Published in final edited form as:

Alzheimers Dement. 2007 April ; 3(2 Suppl): S23–S29. doi:10.1016/j.jalz.2007.01.012.

Vascular Cognitive Change: Perspective from Neurology

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1 Introduction

An increasing number of studies have linked traditional cardiovascular risk factors to heightened risk of Alzheimer's disease and dementia, and emerging data from clinical trials provides tantalizing clues that reducing these risk factors may have cognitive benefits. Thus, interventions designed to modify risk factors for cardiovascular disease also have the potential to significantly reduce the burden of dementia and help preserve cognitive vitality in older adults, an issue of growing public health concern given the dramatic increase in people older than 65. A better understanding of the interaction between vascular pathology and cognitive health, and to what degree risk factor reduction might prevent cognitive decline, has therefore assumed a greater urgency.

Many of the primary risk factors for cardiovascular disease are modifiable (e.g., diet, smoking, physical activity, alcohol use and sleep patterns), and these in turn are thought to modulate physiologic risk factors such as blood pressure, lipids, homocysteine, glucose homeostasis, and body weight, among others. While there is a clear need for more well-designed, randomized and controlled clinical trials to clarify the cognitive benefits of risk factor reduction, existing data is convincing enough to warrant the development of public health guidelines aimed at reducing the risk of late-life cognitive decline among Americans by improving cardiovascular health. Organizations interested in the health of older people have already moved in this direction. One example is the Alzheimer's Association's public health campaign to reduce the risk of dementia, which focuses in part on reducing risk factors for heart disease. The Centers for Disease Control and Prevention has now joined with the Alzheimer's Association in the Healthy Brain Project (HBP), which has similar but broader goals. An expert working group for the HBP has identified cardiovascular health as one of two factors (along with physical activity, which obviously impacts cardiovascular health as well) for which enough data exists to begin to develop translational programs that apply the scientific knowledge to public health recommendations for maintaining cognitive vitality.

The question of how much of the current burden of dementia is attributable to vascular disease has been a vexing one. Historically, the term "hardening of the arteries" was often used in association with senile senescence, suggesting that the pathological basis was due to vascular changes that deleteriously affected blood flow to the brain, just as vascular pathology could lead to blockages affecting cardiac tissue. In the 1980s and 90s, fueled by the discovery of the amyloid precursor protein (APP) and the development of animal models that elucidated the relationship between amyloid plaque burden and Alzheimer's-like symptoms, the focus of

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scientific research on dementia shifted to amyloid build-up as the putative pathogenic process in the disease. Now, the research pendulum appears to be swinging back toward a heightened consideration of vascular changes, as more scientists raise the question of what role vascular disease plays in the pathology and cognitive impairments typical of Alzheimer's and other dementias. The question is important both to the development of appropriate, well-targeted intervention programs designed to prevent cognitive failure and to the treatment of dementia.

2 Vascular risk factors

Epidemiological studies over the last two decades (reviewed elsewhere in this supplement) have revealed a number of cardiovascular risk factors associated with cognitive impairment and dementia. These include modifiable or “lifestyle” factors as described above, nonmodifiable factors (e.g., age, genetic risk factors), and disease-related factors (e.g., hypertension, diabetes, previous stroke or transient ischemic attack (TIA), carotid disease, peripheral vascular disease, and aortic status).

2.1 Lessons from CABG

Studies investigating the cognitive effects of coronary artery bypass surgery (CABG) have provided clues to the relationship between vascular changes and cognitive function. A number of studies have reported cognitive dysfunction in patients following cardiac procedures, including deleterious short- (within a month of surgery) and long-term effects (1-5 years post-surgery)¹. It is widely assumed that cognitive decline is attributable to the use of the cardiopulmonary bypass pump, yet controlled studies are lacking, leaving it unclear whether cognitive change is a result of the cardiopulmonary bypass procedure, the surgery itself, general anesthesia, or underlying vascular pathologies. Recent data suggests that patients who undergo CABG – who are clearly at one end of a spectrum of vascular pathology just by nature of the fact they have enough coronary artery disease to warrant bypass surgery -- may already have a degree of cognitive impairment even prior to surgery.

