

## Review

# Arterial Hypertension and Cognitive Decline Is it More than Pure Coincidence?

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## REZUMAT

### *Hipertensiunea arterială și declinul cognitiv. Mai mult decât o simplă coincidență?*

Odată cu îmbătrânirea populației la nivel global, prevalența atât a hipertensiunii arteriale cât și a declinului cognitiv au înregistrat o creștere semnificativă. Ambele patologii reprezintă cauze majore de morbi-mortalitate – fie ca urmare a riscului de evenimente cardiovasculare pe care îl asociază (în cazul hipertensiunii arteriale), fie prin consecințele în plan socio-economic ale unei patologii extrem de debilitante (cum este cazul demenței). Relația dintre cele două și modul în care hipertensiunea arterială poate induce sau accelera progresia demenței au fost studiate extensiv. Fiziopatologia modificărilor induse de hipertensiune la nivelul patului vascular cerebral care în final induc sau agravează demența au fost investigate de-a lungul timpului suficient cât să avem dovezi clare la acest moment că există o relație de cauzalitate între hipertensiunea arterială cronică și debutul precoce și progresia declinului cognitiv. Cu toate acestea, numeroasele trialuri care au studiat diverse terapii antihpertensive cu scopul de a preveni sau opri progresia demenței au dus aparent la rezultate contradictorii. Este deci neclar până la acest moment dacă anumite medicamente au efect neuroprotector sau dacă debutul mai tardiv și progresia mai lentă a demenței în cazul acestor terapii este pur și simplu o consecință a scăderii valorilor tensionale. Sunt deci necesare studii suplimentare care să clarifice dacă și care ar fi acele medicamente antihpertensive cu adevărat eficiente în limitarea progresiei demenței și declinului cognitiv.

**Cuvinte cheie:** hipertensiune arterială, declin cognitiv, demență, boală Alzheimer

## ABSTRACT

With the ageing of the population the prevalence of both arterial hypertension and cognitive decline has been increasing. Both represent major causes of morbi-mortality – either as a risk factor for major cardiovascular events (as in the case of hypertension), or through its social economic consequences as an extremely debilitating pathology (in the case of dementia). The relationship between the two and the way hypertension can

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induce or accelerate the progression of dementia have been extensively studied. The pathophysiology of alterations in the cerebral vascular bed in the presence of hypertension leading to or aggravating dementia have been well investigated and there is proof enough to link chronic arterial hypertension to early onset and progression of cognitive decline. However, the numerous trials with antihypertensive medications aiming to prevent or stop progression of dementia have up till now contradictory results. It is this far unclear whether certain antihypertensive drugs actually have neuroprotective properties or their actual blood pressure lowering activity is the sole feature leading to delayed onset and progression of dementia. Further studies are needed to clarify if and which antihypertensives are truly efficient in slowing progression of dementia and cognitive decline.

Keywords: arterial hypertension, cognitive decline, dementia, Alzheimer's disease

## INTRODUCTION

The life-span increase recorded during the past decades across the global population has led to an increase in the number of people suffering from dementia. Recent analyses have estimated the worldwide number of people living with Alzheimer's disease (AD) and dementia at between 27 million and 36 million, and projections by Alzheimer's disease International estimate that 115 million people worldwide will be living with AD/dementia by 2050, less developed countries being more affected by these rising numbers(1). Alzheimer's disease is the most prevalent form of dementia – 60-70% cases, while vascular dementia accounts for another 25% of cases(2). Alzheimer's disease is a neurodegenerative pathology associated with the intraneuronal accumulation of hyperphosphorylated proteins and with the extracellular aggregation of  $\beta$  amyloid precursors(3). These structural modifications lead to a metabolic cascade responsible for neuronal death and, subsequently, dementia.

As both vascular dementia (VD) and AD are serious public health issues, research developed during the past years have concentrated on the attempt to identify which the risk factors are and by which means they can be influenced.

Chronic arterial hypertension (HTN), as an important risk factor especially for stroke, is apparently associated with cognitive decline(4).

Research has tried to clarify issues related to the relation between HNT and cerebral circulation. The problem has been analyzed at multiple levels: arterial structure, reactivity of cerebral arteries and the blood-brain barrier.

