

# Risk factors for vascular dementia: Hypotension as a key point

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**Abstract:** Physiologically, the cerebral autoregulation system allows maintenance of constant cerebral blood flow over a wide range of blood pressure. In old people, there is a progressive reshape of cerebral autoregulation from a sigmoid curve to a straight line. This implies that any abrupt change in blood pressure will result in a rapid and significant change in cerebral blood flow. Hypertension has often been observed to be a risk factor for vascular dementia (VaD) and sometimes for Alzheimer disease although not always. Indeed, high blood pressure may accelerate cerebral white matter lesions, but white matter lesions have been found to be facilitated by excessive fall in blood pressure, including orthostatic dysregulation and postprandial hypotension. Many recent studies observed among other data, that there was a correlation between systolic pressure reduction and cognitive decline in women, which was not accounted for by other factors. Baseline blood pressure level was not significantly related to cognitive decline with initial good cognition. Some researchers speculate that blood pressure reduction might be an early change of the dementing process. The most confounding factor is that low pressure by itself might be a predictor of death; nevertheless, the effect of low blood pressure on cognition is underestimated because of a survival bias. Another explanation is that clinically unrecognized vascular lesions in the brain or atherosclerosis are responsible for both cognitive decline and blood pressure reduction. We discuss the entire process, and try to define a possible mechanism that is able to explain the dynamic by which hypotension might be related to dementia.

**Keywords:** vascular dementia, hypotension, low blood pressure, alzheimer disease

As longevity increases worldwide, age-related dementias are burgeoning. Age-related cerebral degenerative changes are coupled therefore with decreased perfusion, usually assumed to be secondary to decreased cerebral metabolic demands (Meyer et al 1999). During aging, the declines in cerebral tissue densities of the gray cortex (polio-araiosis) and of the white matter (leuko-araiosis) reflect neuronal degenerative changes, which progress concurrently with cerebral perfusion declines.

In particular, leuko-araiosis correlates with advancing age, cerebral atrophy, hypoperfusion of white matter, and cognitive impairments (Meyer et al 2000). Leuko-araiosis is detectable in 9%–19% of older ‘normal’ subjects, but is virtually always present in vascular dementia (VaD). Of special interest are the data emerging from the study of Meyer and colleagues (2000): normative subjects destined for later cognitive decline had excessive leuko-araiosis at study entry, suggesting leuko-araiosis is, by itself, a risk factor for cognitive decline.

Thus, the researchers are trying to define the passage between normality, the so-called leuko-araiosis age-related and the excess of the response to the vascular damage, configuring the dementia, as a clinical syndrome. White matter injury may lead to brain atrophy or disrupted cholinergic fibers, but this relation has been incompletely studied. Interestingly, the independent role of asymptomatic lacunar

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infarcts is less clear, with the possible exception of those involving the thalamus. Sensitive and specific definitions of cerebrovascular cognitive impairment are hampered by the fact that cerebrovascular disease is not easily linked to cognitive syndromes, either clinically or pathologically, and the presence of coincident Alzheimer disease (AD) is common. Moreover, it is clear that some individuals may have a slowly progressive, dementing illness caused exclusively by cerebrovascular disease. Some individuals presenting cerebrovascular pathology probably have some component of AD pathology as part of their dementia; this relationship supports the possible interaction between cerebrovascular disease, aging, and the degenerative process.

The literature supports the concept that VaD refers to a broad category of patients, where a multi-faceted cognitive decline is attributed to cerebrovascular disease. It has long been known that cognitive deficits may result from a stroke; yet, only recently, have reports demonstrated that dementia may occur in approximately one-fourth to one-third of stroke cases (Tatemichi et al 1992).

Treatment of vascular cognitive impairment may need to emphasize primary or secondary prevention of vascular risk factors such as hypertension, but some symptomatic treatments are beginning to show modest success.

It should be considered that VaD is not a univocal and unique pathology, and, therefore, even the concept of vascular risk factor should not be schematic, univalent, or used as a single-track way.

## Vascular dementia

The National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) (Roman et al 1993) provided a clinical and diagnostic tool, the so-called NINDS-AIREN criterion. It lists different pathologies, in order to identify patients with different subtypes of VaD: multi-infarct dementia (multiple large and complete infarcts), post-hemorrhage dementia, and subcortical VaD (small-vessel disease). According to NINDS-AIREN, the subcortical VaD (sVaD) is mainly due to lacunar infarct, occurring in distribution of small arterioles, usually in the white matter, basal ganglia, thalamus and pons, or to microinfarct – not seen on macroscopic examination – a small area of cystic or noncystic necrosis surrounded by astrocytes. Incomplete infarct may also be present, due to a selective loss of neurons, myelin, and oligodendrocytes, without cystic necrosis, occurring in the periphery of major artery distribution infarcts (eg, penumbra) or in deep white matter. Incomplete white

matter infarcts are associated with myelin pallor, astrogliosis, and a variable degree of axonal loss. Subcortical VaD now incorporates the old entities of 'lacunar state' and 'Binswanger's disease', and it relates to small vessel disease and hypoperfusion, resulting in focal and diffuse ischaemic white matter lesions and incomplete ischaemic injury (Erkinjuntti 1997; Pantoni et al 2000).