Table 1 summarizes the prevalence of the major risk factors for cerebrovascular disease between two populations of CABG candidates, contrasting studies conducted 20 years apart^{2,3}. The data suggest that the prevalence of hypertension has doubled, while the prevalence of diabetes mellitus and previous stroke has roughly tripled. Carotid bruits have also become more common, rising to 10% from 6%. At the same time, the mean age of individuals for whom bypass surgery is indicated has risen from 52 to 64 years of age. This comparison demonstrates how this population has changed over time, with patients generally being older with more comorbidities – the very factors we associate with vascular disease of both the heart and the brain.

Based on these estimates of risk factor prevalence in candidates for CABG, it has been possible to develop predictive models that estimate the probability of having a post-CABG stroke or encephalopathy (see Figure 1) based on age and other risk factors⁴. The model suggests that in “worst case” scenarios – patients over age 75 who have had a previous stroke or TIA, have one or more carotid bruits, and are hypertensive and diabetic – the risk of having a serious complication following CABG is greater than 50%. This is more than double the risk in a person of similar age with previous stroke but no evidence of carotid bruits, hypertension, or diabetes.

To define the nature of cognitive change and neurological problems following bypass surgery in a controlled manner, we are currently evaluating subjects in a nonrandomized study comparing four groups: CABG patients; off-pump coronary surgery (who undergo an alternative surgical method that does not rely on the cardiopulmonary bypass machine); nonsurgical cardiac controls (NSCC) with diagnosed coronary artery disease but no surgery (some patients in this group do undergo percutaneous cardiac interventions), and heart-healthy

controls (HHC) with none of the previously mentioned risk factors for vascular disease. Off-pump patients were included to try to clarify whether cognitive changes might be due to non-specific effects of major surgery with anesthesia as opposed to effects of the bypass pump itself.

Subjects were evaluated at baseline (preoperatively, in the case of surgical patients), 3 months, 12 months, and 3 years. A 5-year evaluation is underway. In a previous report of this study⁵, we found lower baseline scores on a range of cognitive tests in the groups with coronary artery disease (CAD), compared to heart-healthy controls. Figure 2 shows the results of baseline tests on a range of cognitive domains from this ongoing study, including a language test (Boston Naming Test), a verbal memory test (Rey Auditory Verbal Learning Test), a task measuring psychomotor speed (Grooved Pegboard), and a test of executive function (Trailmaking Test). These results suggest that CABG candidates already have a mild degree of impairment at the time they undergo surgery. However, rather than being generalized to all cognitive domains, the results reveal a pattern of cognitive impairment suggestive of subcortical vascular disease.

This conclusion is based on previous work from a number of different research groups that have identified neuropsychological parameters for the purposes of clinically differentiating between Alzheimer's disease and vascular dementia. The emerging view is that patients with vascular disease typically have relatively well-preserved recognition memory and language, but have deficits in psychomotor and motor speed and in executive functions. This pattern is sometimes referred to as a “subcortical” impairment.

Notably, there was no evidence that CABG patients differed in cognitive test performance from control groups with CAD over a 1-year follow-up period. These results underscore the need for enrolling appropriate control groups in order to accurately interpret longitudinal changes in cognitive performance following bypass surgery.

3 Vascular pathologies

Various terms are used to reflect different levels of cognitive impairment due to vascular pathology, including “vascular dementia”, “vascular cognitive impairment”, and “vascular cognitive disorder”. These terms imply a spectrum of disorders that may result from distinct or overlapping pathological processes, including post-stroke dementia, mixed dementia (vascular disease and Alzheimer's disease), and what has been termed “subcortical small vessel ischemic disease.”

