Living Beyond Our Physiological Means
Small Vessel Disease of the Brain Is an Expression of a Systemic Failure in Arteriolar Function: A Unifying Hypothesis

Charlie S. Thompson, PhD; Antoine M. Hakim, OC, MD, PhD, FRCPC

Background and Purpose—It is our premise that the pathophysiology of small vessel disease in the brain is similar to small vessel disease in other heavily perfused tissues and that the presence of small vessel disease elsewhere in the body foretells its presence in the brain as well as its consequences on cognitive function. The hypothesis presented in this article is that small vessel disease is a systemic condition of aging that is exacerbated by vascular risk factors, which results from dysfunction of arteriolar perfusion. This condition, which we term systemic arteriolar dysfunction, affects the brain as well as a number of extracranial systems.

Summary of Review—Recent literature is synthesized to suggest a possible etiology of this condition, highlighting the multiple pathways that may conspire to produce the endothelial and other vascular changes seen in systemic arteriolar dysfunction.

Conclusions—Regardless of the etiology, we emphasize that small vessel disease is a systemic condition with major healthcare consequences, requiring a new paradigm in the way we practice medicine. Because this condition can be decelerated by control of vascular risk factors, doing so may significantly reduce morbidity, mortality, and healthcare costs.

Key Words: brain ischemia • endothelium • pathology • vascular cognitive impairment • white matter disease

A mple evidence now exists indicating that small vessel disease (SVD) in the brain is the most prevalent neurological disorder ever described. Depending on the age group, its incidence is reported to be 6- to 10-fold that of symptomatic strokes. SVD of the brain, alone or in association with Alzheimer disease, is now also recognized as a major etiologic cause of cognitive deficits leading to dementia. Thus, SVD of the brain is a very significant cause of impaired neurological and cognitive functions, and its impact increases with age.

Recent literature also provides numerous examples of the occurrence of SVD of the brain in settings where other organs such as the kidney, liver, retina, heart, and lung have impaired functions. This led us to ask whether a systemic disease may be at play here, one that increases in severity with age, and thus is increasingly prevalent because of the extended life expectancy, affects the penetrating small vessels at the level of arterioles in multiple organs, and is accelerated by vascular risk factors. Our literature review suggests that this may be a reasonable hypothesis. If so, it would lead to a significant reassessment of our understanding of aging and vascular diseases and point us in new research and therapeutic directions.

Prevalence of Brain Small Vessel Disease in the General Population
In their recent review in the Lancet, Vermeer and colleagues report the incidence of silent brain infarcts seen on serial MRI scans to be 3% per year among elderly people. The prevalence averaged over many studies increases with age: from approximately 6% to 7% at age 60 to 28% at age 80. In the National Heart Lung and Blood Institute-sponsored Cardiovascular Health Study, lacunar infarcts ≥3 mm were found in 23% of all subjects >65 years of age, but increased to 43% in subjects ≥80 years of age. Thus, the incidence of covert brain infarcts increases significantly with age. In 89% of individuals with such lesions, there was no clinical history of stroke or transient ischemic attack, emphasizing the covert (but not silent) nature of this condition. The most recent contribution to the prevalence of SVD in the brain indicated that 10.7% of participants in the Framingham Offspring Study with a mean age of 62±9 years had at least one brain infarct on MRI in the absence of any clinical evidence for stroke. Cumulatively, these studies confirm not only that covert brain infarcts are the most prevalent brain disorder ever described, but that their prevalence increases dramatically with age. Thus, age alone is a major risk factor for brain SVD.

Small Vessel Disease of the Brain: Summary of Clinical, Histological, and Imaging Presentations
Vermeer and colleagues reported that the presence of silent brain infarcts at baseline more than doubles the risk of...
dementia with a hazard ratio of 2.26. Silent thalamic infarcts were associated with a decline in memory performance, whereas nonthalamic infarcts resulted in a decline in psychomotor speed. As well, frontal lobe deficits are prominent in vascular dementia, and the presence of impairments in executive function is a significant and powerful predictor of future functional decline in individuals with vascular dementia.