Small vessel dementia (sVaD) is presumably the most frequently pathological condition observed in elderly patients (Akiguchi et al 1997). sVaD is due to infarcts caused by obstruction of intracerebral vessels of arteriolar size, subcortically represented by the long penetrant arteries. The cause may be micro-emboli from heart valves or atheromatous large vessel lesions, particularly carotid stenosis or special vessel diseases such as collagen or inflammatory diseases (Lishman 1997), amyloid angiopathy (especially the hemorrhagic familial forms), and other hereditary angiopathies.

The major known causative factor of VaD is hypertensive angiopathy. It may assume two forms: cortical plus subcortical, and purely subcortical, referred to as Binswanger's disease or progressive subcortical vascular encephalopathy. The lacunar state may be regarded as a milder form of the latter. The two varieties are basically similar, showing mostly small infarcts of lacunar size up to 10 to 15 mm in diameter (Brun 2004).

Binswanger's disease is marked by lacunar infarcts usually measuring 5–10 mm in diameter and situated in the brain stem and central gray nuclei but above all in the frontal white matter, sparing the cortex and u-fibers. In the white matter the lacunes are surrounded by wide areas of incomplete infarcts with partial loss of axons, myelin and oligodendroglial cells accompanied by a mild astrocytic gliosis causing an extensive cortical undermining and disconnection. This change impresses as the main structural substrate for the functional deficit in Binswanger's disease, explaining, for example, frontal symptoms, gait, and incontinence problems. The small lacunes are probably of lesser importance. The loss of white matter is reflected in a widening of especially the frontal ventricular horns. Portions of less severe incomplete white matter infarcts may not be demonstrable on brain imaging, causing clinical-pathological correlation difficulties (Brun 1994; Englund 2000, 2004).

## Risk factors: Blood pressure

There is an overlap of risk factors between VaD and AD, so much so that it raises some serious questions about vascular contributions to AD. Recognition that cerebrovascular disease causing dementia may be modified by treatment

of cerebrovascular risk factors serves as an important tool for investigating various treatments aimed at secondary prevention of vascular cognitive impairment (Brookmeyer et al 1998).

Hypertension has often been observed to be a risk factor for VaD (Hebert et al 2000; Posner et al 2002; Skoog and Gustafson 2002) and sometimes for AD (Prince et al 1994; Launer et al 1995; Hofman et al 1997) although not always (Morris et al 2001). Hypertension leads to changes in arterioles and eventually to arteriolar occlusive disease and then on to infarction. Hypertension's effects on the brain in VaD or AD could also be related to changes in blood flow or blood-brain-barrier integrity. A large number of epidemiological studies show strong associations between elevations in middle-life blood pressure and the prevalence of later life cognitive impairment and dementia. Early evidence suggest that treatment hypertension in the elderly may be quite successful in reducing incident dementia. In the Syst-Eur trial (Forette et al 1998), cognition was primarily assessed by the Mini-Mental State Examination. Treatment with a calcium channel blocking antihypertensive was associated with a nearly 50% reduction in incident dementia amongst approximately 2000 elderly with isolated systolic hypertension. The conclusions of this study, given the high percentage of elderly suffering with untreated hypertension, are that secondary prevention treatment trials such as Syst-Eur might have a substantial impact on cognitive impairment.

The relation between hypertension, its treatment, and severe white matter lesions has been assessed in 10 European cohorts (van Dijk et al 2004). White matter lesions in the periventricular and subcortical regions were rated separately using semiquantitative measures. Increase in systolic blood pressure levels were associated with more severe periventricular and subcortical white matter lesions. People with poorly controlled hypertension had a higher risk of severe white matter lesions than those without hypertension (van Dijk et al 2004).

Recent works, on the contrary, underline a potential negative effect by decreasing diastolic blood pressure level on the occurrence of severe periventricular white matter lesions.

A high pulse pressure is related to arterial stiffness, which might be considered one of its clinical indicator, and it is associated with an increased risk of dementia (Qiu et al 2003). Therefore, it could be postulated that functional changes of the arterial system are involved in the pathogenesis of dementia (Volpe and Scuteri In Press). Two cross-sectional studies have shown a positive correlation between arterial stiffness and cognitive impairment in subjects with nonvascular

(Nagai et al 2004) or vascular (Mizushima et al 2003) dementia. In a recent cross-sectional study, it has been demonstrated that arterial stiffness was associated with a lower cognitive performance independently of traditional cardiovascular risk factors (Hanon et al 2005; Scuteri et al 2005, 2007). A very recent study (Protogerou et al 2007) showed that, in the frail elderly, a value of diastolic blood pressure inferior of 60 mmHg, is associated with radical decrease of survival, independent from large artery stiffness and left ventricular function, suggesting that more rational antihypertensive therapy, not only based on systolic pressure level is needed.