3.1 Post-stroke dementia

Several studies have investigated the long-term cognitive consequences of stroke. A study of ischemic stroke based on the Columbia Stroke Registry⁶ was one of the first; it examined the frequency of dementia in a cohort of 251 patients age 60 and over who were hospitalized with acute ischemic stroke but not apparently demented prior to stroke. At 3 months post-stroke, 26.3% of the patients met DSM-III-R criteria for dementia. In subjects over 80 years old, the incidence of dementia rose to 52%, compared to only 16% in a matched community control group consisting primarily of subjects' spouses. This was one of the first studies to suggest a progressive cognitive decline following stroke, a decline that often progresses to a dementia syndrome.

A study of similar design, the Helsinki Stroke Study⁷, evaluated the frequency of cognitive decline and dementia 3 months after ischemic stroke in a large cohort of 451 hospitalized patients, aged 55 to 85. Using a standard battery of diagnostic criteria and neuropsychiatric testing, the authors determined that 20% of subjects overall met the DSM-III-R criteria for

dementia. The proportion rose to 26% in subjects 75 to 85 years old. Among those with dementia, 40% had exhibited cognitive decline prior to the ischemic stroke.

These results have raised the question as to whether post-stroke dementia occurs in a brain that is normal prior to stroke. The answer emerging from recent studies is that most of the patients with post-stroke dementia had some degree of cerebrovascular disease prior to the stroke, which presumably compromised cognitive function to some degree. The presumption – which needs to be proven with further studies – is that this at-risk group has had either repeated undiagnosed silent infarcts, or they have some other vascular pathology that has both raised the risk for a major stroke and increased the probability of progressive cognitive dysfunction after stroke.

The incidence of silent strokes is one important factor that complicates the ability to determine if post-stroke dementia occurs in a normal brain, because an individual may appear “normal” when in fact they have suffered silent strokes with no apparent clinical manifestations. In the last 5 years, a few studies have investigated this issue in an attempt to determine the frequency of silent strokes in a given population. The results suggest they are more common than previously thought.

The most comprehensive study to date that has addressed this issue is the Rotterdam Scan Study, which investigated cardiovascular risk factors and silent infarct prevalence in a population-based cohort of 1,077 participants aged 60 to 90⁸. Participants underwent cerebral MRI, and cardiovascular risk factors were assessed by interview and physical examination. The prevalence of silent infarcts vs. symptomatic infarcts by age group was determined (Figure 6). The authors concluded that silent infarcts were 5 times as prevalent as symptomatic infarcts in the general population; that their prevalence increases with age by 8% per year, and that they are more common in women. There was a significant association between hypertension and silent infarcts, but no association was found with other cardiovascular risk factors (e.g., diabetes and smoking). These results illustrate the degree to which silent strokes complicate prediction of post-stroke dementia or cognitive decline, and again underscore the value of MRI data in identifying individuals with previous asymptomatic infarcts who may be at higher risk.

In a follow-up study⁹, the Rotterdam group investigated the association between silent brain infarcts and risk of dementia and cognitive decline in 1,015 of the study participants, who were free of stroke or dementia at baseline. They found that the presence of silent infarcts at baseline more than doubled the risk of dementia after a mean follow-up period of 3.6 years, and accelerated the rate of cognitive decline in elderly persons who did not develop dementia.

Goto et al¹⁰ investigated the presence of silent infarcts in candidates for CABG to better understand the association between pre-surgery MRI finding and post-surgery neurologic dysfunction. Of 421 elderly patients aged 60 and up, 50% had normal MRI, 30% had evidence of “mild” damage from small infarcts, and 20% showed “moderate” damage, presumably from multiple small infarcts or larger lacunar infarcts. Table 2 shows neurological outcomes (stroke and neuropsychological dysfunction) for each group. These results are the best evidence yet for a correlation between pre-existing cerebrovascular disease – much of it unrecognized – and post-bypass cognitive outcomes.