SVD in the brain is characterized by lacunes, which are trabeculated cavities ranging from approximately 0.2 to 15 mm³ in size. They are located almost exclusively in deep regions of the brain with the majority occurring in the pons, the basal ganglia, and/or the internal capsule. Although different types of lacunes are recognized, serial section reconstruction of autopsy specimens has established that most lacunar infarcts lie distal to occlusive lesions of small perforating arteries. These end arteries have no collateral supply and their occlusion results in small, discrete regions of infarction. Lipohyalinosis resulting from fibrinoid necrosis is one of the most common causes of small vessel occlusion. Other less common causes have been described, and lesions due to different causes may have a differential distribution in the brain. Unfortunately, the histopathological description of lacunes at autopsy does not provide much information regarding the initial steps in the arteriolar occlusion and the resulting lacune.

On neuroimaging, SVD in the brain presents as hypodense areas on CT scan or hyperintense ones on MRI. Once the condition is established, SVD in the brain, assessed by imaging, appears to progress in an accelerated fashion. Ovbiagele and his colleagues have shown that if the MRI lesions are already confluent when they are first observed, then their progression over time, assessed by area of brain progressively involved with the disease, is faster than if they are first observed as smaller punctuate lesions.

Hypothesis: Systemic Arteriolar Dysfunction Is a Disease of Aging That Affects Multiple Organs, Results in Brain Small Vessel Disease, and Is Accelerated by Vascular Risk Factors

The literature is increasingly suggesting that when one organ is affected by SVD, it is likely that other organs as well as the brain may also be involved, and cognitive impairment may be an important outcome. We agree with this and show that the simultaneous occurrence of SVD in multiple organs likely increases with age and accelerates in the presence of vascular risk factors. This observation led us to hypothesize that, in fact, we are facing here a condition that affects the arterioles in all vascular beds by the same biochemical process resulting in similar histological abnormalities, which we term systemic arteriolar dysfunction, whose major component is occlusion of the end arterioles. In the interest of brevity, we concentrate our discussion on the retina and the kidney to support the hypothesis that SVD may indeed be a systemic condition.

Association of Small Vessel Disease in the Brain With Retinal and Renal Disease

A number of studies have used data from the Atherosclerosis Risk in Communities (ARIC) Study to establish an association between abnormalities in the retinal vasculature and cerebrovascular disease. Wong and colleagues have shown that retinopathy is associated with poorer cognitive function in middle-aged persons without stroke after controlling for education and other risk factors. It has also been shown that middle-aged persons with cerebral white matter lesions were more likely to have retinal vascular abnormalities and that there is an association between early age-related macular degeneration (ARMD) and cognitive function. Cooper et al reported an association between retinal vascular abnormalities and MRI-defined subclinical cerebral infarcts in the ARIC cohort and suggested that retinal photography may be used to study subclinical cerebrovascular disease. This was supported in a subsequent study by Patton et al. In the population-based Cardiovascular Health Study, there was a modest association between retinopathy and poor cognition and, in persons with hypertension, between retinopathy and dementia. Ding et al have recently confirmed this association. Thus, numerous studies, but particularly those of Wong and his colleagues, have linked the occurrence of SVD in the retina with their occurrence in the brain and cognitive decline.

Another finding from the Cardiovascular Health Study is an association between retinal microvascular abnormalities and a decline in renal function that is independent of the effects of diabetes or hypertension. Chronic kidney disease, particularly vascular nephropathy, is associated with white matter hyperintensity volumes in the brain. In the ARIC Study, individuals exhibiting retinopathy were more likely to develop renal dysfunction than people without these abnormalities. Chronic kidney disease has also been shown to increase the risk of ARMD. The Northern Manhattan Study, a prospective, community-based cohort of which a subset of stroke-free participants underwent MRIs, showed in a multivariate analysis that creatinine clearance of 15 to 60 mL/min was associated with increased volume of white matter hyperintensities. This association of chronic kidney disease with covert lacunar infarction was recently confirmed in a cross-sectional study of community-based elderly Japanese and strengthens the concept that vascular disease of the kidney is associated with brain involvement. More recent studies have also shown that renal vascular disease is associated with cognitive decline. Up to 70% of patients on hemodialysis, ≥55 years of age, have moderate to severe cognitive impairment. A number of studies have also found an association between milder forms of chronic kidney disease not requiring dialysis and cognitive impairment.