An increased arterial stiffness (Scuteri 2007) tends to annul the proper cushion of the walls, the so-called *Windkessel* effect. The cerebral high resting blood flow implies that vessels are more dilated than in other vascular beds; therefore pulsations may extend more deeply towards the smallest vessels (Nichols et al 2005; O'Rourke and Safar 2005). Increased arterial stiffness is responsible for a disproportionate increase in systolic blood pressure and a relative decrease in diastolic pressure; thus, the consequent higher pulse pressure at any given value of mean blood pressure is likely to cause macrovascular damage (Laurent et al 2003) and microvascular disruption (Nichols et al 2005). Physiologically, cerebral autoregulation allows maintenance of constant cerebral blood flow over a wide range of blood pressure (approximately 80 to 200 mmHg). With aging, there is a progressive reshape of cerebral autoregulation from a sigmoid curve to a straight line. This implies that any abrupt change in blood pressure will result in a rapid and significant change in cerebral blood flow (Moretti et al 2006; Volpe and Scuteri In Press). Since stiffer arterial system implies reduced arterial cushioning function, any hemodynamic changes will result in an exaggerated change in blood pressure levels, and high blood pressure levels are as dangerous as low blood pressure levels in older hypertensive subjects (Volpe and Scuteri In Press). Indeed, high blood pressure may accelerate cerebral white matter lesions (Yamamoto et al 1998; Schmidt et al 1999), but white matter lesions have been found to be facilitated also by excessive fall in blood pressure (Nakamura et al 1995; Kario et al 1996; Watanabe et al 1996; Chamorro et al 1997), including orthostatic dysregulation (Matsubayashi et al 1997) and postprandial hypotension (Kohara et al 1999).

## Hypotension and dementia

The traditional general practice teaches that "the lower the blood pressure is, the better the prognosis". Albeit this, low blood pressure as a predictor of increased mortality has been described in a 5-year prospective study in Finland

(Mattila et al 1988) as well as paradoxical survival of elderly men with high blood pressure (Langer et al 1989).

Interpretations of these so-called J-shaped curves between blood pressure, and mortality have always been viewed with caution and skepticism by epidemiologists and statisticians (Fletcher and Bulpitt 1992; Glynn et al 1995). There are many medical situations (diabetes, cardiac damage, hyposurrealism, and idiopathic) where hypotension is a dominant aspect. Many epidemiological studies confirm that chronic low blood pressure does not by itself imply increased cardiovascular risk after adjustment for possible confounding factors. Chronic low blood pressure has been positively associated with a number of clinical symptoms and psychosomatic distress – including unexplained fatigue, depression, and anxiety – and with minor psychiatric morbidity (De Buyzere et al 1998). A causal relationship between low blood pressure and low mood remains uncertain, but a vicious circle should not be excluded (De Buyzere et al 1998). Zhu and colleagues (1998) tried to define the potential role of blood pressure in cognition. In a community cohort of 924 persons aged >75 years with initially good cognition, they observed that there was a correlation between systolic pressure reduction and cognitive decline in women, which was not accounted for by other factors. Baseline blood pressure level was not significantly related to cognitive decline in that sample with initial good cognition. Zhu and colleagues (1998) also speculated that blood pressure reduction might be an early change of the dementing process (see also literature in Gorelick 1997).

Ruitenbergh and colleagues (2001) found that lower systolic and diastolic blood pressures at baseline were associated with a higher risk of dementia at follow-up. This association was observed across all age strata, in men as well in woman and both in AD and VaD. The authors observed a larger decrease in blood pressure in all age categories of prevalent dementia patients compared with subjects without dementia. Subjects with incident dementia also decreased more in blood pressure level than in persons without dementia. This difference was not statistically significant (Ruitenbergh et al 2001). This may reflect that low blood pressure causes or contributes to dementia or that incipient dementia leads a drop in blood pressure (Ruitenbergh et al 2001). Ruitenbergh and colleagues (2001) suggested that for the first part of the proposition, they observed an inverse association between blood pressure and dementia mainly in subjects, who used antihypertensive medication. This may indicate that their hypertension was longer lasting, and perhaps that these patients were more susceptible to pressure drops, causing inadequate cerebral blood flow. That would be particularly

important in vulnerable areas, such as watershed zones and white matter. A second explanation given by Ruitenbergh and colleagues (2001) was that low pressure might be a consequence of an incipient dementia. It was found that blood pressure was lower in subjects with manifest dementia, and those with dementia, who presented lower pressure, declined more rapidly. The possible explanation given by Ruitenbergh and colleagues (2001) is that several areas are involved in pressure regulation; Burke and colleagues (1994) reported a strong correlation between the decrease of the number of C1 neurones in the medulla oblongata and blood pressure dysregulation in Alzheimer patients.