3.2 Mixed dementia

Clarifying the relationship between vascular disease and Alzheimer's disease is critical to better understanding how cardiovascular risk factors influence dementia onset and prevalence. Both pathologies are extraordinarily age-dependent: by the age of 85, 30% to 40% of individuals will have clinically diagnosed Alzheimer's, and the incidence of vascular disease in the “oldest olds” is similar. What then, is the interaction between the two? Do separate pathological processes underlie each, or are they additive?

The Nun Study¹¹ was one of the first large-scale initiatives to address this question. Snowdon et al. examined post-mortem brain tissue of 102 college-educated women whose cognitive function and prevalence of dementia had been previously determined. The authors identified lacunar and larger brain infarcts on autopsy, and quantified senile plaques and neurofibrillary tangles to determine which participants met the neuropathological criteria for Alzheimer's disease. Of the total cohort, 61 subjects met criteria for AD, and 39 had evidence of previous stroke. In the AD group, the rate of dementia of any type varied significantly according to whether or not evidence of a previous stroke was found, from 57% to those without a stroke to 88% in those with stroke. In contrast, only 7% of those without AD pathology (n=41) met diagnostic criteria for dementia, whether or not they had infarcts. These results suggest that people with vascular disease but no evidence of AD pathology have very low rates of dementia, raising questions as to whether and how much vascular pathology worsens the clinical expression of AD.

Several other studies have since examined the interaction of AD and vascular disease, including the Oxford Study¹², which autopsied 103 participants whose cognitive function had been assessed with the Cambridge Cognitive Exam. The presence of stroke was associated with significantly lower cognitive test scores in the group with mild AD (Braak Stage 1 or 2), but made no difference in more severe AD (Braak Stage 3-4 or 5-6). This suggests that cerebrovascular disease significantly worsens cognitive performance in the earliest stages of Alzheimer's disease, but not in later stages. Put another way, in the presence of vascular disease, milder AD impacts cognitive function more severely. This in turn suggests that the two processes are synergistic or additive, though the interactive mechanisms are not known.

3.3 Subcortical small vessel ischemic disease

The association of white matter lesions with vascular disease and risk for cognitive decline or dementia is a similarly not know, despite a large number of published articles that have attempted to correlate white matter pathology with cerebrovascular changes¹³. The literature is inconclusive, with studies variously finding white matter lesions with and without evidence of vascular disease. The impact on cognitive function is also unclear; the combination of white matter lesions and vascular disease is associated with severe cognitive dysfunction in some patients, but other patients with similar pathologies show no signs of cognitive dysfunction. The issue has been difficult to sort out, and may depend upon the location of lesions rather than their presence per se, as suggested by the results of a prospective clinicopathological study of 45 elderly individuals by Kovari et al¹⁴. The authors found no relation between cognitive outcome and either white matter or focal cortical glioses, but did find a significant association between cognitive deficits and microvascular lesions (cortical microinfarcts, periventricular demyelination, and diffuse white matter demyelination).

What is required to help sort out these questions about small vessel disease of the brain? The clinical course of disease does not appear to help explain the underlying pathology, because of the slowly progressive nature of symptoms (as opposed to step-wise). Patient assessment with appropriate neuropsychological tests, including tasks measuring motor and psychomotor speed, do appear to help differentiate vascular disease from Alzheimer's disease, as discussed above, but many studies have not employed these kinds of tests. Brain imaging, in conjunction with detailed cognitive testing, offers the best opportunity for sorting out these issues, particularly techniques that enable measurement of the brain's vascular status, including brain perfusion, better local discrimination of cortical microinfarcts (i.e., with high-resolution imaging), and better characterization of white matter tracts (i.e., with Diffusion Tensor Imaging). An important research goal moving forward, then, is to continue to develop imaging techniques that can distinguish these pathologies and correlate them with cognitive outcomes.

This is also relevant to those candidates for CABG who might have asymptomatic vascular disease going into the procedure.

