fog of misconceptions. Despite substantial evidence to the contrary, the recent view by some that capillaries are the major site of vascular resistance is 1 example. The concept of pericyte-induced changes in capillary diameter has become topical. Pericytes often extend thin processes down the long axis of capillaries, occasionally encircling the circumference of individual vessels. Thus, activation of contractile pericytes may reduce local capillary diameter, a concept supported by some studies but not others. When capillary diameter does change, whether it is active or passive is rarely addressed. To illustrate, hypercapnia increases diameter of arterioles, capillaries, and small venules (with no change in systemic arterial pressure), changes accompanied by a doubling of pressure within the same venules.[9] Thus, increases in diameter of small venules (and likely capillaries) can sometimes occur passively because of increased intravascular pressure, not active vasodilation. This distinction is important when defining underlying mechanisms.

Heterogeneity

The vasculature is incredibly heterogeneous, yet most of what is known in relation to biology and regulation of CBF is based on a few regions and blood vessels. As a result, current mechanistic insight and concepts may or may not be applicable to different regions or brain as a whole. Mechanisms of neurovascular coupling vary across brain regions. The answer to basic questions, such as to what extent are small pial and parenchymal arterioles similar in health and disease is unclear because both common and unique features have emerged. Similarly, much work on the BBB is capillary based, even though the BBB is present but heterogeneous in different vascular segments. Venules are a key site of BBB disruption and for immune cell trafficking, for example.

SVD Caused by Large Arteries

Integration and communication between large and small vessels are key for optimal control of CBF. Atherosclerosis of large arteries contributes to SVD by serving as a site of origin of microemboli. Increased stiffness of large arteries augments pulse pressure and pressure transmission, affecting structure and function of downstream vessels. Conversely, inward remodeling of arteries reduces transmission of pressure, protecting capillaries, venules, and the BBB during elevations in systemic blood pressure. However, such remodeling also reduces vasodilator reserve and increases ischemic injury. Microvascular pressure may be a regulated variable.[10] In addition to hypoperfusion, reductions in microvascular pressure may promote neurohumoral activation that contributes to development of hypertension or other physiological responses.[10] With so much vascular resistance upstream, integration between segments is needed to regulate local perfusion pressure and CBF in response to signals originating more distally. This integration is a poorly understood area of vascular biology.

In summary, when cognitive, noncognitive, and other effects are considered as a whole, the burden of SVD in brain is enormous and still growing. The emerging picture suggests preventing or reversing SVD may have substantial effects on brain and even whole body health that is yet to be fully realized.

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