More recently, Guo and colleagues (1999) tried to examine whether initially low blood pressure is related to the incidence of dementia in a sample of 304 persons, aged 75 to 96 years. The findings showed that compared with individuals with baseline systolic pressure of 140 to 179 mm Hg, those with systolic pressure of 140 mmHg or less had a significantly higher risk of dementia and AD. That was the first study to clearly report an association between relatively low systolic pressure and increased incidence of dementia. Relatively low blood pressure seems to be correlated with dementia even in a preclinical stage. Guo and colleagues (1999) started from the speculation that cerebral blood flow is reduced in dementia patients (Brown and Frackowiak 1991). That was generally thought to be related with reduced metabolic activity of the brain or with a major vascular lesion. The authors hypothesized that the reduction of cerebral blood flow might be related to the impairment of the cerebral autoregulation, secondary to the degenerative disorder. The direct consequence would be a sequential ulterior reduction of blood pressure, due to dysregulation, which might accelerate the lowering of blood perfusion and therefore the underlying degenerative process (Guo et al 1996; Bolster et al 2001; Yamamoto et al 2001; Mehagnoul-Schipper et al 2002; Nilsson et al 2007). Lower systolic blood pressure was associated with cognitive decline and dementia. Earlier history of arterial hypertension was related to an increased risk of impaired cognition and dementia. Nilsson and colleagues (2007) interpreted these results as a potential expression of the frailty and deteriorated vitality of the oldest elderly, in keeping constantly the autoregulation capabilities of the normal brain, and expressed their concern, due to this frailty, on the real impact of lowering pressure in oldest age.

## Our impression

The reason is unknown, but frontal lobes have a metabolism rate under basal condition that is 20% more than that of the



other brain areas (Moretti et al 2006). And it is also well known that age-related cognitive modifications are related to frontal dysfunctions (Levine et al 1997; Esposito et al 1999; Kramer et al 1999), due to a reduction of brain reserve capacity. This brings an aged individual closer to the level of insufficiency where only minor additional lesions may be required to precipitate dementia. The degenerative aging changes, though milder, repeat much of the pathology of AD.

In VaD, especially in subcortical vascular type, there is an accentuated expression of what is found in old age (Moretti et al 2006). The importance of aging in this context is emphasized by the finding that VaD is the most common form of organic dementia after the age of 85. The complete and incomplete white matter infarction, frequently coexisting, would, by virtue of their high prevalence, be the underlying substrate in the recognition of white matter disease (de Reuck 2000), leukoencephalopathy, or leukoaraiosis (Hachinski 1994).

The vessels show a degeneration of the smooth muscle layer, which is replaced by collagen in a hyaline fibrosis, leading to a subtotal luminal occlusion. These arterioles share traits with nonhypertensive lipohyalinosis (Zhang et al 1994), as well as with hypertensive arteriolosclerosis, and may concur with hypertensive changes. Anatomically, the smaller resistance blood vessels undergo degenerative changes consisting of thickening and fibrosis of the media (in muscular arteries) and intima, and patchy degeneration of smooth muscle cells producing luminal narrowing and increased vascular resistance. Although the resting CBF is the same in normotensive and hypertensive individuals, these structural changes limit the capacity of the resistance vessels for maximal vasodilatation and impair tolerance of lower blood pressures, while improving tolerance to hypertension through vasoconstriction of these same vessels. Long-term antihypertensive treatment can reverse these adaptive changes and shift the autoregulation curve back to its normal range, although only limited reversibility occurs in elderly hypertensive patients.

A primary hemodynamic etiology of vascular dementia concerns the cerebral hypoperfusion that affects either the whole brain, the deep central white matter or specific regions that are more susceptible to damage due to focal vascular pathology.

The most common cause of hemodynamic disturbances with a drop in blood pressure is that of cardiovascular failure (Salloway 2003). Cardiac disease and cardiovascular failure contribute considerably to the development of VaD (Salloway 2003), not only through cardiac embolism but

also from the effects of hemodynamic insufficiency. The effects of arrhythmia here will be a cerebral, notably episodic hypoperfusion, extended far along the penetrating arterioles and resulting in deep white matter damage (Salloway 2003). Secondary causes of hypoperfusion are dysautonomias, which constitute the set of disease states in which an abnormality of the autonomic nervous system (ANS) is critical to the pathogenesis. An age-related impairment of the vascular autoregulation due to impaired functioning of the autonomic nervous system can lead to symptom-producing blood pressure lability in the elderly. Additionally, age-related arteriolar changes, including endothelial changes, have been suggested to reduce the baroreflex activity and thereby predispose for deleterious blood pressure falls (Salloway 2003). The prevalence of orthostatic and nonorthostatic hypotension reached 50% in clinically evaluated VaD cases (Salloway 2003; Mirski 2005).