4 Treatment of vascular change/dementia

4.1 Treating risk factors

Given the increasing number of published studies suggesting that traditional cardiovascular risk factors also increase the risk of dementia and cognitive decline, it is reasonable to ask whether treating risk-conferring conditions (e.g., smoking, diabetes, hypertension, etc.) can delay the progression of cognitive dysfunction. A number of population-based studies have examined this (reviewed elsewhere in this supplement). Here, we briefly review findings from a few studies that may provide clues to the interaction of vascular disease and Alzheimer's based on the outcomes of therapeutic interventions designed to modify physiological risk factors.

4.1.1 Hypertension—A recent review of the literature on cognitive health¹⁵, conducted as part of the NIH Emotional and Cognitive Health Project, cited hypertension as the cardiovascular risk factor most robustly linked to cognitive decline based on epidemiological data. There is also some evidence from observational studies that treating hypertension reduces risk of dementia, but the results are mixed. For example, Qiu et al¹⁶ found that in a community-based cohort of 947 dementia-free individuals age 75 and older, both high and low blood pressure was associated with an increased risk of Alzheimer's disease, and that antihypertensive treatment decreased the risk. Data from Peila et al¹⁷ suggest that treating elevated blood pressure in midlife may reduce the risk for cognitive impairment later on.

Results of randomized clinical trials examining whether antihypertensive treatment can reduce cognitive decline are also mixed. In a follow-up study to the Syst-Eur Study, a placebo-controlled, double-blind randomized trial, Forette et al¹⁸ found that long-term antihypertensive therapy reduced the risk of dementia by 55%, compared with controls. This study supports the emerging view that when begun early, antihypertensive treatment can reduce dementia risk, but blood pressure treatment in older individuals may have little benefit for cognitive outcomes. Tzourio et al¹⁹ also found positive results for dementia and cognitive decline in a double-blind, placebo-controlled trial with 6,105 participants with prior stroke or transient ischemic attack, who were randomized to receive either combination therapy with an ACE inhibitor (perindopril) and a diuretic (indapamide), or placebo. During a mean follow-up of 3.9 years, dementia was documented in 6.3% of the treated group vs. 7.1% of the placebo group, a relative risk reduction of 12%. Cognitive decline occurred in 9.1% of the actively treated group vs. 11% of the controls, a relative risk reduction of 19%. Notably, 26% of the participants had recurrent stroke, and it was this group that determined the benefit. In the absence of recurrent stroke, there was no clear effect on either dementia or cognitive decline.

In contrast, Lithell et al²⁰ found no difference in cognitive outcomes in a post-hoc analysis of 2,098 participants who had received either placebo or candesartan, an angiotensin-II antagonist, as part of a prospective controlled trial. In a follow-up analysis of the data from all 4,937 participants, Skoog et al²¹ examined whether baseline cognitive function affected outcomes, finding that participants with lower cognitive function (defined as MMSE score of 24-28) at the time of study enrollment had a higher incidence of dementia than those with higher cognitive function (MMSE score of 29-30). MMSE scores declined less in the treated group who had lower baseline cognitive function.

A similarly ambiguous picture is emerging from the results of intervention studies examining whether treatments for other cardiovascular risk factors, including statins, nonsteroidal anti-inflammatory drugs, and aspirin, have a cognitive benefit. In the case of statins, the early

promise hinted at by observational studies that linked use of the drugs for hypercholesterolemia to decreased AD risk has largely not been borne out in controlled studies (see for example 22, 23.) Two large randomized trials are underway that may help settle the question.

4.1.2 Vascular disease or AD?—The central questions of whether, and to what degree, a patient has vascular disease, AD, or some mix of each are major confounding factors in any intervention trial aimed at reducing dementia and cognitive decline, and may explain the mixed results from antihypertensive and statin trials. There is also a clinical problem: should a patient with vascular cognitive change be treated with the same drugs as a patient with Alzheimer's disease? No drug is currently indicated for vascular dementia, but it is not uncommon for AD drugs to be used. There is some evidence that the cholinesterase inhibitors, donepezil and galantamine, may be beneficial to patients with vascular disease, but the data is limited to two randomized, controlled studies in both cases (see 24 and 25 for reviews). Data on the efficacy of memantine in vascular disease is also lacking; pooled data from two six-month studies suggest the drug has a small beneficial effect on cognition and behavior, but not on global measures of clinical improvement²⁶. Low-dose aspirin therapy might seem like a logical choice for vascular disease, but there is very little data supporting a benefit in this population (see for example 27). These observations underscore both the need for further studies and the importance of better defining AD, VD, and mixed dementia in clinical trial populations.