Vascular Risk Factors Accelerate Small Vessel Disease in the Brain

If SVD of the brain increases with age and shares involvement with other organs, it is equally clear that the condition is accelerated by vascular risk factors. Beyond aging, arterial hypertension is the most important risk factor for brain SVD. The average prevalence of MRI-defined silent brain infarcts in patients with hypertension with an average age of 69 years was 43% with a range of 20% to 86%. Although in most studies, hypertension is based on isolated blood pressure measurements, the consistency of the studies suggests strongly that hypertension plays a crucial role in the devel-
opment and acceleration of SVD of the brain. Having said that, it must be remembered that patients with brain SVD can be normotensive, supporting our hypothesis that brain SVD is associated with aging. Nevertheless, people with SVD are more likely to have both high blood pressure values and a different circadian blood pressure rhythm, consistent with the demonstration of impaired cerebral autoregulation in patients with hypertension who have severe SVD.

Another condition in which MRI brain lesions of SVD are very prevalent is diabetes. In the summary table reported by Vermeer and her colleagues, patients with this condition had by the average age of 62 years a range of 13% to 82% involvement with SVD in the brain (average 38%). Finally, the other conditions in which the prevalence of SVD of the brain is >30% include patients with ischemic strokes, coronary artery disease, and those with asymptomatic carotid stenosis. Regardless of condition, however, the older the average age of the affected group, the higher the percentage of patients affected by covert infarcts in the brain.

Several authors have made reference to the similarity between the pathophysiology of stroke and that of ARMD. Wong and colleagues have reported that persons with early-stage ARMD had a higher incidence of clinically reported stroke than those without the disease. Ischemia and oxidative stress of the retina are likely early events in macular degeneration. Ikram and his colleagues measured retinal arteriolar and venular diameter in individuals followed 3 to 5 years later by an MRI study of the brain. They reported that larger venular diameters were associated with the progression of cerebral SVD and an increased risk stroke and cerebral infarction. Subsequently, they proved that larger retinal venular diameter is associated with lower arteriolar oxygen saturation and suggested that venular widening reflects a lower oxygen supply to the brain. Similarly, Black and colleagues have recently described venular involvement in brain SVD. Finally, Sakata and colleagues reported that reduction in perifoveal capillary blood flow velocity precedes the increase in retinal thickness and suggested that long-term reduction in blood flow velocity may be the underlying etiology of ARMD.

The risk factors for kidney dysfunction are well known and include hypertension, diabetes, and vascular disease. Kang et al concluded that glomerular and tubulointerstitial scarring correlate directly with the loss of the microvasculature. Recent studies have shown that measures of renal function such as serum levels of creatinine are strong predictors of risk of stroke and cardiovascular events in the elderly.

Finally, our hypothesis does not exclude the possibility that SVD in one organ might accelerate the involvement of other organs mediated through the release of certain factors or the aggravation of common risk factors. For instance, Iadeola and Davison have reviewed eloquently how hypertension, which may be triggered by brain hypoperfusion, may alter the structure and function of cerebral and other blood vessels, whereas Touyz has reviewed the clinical significance of the signaling molecules associated with hypertension.

Beyond the Brain, the Retina, and the Kidney

As suggested, we limited our literature review to the retina and the kidney out of expediency, but cognitive impairment is known to occur in other conditions in which the primary pathology is thought to be vascular. A recent report suggests that 25% to 50% of patients with heart failure have cognitive impairment. Bokura and colleagues reported that patients with metabolic syndrome have associated silent ischemic brain lesions, whereas their myocardium metabolizes glucose anaerobically and its small vessels have thickened walls and are markedly narrowed. Diabetes is also a known risk factor for vascular dementia. These associations make the link between vascular disease and involvement of the brain with SVD even more relevant.