The possible reason that relates lower blood pressure, dysregulation of cerebral blood flow and vascular dementia, is the pivotal role of acetylcholine (ACh). ACh regulates the cerebral blood flow through the parasympathetic innervation of the circle of Willis and of the pial vessels (Vasquez and Purve 1979), and it causes significant arterial relaxation by promoting the synthesis of vasodilator agents (Vanhoutte 1989).

Preclinical research using the spontaneously hypertensive stroke-prone rat model of VaD has shown a significant reduction in the levels of ACh and choline in the cortex, hippocampus, and cerebrospinal fluid compared with normal rats (Kimura et al 2000). When compared with normal rats, spontaneously hypertensive stroke-prone rats have significantly lower levels of acetylcholine in the cerebrospinal fluid (CSF) (Togashi et al 1994). In the latter study, the differences in CSF levels between normal rats and stroke prone rats increased with age, suggesting progressive deterioration of central cholinergic function in hypertensive stroke prone rats.

The cholinesterase inhibitor epistigmine has been shown to improve blood flow in the Sprague-Dawley rat with tandem occlusion of left middle cerebral and common carotid arteries. Epistigmine also enhanced the ischemia-induced rostral shift of cerebral blood flow maximum in the contralateral hemisphere and the redistribution of cerebral blood flow, a phenomenon possibly related to recovery of function (Scremin et al 1997).

As with other types of dementia, the pathological changes observed in patients with VaD appear to be associated with cholinergic deficits. Compared with normal rats, rat models of VaD have shown significantly reduced levels

of the neurotransmitters ACh and choline in the cortex and hippocampus (Togashi et al 1996), which appear to correlate with impaired learning and memory (Togashi et al 1996).

In humans, post-mortem studies have shown that choline acetyltransferase (ChAT) activity is reduced in VaD patients, compared with controls (Wallin et al 1989). Furthermore, clinical studies have indicated that patients with subcortical VaD have significantly lower concentrations of ACh in the cerebrospinal fluid, and that these decreases are strongly correlated with cognitive deficits (Wallin et al 1989). The number of muscarinic cholinergic receptors is also markedly reduced in VaD and mixed dementia patients (Sakurada et al 1990). In addition, the level of ACh in the cerebral fluid of VaD patients is significantly lower than in controls, but is similar to the level observed in AD patients (Szilagy et al 1987).

Very recently, to prove the role of ACh in vessel regulation muscarinic receptors, M5, have been studied. The M5 muscarinic receptor is the most recent member of the muscarinic acetylcholine receptor family (M1-M5) to be cloned. Because M5 receptor mRNA has been detected in several blood vessels, Yamada and colleagues (2001) investigated whether the lack of M5 receptors led to changes in vascular tone by using several *in vivo* and *in vitro* vascular preparations in knockout mice. Strikingly, acetylcholine, a powerful dilator of most vascular beds, virtually lost the ability to dilate cerebral arteries and arterioles in *M5R*<sub>-/-</sub> mice. This effect was specific for cerebral blood vessels, because acetylcholine-mediated dilation of extracerebral arteries remained fully intact in *M5R*<sub>-/-</sub> mice.

Harrison and colleagues (2002) demonstrated that the intensity of the intrinsic signals generated from a brain activated region depends on local vascular density. Moreover, it has been demonstrated that the vascular dilatation responsible for the increase in blood flow evoked by neural activity is propagated in a retrograde fashion to upstream arterioles located outside the activated area (Iadecola et al 1997). This phenomenon termed retrograde vasodilation serves the purpose of dilating upstream arterioles that are critical for regional flow control.

Thus, it can be stated that:

1. The cerebral blood flow is mainly regulated by arterioles.
2. The signal level of brain activation depends on the local vascular density, and mostly on their vasodilatation.
3. In sVaD, arterioles smooth muscle layer is replaced by collagen in a hyaline fibrosis, leading to a subtotal luminal occlusion.
4. ACh intimately regulates the cerebral blood flow through the parasympathetic innervation, and it causes significant arterial relaxation by promoting the synthesis of vasodilator agents.
5. There is a macroscopic reduction of ACh in sVaD.

Therefore, it might be hypothesized that the damage of arteriole causes a reduction of cerebral blood flow. The other macroscopic consequence is the disruption of the cerebral autoregulation. The dysregulation is augmented by the reduction of ACh. These aspects might determine the sensitiveness of old patients, and especially demented patients, to hypotension. Each clinical condition that may lead to hypotension might accelerate the underlying degenerative process.

To determine if hypotension is a cause or a consequence of VaD, further studies will be necessary. The present review raises concern about a risk for the aging or the pathological brain from blood pressure lowering.