## Arterial hypertension and the cerebral vascular bed

Arterial hypertension associates an increase in peripheral vasoreactivity, which translates either to a reduction of vascular lumen or a decrease in the number of arterioles, a phenomenon present also in the cerebral vascular bed. One of the most important studies conducted by Sokolova et al on hypertensive animal models showed a reduction of 25-50% in the number of pial arteries and intracerebral capillaries (5). Other authors, Coyle and Heistad, showed that the number of collateral arteries between the medial cerebral artery and the anterior cerebral artery is the same both in hypertensives and normotensives(6). The difference appears to come from the fact that Sokolova carried out research on models with secondary HTN, where animals had a longer duration of HTN with higher blood pressure (BP) values.

The loss of a large number of arterioles and cerebral capillaries leads to a reduction in cerebral blood flow which in time is develops into chronic cerebral hypoperfusion. This reduction in capillary numbers may be responsible for the risk of cognitive impairment and eventually vascular dementia in patients with HTN(7). However this is only a hypothesis; there are still many questions to be answered. Namely, it is not yet clear whether a good control of BP values can alter the loss of capillaries and whether this process is or not reversible. Surely, perfecting the imagistic methods will improve the chances to answer such issues.

Arterial hypertension also alters the vascular wall on a structural level, a process known as vascular wall remodeling(8). This process can be quantified

using remodeling parameters –the remodeling index (changes in media-to-lumen or wall-to-lumen ratio in the case of eutrophic remodeling) and the growth index (the percent changes in wall cross-sectional area in the case of hypertrophic remodeling)(9)(10). These HTN related changes of vascular wall at a structural level are some of the most studied topics in cerebral circulation research. It is considered that cerebral artery hypertrophy and remodeling are adaptive processes which reduce arterial wall stress and protect arterioles and capillaries from increases in BP levels. Arterial hypertension increases arterial wall stress, and in order to balance it, the vascular wall thickens, which is associated with a decrease in lumen diameter and an increase in wall/lumen index. These changes have prognostic value for target organ damage and subsequent cardiovascular events(11). Studies have shown that isolated HTN is not the only stimulus for the reduction in vascular wall. Several alterations in arterial wall smooth muscle cell organization have been identified. Different positioning of muscle cells is associated with a reduction in adventitial thickness. It is supposed that these areas represent the weak point where hemorrhages occur.

The vascular remodeling process is also influenced by the renin-angiotensin-aldosterone system (RAAS). Many studies using either angiotensin-conversion-enzyme inhibitors (ACE) or angiotensin receptor blockers (ARBs) have proved that a simple reduction of BP values alone is not sufficient to influence vascular remodeling, but rather their direct influence on the RAAS is the one responsible for influencing vascular wall remodeling (12,13,14, 15). Angiotensin II and aldosterone have been linked to the overproduction of reactive oxygen species (ROS), especially superoxide – a ROS proven to be involved in vascular wall remodeling in peripheral arteries in hypertensive rats(16)(17). In these animals, therapy with Tempol (a superoxide dismutase mimetic agent) prevents lumen diameter reduction in the medial cerebral artery, normally seen in spontaneously hypertensive stroke-prone rats (SHSPR)(18). Vascular wall remodeling is a process characterized by a degradation of the extracellular matrix along with its reorientation so that it can allow certain movements of smooth muscle cells inside the arterial wall. The degradation of the extracellular matrix is a result of matrix metallo-proteinases (MMP) activity(19), which is modulated by the RAAS. The mineralocorticoid receptor antagonists

reduce MMP-13 in the large cerebral arteries of SHSPR (20). Non-specific MMP inhibitors (such as doxycycline) reduces the extent of lesions produced by the occlusion of the medial cerebral artery(21). A reduction in vascular wall remodeling at the site of the posterior cerebral artery of rats has been also observed with rosiglitazone, an activator of the peroxisome proliferator-activated receptor- $\gamma$ , with no effect on BP levels(22). Statins, inhibitors of 3-hidroxi-3metrilglutanil-CoA, are also effective on preventing vascular wall remodeling. Simvastatin reduces wall thickness and increases lumen diameters in hypertensive rats(23)(24).

The remodeling process can also be hypertrophic resulting in an increase in arterial wall volume as a consequence of smooth muscle cells hypertrophy by either increase in cell volume or number (hyperplasia). These changes are controlled by the membrane transport processes which regulate the ion loss (Na, K and Cl) or the loss of amino acids, polyols and methyl amines(25). Somewhat controversial in the process of cerebral vascular wall remodeling remains the Cl ion channel, whose activity involves control of smooth muscle cell volume, proliferation and apoptosis(26). A reduction in channel activity has been observed in rats treated with simvastatin(24). It is also possible that this channel is activated by changes in the Calcium channel, however the actual connection between the two remains to be discovered.