**Histological Findings in the Brain and Extracranial Organs Involved With Small Vessel Disease**

The vast majority of lacunes associated with SVD are found in the basal ganglia, thepons, or the periventricular white matter. These anatomic regions are served by vessels that are of similar small diameter, tend to arise directly from large arteries, and have few, if any, branches or anastomosing vessels. Few lacunes are found in better perfused areas of the brain. Thus, SVD likely arises from dysfunction of arterioles leading to an obstruction that cannot be mitigated by collateral perfusion. A universal feature of SVD and other conditions associated with cognitive impairment is a thickening of the basement membrane of arterioles and capillaries. Other microvascular abnormalities reported in the studies referred to here are perivascular deposits of collagen (fibrosis), membranous inclusions in the basement membrane, which often splits and is partially duplicated, and atrophy of small vessels with amyloid deposits. Also noted is the replacement of the smooth muscle cells of arterioles by fibrohyaline material. Rosenblum distinguishes fibrinoid necrosis from hyalinization of the vessel wall and confirms that the former appears identically in many arteriolar beds. The resulting thickening of the arteriolar wall and narrowing of the vascular lumen eventually lead to occlusion. A popular hypothesis is that in the brain, these microvascular abnormalities result in an inability of the blood vessels to maintain and autoregulate cerebral blood flow and therefore predispose small regions of the brain parenchyma served by each vessel to ischemia. A number of observations also suggest that vascular leakage is associated with SVD in the brain (reviewed by Wardlaw et al), and damage to the blood–brain barrier has been reported in several other conditions associated with cognitive impairment.

A common feature of aging in the kidney is the presence of hyaline leading to arteriolosclerosis, a vascular lesion thought to be due to the accumulation of various serum proteins extending into the subendothelial space and media. The hyaline deposits may or may not obstruct the lumen of the vessels, but even nonobstructive hyaline arteriolosclerosis is a morphological correlate of loss of autoregulation and the creation of hypoxic microenvironments, and because hypoxia itself is a profibrinogenic stimulus, it has been suggested that hypoxia is responsible for the initiation of chronic kidney disease.

The extensive review by Green on the histopathology of ARMD points to the development of basal deposits as the
early morphological hallmark of ARMD, which become ophthalmoscopically detectable with the appearance of changes in the pigment epithelium, soft drusen formation, and choroidal neovascularization. Importantly, this review points to the widespread deposition of collagen, with its distinct periodicity, in the basal laminar deposits. Thus, there are important similarities in the histopathological appearance of the small vessels in the 3 organs we selected, all of which are exquisitely dependent on adequate perfusion for optimal function, suggesting a common etiology as an explanation for their common involvement in clinical studies.

Metabolic Pathways Implicated in the Etiology of Small Vessel Disease

Endothelial dysfunction has been proposed as an early event in SVD\textsuperscript{57,80–82} and other fibroproliferative diseases.\textsuperscript{73–85} When the endothelium is damaged, a complex inflammatory and genomic response initiates a positive feedback cycle of injury, immunologic induction, and amplification. The Figure shows some of these metabolic events in the brain, but some of the pathways shown may also exist in other organs affected by SVD. Increased expression of hypoxia-inducible factor 1 is a well-studied response to lower oxygen levels in many tissues. Hypoxia-inducible factor 1 regulates the transcription of hundreds of genes in a cell type-specific manner and acts to promote survival under unfavorable conditions. However, recent studies have shown that hypoxia-inducible factor activation can also promote tissue fibrosis.\textsuperscript{86–88} Other multifunctional cytokines upregulated in ischemia and, in a variety of other pathological conditions, are members of the transforming growth factor beta (TGF-\(\beta\)) family.\textsuperscript{89,90} In the brain, TGF-\(\beta\)1 has neuroprotective functions under some conditions;\textsuperscript{91,92} however, chronic overproduction may promote microvascular degeneration.\textsuperscript{93} TGF-\(\beta\) is also a key mediator of fibrosis in a variety of tissues and has been shown to induce expression of components of the extracellular matrix and other genes that act to regulate the composition of the extracellular matrix.\textsuperscript{94} Thus, the etiology of SVD in the brain may have mechanisms in common with the etiology of fibrosis in other tissues.