5 Preventative interventions

In each major category of vascular dementia – post-stroke dementia, mixed dementia and subcortical small vessel ischemic disease – the available data points to some obvious intervention strategies. In post-stroke dementia, the key is clearly to prevent further strokes. Public health measures aimed at reducing stroke have had success in reducing stroke rates nationally, so rigorous intervention in people who have had strokes could have a significant impact on post-stroke dementia. In mixed dementia, the goal is not only to prevent damage from infarcts, but also to prevent ischemic small vessel disease. Preventing small vessel disease is also critical to reducing subcortical small vessel ischemia, but it is not clear yet just how best to do that, in part due to the lack of good outcome measures in terms of structural/functional brain changes.

6 Summary

In summary, the interaction between vascular changes and Alzheimer's disease is a critical question that remains to be fully elucidated. Based on the evidence to date, it is logical to assume that any given individual with dementia may have some degree of vascular pathology and some degree of AD pathology. Current diagnostic paradigms do not go far enough in terms of differentiating underlying pathologies; only brain imaging – MRI in particular – can reveal subsymptomatic cerebrovascular changes. Similarly, there is scant evidence-based data to guide clinicians in the treatment of vascular dementia or mixed dementia that may be primarily a result of, or worsened by, vascular pathology. The existing data does suggest that preventing further cerebrovascular disease – whether silent or symptomatic stroke or small vessel disease – is one clear strategy for intervening to potentially reduce the burden of cognitive impairment and dementia.

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Fig. 1.

Probabilities of either stroke or encephalopathy following coronary artery bypass graft (CABG) by risk factor and risk factor combinations.³ Relative probabilities (in % of CABG patients) are based on risk factor prevalence data shown in Table 1.

Abbreviations: CB, carotid bruit; DM, diabetes mellitus; HTN, hypertension

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Fig. 2.

Baseline cognitive test results from an ongoing longitudinal study designed to better define the nature of cognitive changes in patients undergoing CABG in comparison to non-CABG patients or controls. Results suggest a pre-existing pattern of cognitive changes in CABG candidates, who are presumed to have significant cerebrovascular disease, that generally spares language (a) and memory (b) abilities but more strongly affects motor/psychomotor speed (c) and executive function (d).⁴

Abbreviations: CABG, coronary artery bypass graft; HC, healthy controls; NSC, non-surgical controls; OPCAB, off-pump coronary artery bypass

Fig. 3.
Prevalence of silent vs. symptomatic infarcts by age, from the Rotterdam Scan Study [8].

Table 1

Prevalence of risk factors for cerebrovascular disease among CABG patients.

<u>Risk factors</u>	<u>Duke 1983¹</u>	<u>JHH 2003²</u>
HTN	38%	77%
DM	10%	36%
CVD/CVA	2%	6%
CB	6%	10%
Mean age	52 yrs.	64 yrs.

Abbreviations: CABG, coronary artery bypass graft; CB, carotid bruit; CVA, cerebrovascular attack; CVD, cerebrovascular disease; DM, diabetes mellitus; HTN, hypertension; JHH, Johns Hopkins Hospital

Table 2Postoperative neurological outcomes by pre-operative MRI status¹⁰

MRI findings	CVA	NP
Normal [n= 212]	1.4%	7%
Small infarcts [n= 126]	5.6%	13%
Multiple infarcts [n= 83]	8.4%	20%

Abbreviations: CVA, cerebrovascular attack; MRI, magnetic resonance imaging; NP, neuropsychological dysfunction