The vascular wall remodeling process has hemodynamic effects. In hypertensive patients it tends to normalize or reduce blood flow as a result of increases in pressure levels by increasing peripheral vascular resistance(27)(28). Although it is considered that blood flow at rest is relatively normal in the hypertensive patient, studies have shown that in the elderly hypertensives it is reduced in some areas of the brain such as the occipital-temporal area, the prefrontal cortex and the hippocampus(29). Hypertensives that are not efficiently controlled have weaker cerebral blood flow with aging. This is independent of atherosclerosis and can be the consequence of both structural and functional changes in the cerebral arteries(30).

### Cerebral artery vasoreactivity

Cerebral artery reactivity is another issue that has been intensively studied in the hypertensive patient. Cerebral blood flow is not influenced solely by the structure of cerebral vessels. Very interesting data

has emerged from the study of the modality in which they contract or dilate in the normotensive and in the hypertensive patient. The cerebral circulation maintains perfusion at a constant pressure independently of variations of blood pressure through an autoregulation mechanism. This is true for BP values varying from 60 to 150 mmHg(31). The mechanisms that have been hypothesized to contribute to this phenomena are the neuron production of nitric oxide (NO)(31)(32)(33)(34)and the sympathetic and parasympathetic nervous systems(35)(36). Recently, Koller and Toth have shown that blood flow itself can have an autoregulation role(37). For example, an increase in blood flow cause dilate basilar arteries, but also constrict the anterior cerebral artery. In conclusion, a pressure under the autoregulation level leads to a lower perfusion, which can lead to an ischemic lesion. In contrast, a pressure above the autoregulation level leads to an increased blood flow which can lead to vasogenic edema.

#### **Cerebral artery myogenic activity**

The activity of the smooth muscles in the arterial walls plays an important role in the autoregulation of the cerebral blood flow. Muscle cells reactivity intervenes in the artery's ability to modify tone in order to face intraluminal pressure fluctuations and maintain constant blood flow. This response is a characteristic of the smooth muscle cells. Myogenic reactivity is itself modelled by the endothelium through several other mechanisms: NO, prostacyclin, endothelium-derived-hyperpolarizing factor (EDHF).

The most studied mechanism of endothelial regulation of vascular tone is through the means of NO production. NO is synthesized by the endothelium of cerebral arteries and its serum levels are reduced in the presence of hypertension(38). A series of substances which are considered to have an effect on the activity of the endothelial NO synthase (eNOS) have been studied. Thus, cilostazol, a phosphodiesterase 3 inhibitor with antiplatelet properties, increases cerebral levels of eNOS, which has been associated with an increase in cerebral blood flow following ischemia(39). This effect is similar in animals treated with aspirin or clopidogrel which suggests that the effect of cilostazol is not related to its antiplatelet activity but rather to an amelioration of endothelial function(40).

NO dependent dilation is also influenced by the oxidative stress which is increased in the case of

hypertensives(41). Under these circumstances there is an excess of superoxide dismutase which interacts with NO, decreasing its levels in the cerebral arteries and thus influencing endothelial function. More recently the role of transient receptor potential has been described (TRP). It seems that TRP vanilloid 4 contributes to cerebral vasoconstriction(42).

#### **Hypertension and the blood-brain barrier**

Arterial hypertension also influences the activity of the blood brain barrier. Its role is to ensure a selective physical and biochemical permeability in order to preserve central nervous system homeostasis. This characteristic is determined by the composition of the neuro-vascular unit. The most studied component of this unit is the endothelial cell. It seems however that both astrocytes and pericytes have a role in this regard. It has been observed that in case of hypertension the number of pericytes increases(43)(44)(45)(46). Arterial hypertension increases blood brain barrier permeability. This is also influenced by the inflammatory cytokines whose levels are as well increased in the presence of hypertension(i.e. interleukin 6, TNF $\alpha$  etc.).

As a conclusion, one can affirm that arterial hypertension has a detrimental effect on cerebral arteries, at both structural and functional level. This has implications not only on cerebral ischemia, but also on dementia and cognitive decline which are secondary to vascular changes.