The extensive deposition of collagen and other extracellular matrix components that is characteristic of fibrosis is thought to be the result of deregulation of fibrogenesis, a normal part of the wound healing response that occurs in almost all tissues after exposure to a destructive stimulus. In the brain, it is presumed that this then results in an inability of the blood vessels to maintain and autoregulate cerebral blood flow and therefore predisposes to ischemia,\textsuperscript{95} leading to localized ischemic areas of necrosis and cavitation (ie, lacunar infarction) or diffuse rarefaction.\textsuperscript{96} The mechanism of infarction is related either to occlusive thrombosis (perhaps exacerbated by the hypercoagulable state associated with essential hypertension)\textsuperscript{96} or to a nonocclusive poststenotic hypoperfusion.\textsuperscript{97}

A feature common to all fibrotic tissue studied is the presence of activated, collagen-secreting, \(\alpha\)-smooth muscle actin expressing myofibroblasts. Recent studies have established multiple sources for these cells with the proportion of cells from each source varying from tissue to tissue. Circulating bone marrow-derived fibrocytes are rapidly recruited to damaged tissue and perform a variety of functions in wound repair.\textsuperscript{98} They respond to TGF-\(\beta\) by expressing the specific myofibroblast marker, \(\alpha\)-smooth muscle actin, and participate in wound healing by secreting Type I collagen, matrix metalloproteinase-9, and a host of signaling molecules. This leads to positive feedback loops that accelerate vascular compromise. Studies of fibrosis in a variety of tissues have established that collagen-secreting cells may also derive from resident epithelial cells by way of a mechanism termed epithelial–mesenchymal transition.\textsuperscript{99} Epithelial–mesenchymal transition is involved in inducing the formation of fibroblasts after injury.\textsuperscript{100} Under the influence of combinations of cytokines, including TGF-\(\beta\), epithelial cells begin to secrete matrix metalloproteinases that degrade the extracellular matrix.\textsuperscript{101,102} They downregulate the expression of
proteins that form tight junctions and upregulate expression of proteins required for the formation of filopodia and lamellipodia as they become motile myofibroblasts. These cells then participate in the extensive remodeling of the extracellular matrix that is characteristic of fibrosis. Experimental evidence has accumulated suggesting that endothelial cells may also undergo a transition to a motile, collagen-secreting mesenchymal cell type. Endothelial-to-mesenchymal transition has been reported to contribute to cardiac fibrosis and to the vascular remodeling initiated by pulmonary hypertension. Thus, the pathophysiology of SVD is complex involving many interacting pathways.

Questions, Some Answers, and Messages Arising From This Hypothesis

Our hypothesis that SVD is an expression of a systemic condition, which becomes more prevalent with advancing age and is accelerated by vascular risk factors, can result in a number of research questions and brings to mind new investigative ideas. If the hypothesis is proven by further research at the preclinical level, then certain clinical messages will be worth considering, and new therapeutic approaches may arise, which we discuss subsequently.

New Preclinical Research Directions

There are preliminary animal models in which SVD has been described in certain vascular beds, but they need to be further developed. An interesting way of testing the hypothesis advanced here would be to examine the vascular beds in multiple organs simultaneously in aged rodents, with and without superimposed vascular risk factors, and combine this exploration with cognitive evaluation. If systemic arteriolar dysfunction is indeed a consequence of aging, then it would be worthwhile to test some of the etiologic concepts advanced in this review. Would blocking TGF-β improve arteriolar function in the setting of SVD? Can the rate at which collagen accumulates in the setting of SVD be modulated? To develop targets for the eventual treatment of vascular cognitive impairment, it will be important to identify the source of collagen-secreting cells as well as the identity and source of cytokines and other signaling molecules that contribute to the progression of the condition. The role of inflammation in the progression of systemic arteriolar dysfunction is an important area of further study as has already been suggested.

Several animal models of ARMD have been developed, and they may suggest ways of approaching the development of models of brain SVD. One model of ARMD was obtained by immunizing mice with mouse serum albumin adducted with carboxyethylpyrrole, a hapten present in drusen and plasma from ARMD-affected individuals. The immune system of the mice responded to this by depositing complement below the retinal pigment epithelium with lysis of some of these cells, releasing cytokines. These in turn triggered movement of macrophages, a process that had been explored in other studies. Transgenic mice overexpressing vascular endothelial growth factor have also been used to model ARMD. Finally, Tsubota and colleagues showed that mice deficient in Cu, Zn-superoxide dismutase have features typical of the human form of ARMD.

Thus, there are a number of new ideas that are worthy of laboratory investigation to elucidate the rate and the extent of arteriolar dysfunction as well as its causes.

