Arterial Stiffness and Alzheimer Disease, a simple association?

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13th EUGMS Congress
Nice, 20-22 Septembre 2017
Disclosures

- Honoraria
  - Fukuda
  - Novartis

No other conflict of interest
“A man is as old as his arteries”

Dr. Thomas Sydenham
Arterial aging, stiffness, and blood pressure regulation

Art. Stiffness

Compliant arteries

Stiff arteries

Incident wave
Return of reflected wave
Arterial pulse wave

Time

Time

148/90
168/80
Arterial stiffness: A major determinant of morbidity/loss of autonomy/mortality

- Heart Failure
- Stroke
- Coronary heart disease
- Renal failure

And
- Vascular dementia

But also…
- Alzheimer disease
Arterial stiffness and cognitive status in older adults
Arterial stiffness is increased in patients with MCOI, AD and vascular dementia.

Hanon et al, *Stroke* 2005
Aortic stiffness, Leucoaraëïosis and Cognitive impairment: ADELAHYDE study

A. Kearney-Schwartz et al, Stroke 2008
Aortic stiffness, and leucoaraiosis are independent determinants of cognitive impairment in hypertensive subjects over 60 yo: The ADELAHYDE study

A. Kearney-Schwartz et al, Stroke 2008
Baseline values of arterial stiffness and BP in «decliners» and «non-decliners» over a 2-year follow-up period. The PARTAGE study (>80 yo living in NHs)

Fig. 2. Adjusted arterial stiffness and mean BP values according to MMSE decline. *Comparisons were performed using trend ANOVA. Data were adjusted for MBP (except for MBP comparison), age, education level, HR, BMI, and baseline MMSE and ADLs.
Baseline values of arterial stiffness and BP in « decliners » and « non-decliners » over a 2-year follow-up period. The PARTAGE study (>80 yo living in NHs)

Fig. 3. Analysis of baseline factors associated with “decliner” status using multiple logistic regression model. BPM, beats per minute; CI, confidence interval.
Aortic Stiffness and the Risk of Incident Mild Cognitive Impairment and Dementia

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Background and Purpose—Aortic stiffening increases the transfers of high pressure and flow pulsatility to small cerebral vessels potentially causing the accumulation of vascular brain injury. Our aim was to investigate the prospective association of aortic stiffness with the risks of incident mild cognitive impairment and dementia.

Methods—We studied 1101 dementia-free Framingham Offspring study participants (mean age, 69±6 years; 54% women). Aortic stiffness was measured as carotid–femoral pulse wave velocity using applanation tonometry and modeled as a linear variable and the top 2 quintiles (>11.4 m/s). Outcomes were the 10-year risk of incident mild cognitive impairment and dementia, including clinically characterized Alzheimer disease. We observed 106, 77, and 59 events of mild cognitive impairment, all-cause dementia, and clinical Alzheimer disease, respectively.

Results—After adjustment for age and sex, higher continuous aortic stiffness predicted an increased risk of mild cognitive impairment (hazard ratio, 1.40 [95% confidence interval, 1.13–1.73]), all-cause dementia (hazard ratio, 1.45 [95% confidence interval, 1.13–1.87]), and Alzheimer disease (hazard ratio, 1.41 [95% confidence interval, 1.06–1.87]). In risk factor–adjusted statistical models, aortic stiffness remained a significant predictor of mild cognitive impairment but not incident dementia. In nondiabetic patients, the top 2 quintiles of aortic stiffness were associated with a higher risk of incident all-cause dementia across all statistical models.

Conclusions—Aortic stiffness was an independent predictor of incident mild cognitive impairment in the whole sample and with incident dementia in nondiabetic patients. Our findings suggest aortic stiffness as a potentially modifiable risk factor for clinical cognitive impairment and dementia.  