#### **Hypertension and cognitive decline**

Several studies have been conducted to prove the connection between arterial hypertension and cognitive decline. However, results have been questionable because of methodology, patient enrollment modality etc. Nevertheless, most of these studies have proven a relation between arterial hypertension with an onset around the age of 50 years, cognitive decline and AD. The initial Framingham heart study publication on stroke has been one of the first to prove this relation in 1965(47). These data have been later confirmed by Kilander et al (48)and by the EVA study (Epidemiology of Vascular Ageing) (49). In the latter, which was conducted on patients with an average age of 65 years, the risk for cognitive decline was 2.8 times higher in hypertensives followed-up for only 4 years. Arterial hypertension increases not only the risk for cognitive decline but also for vascular dementia and AD. The Honolulu Asia Aging Study carried out on 3703 patients with

arterial hypertension showed that they have an increased risk for dementia after 25 years of disease evolution(50). Other studies showed that an increase in BP over 140 mmHg is associated with an increased risk of AD. Correlation studies have been proposed to investigate the relationship between pulse pressure and risk for dementia. Longitudinal studies from the Kungsholmen Project showed that high systolic BP with low diastolic BP are responsible for an increased risk for AD(51). The study also proved a positive association between arterial stiffness measured by pulse wave velocity (PWV) and cognitive decline. An interesting element is that in patients with AD the BP values decrease – a phenomena which has not yet been explained and that may come as a consequence of decreased levels of physical activity or of weight loss.

Another explanation could come from the effect that prefrontal lesions present in AD have on the autonomous nervous system leading to a decrease in BP values. The study conducted by Bellew et al on 700 patients with AD showed an acceleration on cognitive decline in patients under 65 years of age(52).

In conclusion, it can be considered that the relationship between arterial hypertension and cognitive decline is much more complex, and clearly not linear. Chronic arterial hypertension predisposes to cognitive decline and the onset of dementia. On the other hand, when AD is also present and progresses, BP values tend to decrease.

### **Blood pressure lowering therapies and cognitive decline**

Ever since studies showed the relationship between arterial hypertension and cognitive decline there have been several attempts to observe whether correct treatment of HTN can prevent vascular changes. Cognitive function of patients included in the study has been evaluated mostly by MMSE (mini mental state examination). Six large randomized studies were conducted on patients under antihypertensive therapy in whom cognitive function and the way it correlated to blood pressure values were observed(53)(54)(55)(56)(57)(58)(59).

The MRC study was the first to follow-up on cognitive function. Study medication included diuretic or beta blockers, and patient follow-up was carried out for 54 months. This study found no differences between the two groups (therapy vs placebo) in respect to cognitive function. This could be the

effect of a superficial neuropsychiatric evaluation and a short follow-up period(53).

The SHEP (systolic hypertension in the elderly program) study did not find significant differences between the treated hypertensives and the placebo group either. In this study 4736 hypertensive patients were enrolled to receive diuretic or beta blockers, and were followed up for 5 years. The absence of significant differences may have been influenced by the lack of neuropsychological data in many of the patients(54).

SYS-EUR (the systolic hypertension in Europe study) investigated whether antihypertensive treatment in older patients with isolated systolic HTN is related to stroke mortality and morbidity. Patients were administered a calcium channel blocker (Nitrendipine) in association, when needed, with a diuretic (Hydrochlorothiazide) and/or an ACE inhibitor (Enalapril) or placebo. There was a 2 years follow-up, however the study was stopped prematurely because of the positive results showing obvious stroke prevention in the active treatment arm. Moreover, a reduction of 50% in dementia rate was observed in the treated group(55). Same favorable results were obtained after 4 years follow-up(56). These studies brought proof that correct treatment of 1000 patients for 5 years will prevent 20 new cases of dementia.

The PROGRESS study (the Perindopril protection against recurrent stroke study), observed 6105 patients with a history of one stroke with the main objective of evaluating whether treatment with Perindopril ± Indapamide can reduce stroke recurrence. The secondary objective was to evaluate the relation between hypotensive therapy and cognitive decline or dementia. Even though blood pressure values decreased, the incidence of dementia in treated patients did not decrease significantly. Statistical significance was obtained only in the case of rate of cognitive decline, which was lower in group of treated patients(57).

The HOPE study enrolled 9297 subjects with vascular disease who were followed-up for 4.5 years while treated with Ramipril or placebo. The results showed benefits regarding cognitive function and language disorders in the active treatment group(58).