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## References

- Akiguchi I, Tomimoto H, Suenaga T. et al. 2007. Alterations in glia and axons in the brains of Binswanger's disease patients. *Stroke*, 28:1423-9.
- Bolster BD, Serfaty JM, Atalar E. 2001. In vivo measurements of pulse wave in small vessels using intravenous MR. *Magn Reson Med*, 45:53-60.
- Brookmeyer R, Gray S, Kawas C. 1998. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *Am J Public Health*, 88:1337-42.
- Brown WD, Frackowiak RSJ. 1991. Cerebral blood flow and metabolism studies in multi-infarct dementia. *Alzh Dis Assoc Dis*, 5:131-43.
- Brun A. 2004. The neuropathology of vascular dementia and its overlap with Alzheimer's Disease. In: O'Brien J, Ames D, Gustafson L, et al. Eds. Cerebrovascular disease, cognitive impairment and dementia. London: Martin Dunitz, pp. 103-16.
- Burke WJ, Coronado PG, Schmitt CA, et al. 1994. Blood pressure regulation in Alzheimer's disease. *J Auton Nerv Syst*, 1994; 48:65-71.
- Chamorro A, Pujol J, Saiz A, et al. 1997. Periventricular white matter lucencies in patients with lacunar stroke: a marker of too high or too low blood pressure? *Arch Neurol*, 54:1284-8.
- De Buyzere M, Clement DL, Duprez D. 1998. Chronic low blood pressure: A review. *Cardiovasc Drugs Ther*, 12:29-35.
- De Reuck J. 2000. White matter disease: anatomical and physiological features in relation to modern cerebral blood flow techniques. In: Pantoni L, Inzitari D, Wallin A, Eds. The Matter of White Matter. Clinical and Pathophysiological Aspects of White Matter Disease Related to Cognitive Decline and Vascular Dementia. Current Issues in Neurodegenerative Diseases, Vol 10. Utrecht: Academic Pharmaceutical Productions, pp. 211-22.
- Englund E. 2000. Neuropathology of white matter disease: parenchymal changes. In: Pantoni L, Inzitari D, Wallin A, Eds. The Matter of White Matter. Clinical and Pathophysiological Aspects of White Matter Disease Related to Cognitive Decline and Vascular Dementia. Current Issues in Neurodegenerative Diseases, Vol 10. Utrecht: Academic Pharmaceutical Productions, pp. 223-46.