Key Words: Alzheimer disease ■ brain ■ dementia ■ risk factors ■ vascular stiffness
### Table 2. Aortic Stiffness and the 10-Year Risk of Incident Mild Cognitive Impairment and Dementia

<table>
<thead>
<tr>
<th>Event</th>
<th>Continuous CFPWV</th>
<th>Top 2 quintiles of CFPWV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exposure Model</td>
<td>No. of Cases/Subjects</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>106/1068</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>104/1016</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>104/1000</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>98/976</td>
</tr>
</tbody>
</table>

Model 1 adjusts for age and sex. Model 2 includes additional adjustment for education and apolipoprotein E4 allele status. Model 3 includes additional adjustment for mean arterial pressure, prevalent diabetes mellitus and high-density lipoprotein-cholesterol. Model 4 includes additional adjustment for atrial fibrillation, current smoking, prevalent cardiovascular disease, heart rate, total cholesterol, depressive symptoms, central adiposity, and treatment for hypertension. CFPWV indicates carotid–femoral pulse wave velocity; CI, confidence interval; and HR, hazard ratio.
… We demonstrate that high aortic stiffness, measured as CF-PWV, was an independent predictor of incident MCI in the whole sample and of incident dementia in nondiabetic patients. Limiting aortic stiffening with aging, through healthy lifestyle, diet, and possible pharmacological therapy may thus help protect against later life vascular brain injury and cognitive impairment.

Possible mechanisms of these associations

• Hypoxia
• Inflammation
• ??
Hypoperfusion et Maladie d’Alzheimer
Hypoxia increases - secretase cleavage of APP and Amyloid deposition in APP23 transgenic mice.

PNAS, 2006; vol. 103, no. 49: 18727–18732
As vascular dysfunction is thought to occur years or even decades ahead of the clinical manifestation of AD, quantitative measurements of cerebral vasomotion could predict microvascular dysfunction at an early stage of the disease, and contribute to assess the efficiency of therapeutic interventions.
# Inflammation and family history of Alzheimer Disease

## Table 3. Inflammation in Offspring With and Without a Parental History of Late-Onset AD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Present (n = 206)</th>
<th>Absent (n = 200)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production capacity of inflammatory cytokines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-1β, pg/mL</td>
<td>13 091 (380)</td>
<td>10 548 (580)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IL-1ra, pg/mL</td>
<td>10 695 (426)</td>
<td>11 030 (448)</td>
<td>.5</td>
</tr>
<tr>
<td>IL-1β:IL-1ra</td>
<td>1.38 (0.06)</td>
<td>1.10 (0.05)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Tumor necrosis factor α, pg/mL</td>
<td>8551 (466)</td>
<td>7147 (357)</td>
<td>.008</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>96 031 (2809)</td>
<td>88 226 (2827)</td>
<td>.04</td>
</tr>
<tr>
<td>IL-8, pg/mL</td>
<td>26 888 (1972)</td>
<td>23 523 (2557)</td>
<td>.2</td>
</tr>
<tr>
<td>IL-10, pg/mL</td>
<td>5526 (165)</td>
<td>5022 (189)</td>
<td>.06</td>
</tr>
<tr>
<td>Interferon-γ, pg/mL</td>
<td>6369 (616)</td>
<td>4402 (463)</td>
<td>.01</td>
</tr>
<tr>
<td>Circulating markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>1.36 (0.1)</td>
<td>1.33 (0.1)</td>
<td>.7</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>1.20 (0.1)</td>
<td>1.26 (0.1)</td>
<td>.7</td>
</tr>
</tbody>
</table>

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E. Van Exel et al., Arch Gen Psych 2009
Amyloid intensifies VSM cell induced inflammatory response and de-differentiation.

Vascular smooth muscle cells treated with Aβ 1-40 exhibit higher inflammatory response to interleukin-1.

Vromman A et al, Aging Cell 2013
Amyloid context intensifies VSM inflammatory response

Vromman A et al, Aging Cell 2013
Risk factors for COGNITIVE DECLINE

M. Baumgart et al Alzheimer’s & Dementia 11 (2015) 718-726
Risk factors for DEMENTIA

Fig. 2. Strength of evidence on risk factors for dementia.

M. Baumgart et al Alzheimer’s & Dementia 11 (2015) 718-726
CONCLUSIONS

• Fight against accelerated arterial stiffening and its consequences may be one of the most relevant strategies for preventing cognitive decline and dementia