New Clinical Research Ideas

Our review points to the involvement of multiple organs with SVD, but it is important to remember that understanding this process would have benefits to brain diseases beyond covert cerebral infarction, because many conditions not covered here share similar vascular pathology. Small vessel pathology almost certainly underlies the cognitive impairment occurring in Alzheimer disease, Parkinson disease, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, poststroke cognitive impairment, aging, and hypertension. These are major causes of decreased quality of life in society and elucidating their etiology through testing of the hypothesis we are advancing can have major beneficial consequences.

If proven, our hypothesis should lead to the design of perhaps more complex, but certainly more efficient, clinical trials. If a therapeutic trial is being conducted to test benefits in lacunar infarction, the trial should be extended to investigate benefits to multiple other organs. Does renal dialysis benefit cognitive function and improve retinal pathology? Would statin medications have multisystem benefits? Ning Cheung and colleagues have recently concluded that diabetic retinopathy predicts the incidence of ischemic strokes independently of other risk factors. In support of this relationship, reductions in hard exudates in the retina have been reported in response to serum lipid-lowering agents, treatment with cholesterol synthesis inhibitors, plasmapheresis, and low-density lipoprotein precipitation. As well, macular hard exudates disappeared in 2 patients with diabetes mellitus after the introduction of hemodialysis. One would have liked to see the effect of these trials on other organs. This approach would clearly render trials more complicated requiring extensive data and sample collection, but the benefits would be significant arising from a reduction in the number of trials performed to test benefits to various organs independently.

Two other ideas come to mind in this context. Individuals with severe periventricular white matter lesions and carotid artery stenosis have higher levels of sP-selectin and soluble vascular cell adhesion molecule-1 (sVCAM-1) than those without. Hassan et al have reported that patients with cerebral SVD have elevated plasma levels of markers of endothelial activation and damage such as intracellular adhesion molecule 1, thrombomodulin tissue factor, and tissue factor pathway inhibitor. Van Dijk and colleagues confirmed a relationship between inflammation and the severity and progression of cerebral SVD independent of other cardiovascular risk factors and severity of carotid atherosclerosis. Thus, trials should include the testing of biomarkers that may predict susceptibility to SVD as well as its onset and progression. Second, genetic predisposition is clearly a factor in SVD. In human studies, Klein and colleagues have found that a common variant in the complement factor H gene was strongly associated with ARMD. Other studies have also demonstrated an increase in risk for geographic atrophy and
choroidal neovascularization with the occurrence of single nucleotide polymorphisms in the promoter of Htra serine peptidase 1 and in age-related maculopathy susceptibility locus 2.126 Thus, further studying polymorphisms that can make individuals more susceptible to SVD is an important clinical research direction.

Refining Our Message and Reorganizing Clinical Care of Stroke

The current emphasis that patients should recognize the symptoms of stroke and react by accessing care urgently is appropriate in view of the availability of thrombolytic therapy in the hyperacute phase, yet it is clear that for covert strokes, a condition that has severalfold the incidence of symptomatic strokes, we lack a defined set of warning signs that we can pass on to the public. Perhaps a “senior moment,” if it occurs on a background of vascular risk factors, is an event worthy of rapid medical attention, including cognitive evaluation and MRI examination. This implies that neurologists and other practitioners should become familiar with and adopt efficient cognitive testing tools that they can apply in the office.

At the clinical level, each medical subspecialty may see only the damage done by SVD to its organ of preference. Thus, a neurologist may see adults who are only reporting subtle cognitive difficulties without classical stroke findings and direct their therapy toward cognitive rehabilitation, whereas the ophthalmologist may treat ARM D by attempting to stop the neovascularization that is a consequence, not the etiology, of this condition, but not address the underlying vascular risk factors or explore the damage the same disease etiology, of this condition, but not address the underlying vascular risk factors or explore the damage the same disease

Acknowledgments

We thank our colleagues at the Heart and Stroke Foundation Centre for Stroke Recovery and the Canadian Stroke Network for their support, encouragement, and patience during the writing of this article.

Disclosures

None.

References


Living Beyond Our Physiological Means: Small Vessel Disease of the Brain Is an Expression of a Systemic Failure in Arteriolar Function: A Unifying Hypothesis
Charlie S. Thompson and Antoine M. Hakim

Stroke. 2009;40:e322-e330; originally published online February 19, 2009;
doi: 10.1161/STROKEAHA.108.542266
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/40/5/e322

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/