The SCOPE study (the study of cognition and prognosis in the elderly) followed-up 4964 elderly (70-89 years old) hypertensive subjects for 3.7 years to evaluate the effect of ARBS ± a diuretic on cog-

nitive function. The placebo group, however, received antihypertensive treatment with an ARB (for ethical reasons) when needed, and thus the difference in BP levels between the group was small. There were no significant differences in respect to cognitive function or dementia. However, this result should be interpreted considering the small differences in BP values and the short follow-up period(59).

HYVET-COG (Hypertension in the very elderly trial – cognition function assessment) has enrolled elderly hypertensive subjects over 80 years of age with no clinical diagnosis of dementia at baseline who received 1-5 mg slow release Indapamide, with the option of 2-4 mg Perindopril, or placebo. After 2.2 years of follow-up there was a significant decrease in stroke incidence which led to an early stop of the study.

A meta-analysis by Bierkenhager et al. showed that a decrease in systolic BP  $> 5$  mmHg led to a 25% decrease in risk for dementia. The authors insisted on the fact that calcium channel blockers could be more efficient (SYST-EUR) in this respect when compared to RAAS blockers (SCOPE, PROGRESS-monotherapy).

Another meta-analysis, by Birns et al, on 16 randomized trials, respectively 19501 patients, showed there is a modest but significant improvement of cognitive function in patients under antihypertensive therapy. Blood pressure lowering therapy seems to have different effects on the components of cognitive function, thus improving memory (immediate and delayed), without influencing executive function.

Even though results are promising, larger and better standardized randomized trials are needed in order to settle these controversial results and better characterize the relation between blood pressure lowering therapy and cognitive function or dementia.

Effects of antihypertensive therapy other than BP lowering to prevent dementia

An important objective of research has been to describe how RAA system blockers act to prevent dementia, through other effects than lowering BP(57)(60). Fournier hypothesized that angiotensin receptor blockers have an advantage on ACE inhibitors in preventing stroke and cognitive decline(61). Light on this matter might come from trials ONTARGET(62)and TRANSCEND(63), both using Telmisartan, anARB with effective per-

oxisome proliferator-activated receptor gamma stimulation activity. After 56 months follow-up in ONTARGET found cognitive impairment in 8% of patients allocated to Ramipril and to the combination Ramipril+Telmisartan and in 7% of patients allocated to Telmisartan alone. Results for cognitive decline in the same categories were 17% of patients in all three groups. TRANSCEND investigated only the effect Telmisartan has compared to placebo, and found cognitive decline after follow-up in 17% vs 16% of studied patients.

PROFESS (Prevention regiment for effectively avoiding second strokes) investigated the effect of ARBs on cognitive function(64). Here, no significant differences could be found between the group receiving treatment and the placebo-controlled group in terms of cognitive decline or dementia. This outcome was interpreted as a result of short patient follow-up and numerous discontinuities in medication administration recorded during the study.

Figaro et al report that therapy with Telmisartan and Hydrochlorothiazide leads to a significant improvement in cognitive function in comparison to ACE inhibitor therapy (Lisinopril) and Hydrochlorothiazide.

Even though the exact mechanism through which ARBs may have this advantage over ACE inhibitors is still unclear, Tsukuda et al have proved that low dose Telmisartan has a preventive effect on cognitive decline and AD in laboratory animals(65). This may be a result of ARBs capacity to reduce inflammation through PPAR-gamma activation and would thus add to their BP lowering effect.

## CONCLUSIONS

Currently, we have large epidemiologic proof to argument the association between hypertension, especially with adult onset, and cognitive decline and dementia, be it vascular dementia or AD. Once this pathology occurs, a tendency of BP levels to drop has been recorded, the physiopathology of this remaining for now unclear. Cerebrovascular degenerative lesions secondary to HTN seem to contribute to the early onset of AD. Longitudinal studies examining the possible benefit of antihypertensive medication on cognitive decline have brought promising results thus far. There is, however, a need for further studies comparing different classes of antihypertensive medication in order to clearly and completely

describe their effect on the risk for dementia and to clarify whether any of them has a larger benefit than others. Research needs to clarify which of the anti-hypertensive medications have specific neuroprotective properties or whether they simply act as blood pressure lowering agents which increase cerebral perfusion. Moreover, the best BP levels for optimizing cerebral perfusion and preventing cognitive decline in elderly people still need further research.

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