- Englund E. 2004. White matter pathology of vascular dementia. In: O'Brien J, Ames D, Gustafson L, et al. Eds. *Cerebrovascular disease, cognitive impairment and dementia*. London: Martin Dunitz, pp. 103–16.
- Erkinjuntti T. 1997. Vascular dementia: challenge of clinical diagnosis. *Int Psychogeriatr*, 9:77–83.
- Esposito G, Kirkby BS, Van Horn JD, et al. 1999. Context-dependent, neural system-specific neuropsychological concomitants of aging: mapping PET correlates during cognitive activation. *Brain*, 122:963–79.
- Fletcher AE, Bulpitt CJ. 1992. How far should blood pressure be lowered? *N Engl J Med*, 326:251–4.
- Forette F, Seux ML, Staessen JA, et al. 1998. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet*, 352(9137):1347–51.
- Glynn RJ, Field TS, Rosner B, et al. 1995. Evidence for a positive linear relation between blood pressure and mortality in elderly people. *Lancet*, 345:825–9.
- Gorelick PB. 1997. Status of risk factors for dementia associated with stroke. *Stroke*, 28:459–63.
- Guo Z, Vintanen M, Fratiglioni L, et al. 1996. Low blood pressure and dementia in elderly people: the Kungsholmen Project. *BMJ*, 312:805–8.
- Guo Z, Vintanen M, Winblad B, et al. 1999. Low blood pressure and incidence of dementia in a very old sample: dependent on initial cognition. *J Am Geriatr Soc*, 47:723–6.
- Hachinski V. 1994. Vascular dementia: a radical redefinition. *Dementia*, 5:130–2.
- Hanon O, Haulon S, Lenoir H, et al. 2005. Relationship between arterial stiffness and cognitive function in elderly subjects with complaints of memory loss. *Stroke*, 36:2193–2197.
- Harrison RV, Harrel N, Panedar J, et al. 2002. Blood capillary distribution correlates with hemodynamic based functional imaging in cerebral cortex. *Cer Cortex*, 12:225–33.
- Hebert R, Lindsay J, Verreault R, et al. 2000. Vascular dementia: incidence and risk factors in the Canadian study of health and aging. *Stroke*, 31:1487–93.
- Hofman A, Ott A, Breteler MM, et al. 1997. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. *Lancet*, 349:151–4.
- Iadecola C, Yang G, Ebner T, et al. 1997. Local and propagated vascular responses evoked by focal synaptic activity in cerebellar cortex. *J Neurophysiol*, 78:651–9.
- Kario K, Matsuo T, Kobayashi H, et al. 1996. Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensive patients: advanced silent cerebrovascular damage in extreme dippers. *Hypertension*, 27:130–5.
- Kimura S, Saito H, Minami M, et al. 2000. Pathogenesis of vascular dementia in stroke-prone spontaneously hypertensive rats. *Toxicology*, 153:167–87.
- Kohara K, Jiang Y, Igase M, et al. 1999. Postprandial hypotension is associated with asymptomatic cerebrovascular damage in essential hypertensive patients. *Hypertension*, 33: 565–568.
- Kramer AE, Hahn S, Gopher D. 1999. Task coordination and aging: explorations of executive control processes in the task switching paradigm. *Acta Psychol (Amsterdam)*, 101:339–78.
- Langer RD, Ganiato TG, Barrett-Conner E. 1989. Paradoxical survival of elderly men with high blood pressure. *BMJ*, 298:1356–1358.
- Launer LJ, Masaki K, Petrovitch H, et al. 1995. The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. *JAMA*, 274:1846–51.
- Laurent S, Katsahian S, Fassot C, et al. 2003. Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. *Stroke*, 34:1203–6.
- Levine B, Stuss DT, Milberg WP. 1997. Effects of aging on conditional associative learning: process analyses and comparison with focal frontal lesions. *Neuropsychology*, 11:367–81.
- Lishman WA. 1997. Cerebrovascular disorders. In: Lishman WA, Ed. *Organic Psychiatry. The Psychological Consequences of Cerebral Disorder*. 3rd ed. Oxford: Blackwell Science, pp. 375–430.
- Matsubayashi K, Okumiya K, Wada T, et al. 1997. Postural dysregulation in systolic blood pressure is associated with worsened scoring on neurobehavioral function tests and leukoaraiosis in the older elderly living in a community. *Stroke*, 28:2169–73.
- Mattila K, Haavisto M, Rajala S, et al. 1988. Blood pressure and five years survival in the very old. *BMJ*, 296:887–9.
- Mehagnoul-Schipper DJ, Colier WN, Hoefnagels WH, et al. 2002. Effects of furosemide versus captopril on post-prandial and orthostatic blood pressure and on cerebral oxygenation in patients  $\geq 70$  years old of age with heart failure. *Am J Cardiol*, 90:596–600.
- Meyer JS, Rauch G, Rauch RA, et al. 2000. Risk factors for cerebral hypoperfusion, mild cognitive impairment, and dementia. *Neurobiol Aging*, 21:161–9.
- Meyer JS, Rauch GM, Crawford K, et al. 1999. Risk factors accelerating cerebral degenerative changes cognitive decline and dementia. *Int J Geriatr Psychiatry*, 14:1050–61.
- Mirski MA. 2005. Pharmacology of blood pressure management during cerebral ischemia. American Academy of Neurology (AAN) Miami, 2005; 5PC-004: pp. 456–69.
- Mizushima Y, Oobasawa H, Yoshida S, et al. 2003. Pulse wave velocity in persons with vascular dementia. *J Am Geriatr Soc*, 51:1329–30.
- Moretti R (Ed). 2006. Subcortical vascular dementia. New York: NOVASCENCE Publisher Inc.
- Morris MC, Scherr PA, Hebert LE, et al. 2001. Association of incident Alzheimer disease and blood pressure measured from 13 years before to 2 years after diagnosis in a large community study. *Arch Neurol*, 58:1640–6.
- Nagai K, Akishita M, Machida A, et al. 2004. Correlation between pulse wave velocity and cognitive function in nonvascular dementia. *J Am Geriatr Soc*, 52:1037–8.
- Nakamura K, Oita J, Yamaguchi T. 1995. Nocturnal blood pressure dip in stroke survivors: a pilot study. *Stroke*, 26:1373–8.
- Nichols WW, O'Rourke MF. 2005. McDonald's blood flow in arteries: Theoretical, Experimental and Clinical Principles, 5th ed. London: Hodder Arnold.
- Nilsson SE, Read S, Berg S, et al. 2007. Low systolic blood pressure is associated with impaired cognitive function in the oldest old: longitudinal observations in a population-based sample 80 years and older. *Aging Clin Exp Res*, 19:41–7.
- O'Rourke MF, Safar ME. 2005. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. *Hypertension*, 46:200–4.
- Pantoni L, Rossi R, Inzitari D, et al. 2000. Efficacy and safety of nimodipine in subcortical vascular dementia: a subgroup analysis of the Scandinavian Multi-Infarct Dementia Trial. *J Neurol Sci*, 175:124–34.
- Posner HB, Tang MX, Luchsinger J, et al. 2002. The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function. *Neurology*, 58:1175–81.
- Prince M, Cullen M, Mann A. 1994. Risk factors for Alzheimer's disease and dementia: a case-control study based on the MRC elderly hypertension trial. *Neurology*, 44:97–104.
- Protogerou AD, Safar ME, Iaria P, et al. 2007. Diastolic blood pressure and mortality in the elderly with cardiovascular disease. *Hypertension*, 50:172–87.
- Qiu C, Winblad B, Viitanen M, et al. 2003. Pulse pressure and risk of Alzheimer disease in persons aged 75 years and older: a community-based, longitudinal study. *Stroke*, 34:594–9.
- Roman GC, Tatemichi TK, Erkinjuntti T, et al. 1993. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN international work group. *Neurology*, 43:250–60.
- Ruitenberg A, Skoog I, Ott A, Aevrasson O, et al. 2001. Blood pressure and risk of dementia: results from the Rotterdam Study and the Gothenburg H-70 study. *Dementia Geriatr Cog Dis*, 12:33–9.
- Sakurada T, Alufuzoff I, Winblad B, et al. 1990. Substance P like immunoreactivity, choline acetyltransferase activity and cholinergic muscarinic receptors in Alzheimer's disease and multi-infarct dementia. *Brain Res*, 521(1–2):329–32.

- Salloway S. 2003. Subcortical vascular dementia: Binswanger's and CADASIL. American Academy of Neurology (AAN) 2003; Honolulu: 8AC.006-2: pp. 1–29.
- Schmidt R, Fazekas F, Kappeller P, et al. 1999. MRI white matter hyperintensities: three-year follow up of the Austrian Stroke Prevention Study. *Neurology*, 53:132–9.
- Scremin OU, Li MG, Scremin AM, et al. 1997. Cholinesterase inhibition improves blood flow in the ischemic cerebral cortex. *Brain Res Bull*, 42:59–70.
- Scuteri A, Brancati AM, Gianni W, et al. 2005. Arterial stiffness is an independent risk factor for cognitive impairment in the elderly: a pilot study. *J Hypertens*, 23:1211–16.
- Scuteri A, Tesaro M, Appolloni S, et al. 2007. Arterial stiffness as an independent predictor of longitudinal changes in cognitive function in the older individual. *J Hypertens*, 25:1035–40.
- Skoog I, Gustafson D. 2002. Hypertension and related factors in the etiology of Alzheimer Disease. *Ann NY Acad Sci*, 177:19–36.
- Szilagy AK, Nemeth A, Martini E, et al. 1987. Serum and CSF cholinesterase activity in various kind of dementia. *Eur Arch Psychiatry Neurol Sci*, 236:309–11.
- Tatemichi TK, Desmond DW, Mayeux R, et al. 1992. Dementia after stroke: baseline frequency, risks and clinical features in a hospitalised cohort. *Neurology*, 42:1185–93.
- Togashi H, Kimura S, Matsumoto M, et al. 1996. Cholinergic changes in the hippocampus of stroke-prone spontaneously hypertensive rats. *Stroke*, 27:520–6.
- Togashi H, Matsumoto M, Yoshioka M, et al. 1994. Neurochemical profiles in cerebrospinal fluid of stroke-prone spontaneously hypertensive rats. *Behav Lett*, 166:117–20.
- van Dijk EJ, Breteler M, Schmidt R, et al. 2004. The association between blood pressure, hypertension, and cerebral white matter lesions. *Hypertension*, 44:625–50.
- Vanhoutte PM. 1989. Endothelium and control of vascular function. State of the art. *Hypertension*, 13:658–67.
- Vasquez J, Purve MJ. 1979. The cholinergic pathway to cerebral blood vessels. I. Morphological studies. *Pflugers Arch*, 379:157–63.
- Volpe M, Scuteri A. 2008. Management of risk factors in vascular dementia: hypertension. In: Moretti R, Torre P, Eds. *Vascular Dementia. Hot Topics in Neurology and Psychiatry*. In press.
- Wallin A, Blennow K, Gottfries CG. 1989. Neurochemical abnormalities in vascular dementia. *Dementia*, 1:120–30.
- Watanabe N, Imai Y, Nagai K, et al. 1996. Nocturnal blood pressure and silent cerebrovascular lesions in elderly Japanese. *Stroke*, 27:1319–27.
- Yamada M, Lamping KG, Duttaroy A, et al. 2001. Cholinergic dilation of cerebral blood vessels is abolished in M5 muscarinic acetylcholine receptor knockout mice. *PNAS*, 98(24):14096–101.
- Yamamoto Y, Akiguchi I, Oiwa K, et al. 1998. Adverse effect of nighttime blood pressure on the outcome of lacunar infarct patients. *Stroke*, 29:570–6.
- Yamamoto Y, Akiguchi I, Oiwa K, et al. 2001. Twenty four hour blood pressure changes in the course of lacunar disease. *Cerebrovasc Dis*, 11:100–6.
- Zhang WW, Badonic T, Haag A, et al. 1994. Structural and vasoactive factors influencing intracerebral arterioles in cases of vascular dementia and other cerebrovascular disease: a review. *Dementia*, 5:153–62.
- Zhu L, Viitanen M, Guo Z, et al. 1998. Blood pressure reduction, cardiovascular disease, and cognitive decline in the Mini-Mental State Examination in a community population of normal very old people: a three year follow-up. *J Clin Epidemiol*, 51(5):385–91.