Predictive value of arterial stiffness for WHITE MATTER LESIONS AT BRAIN MRI and cognitive decline the COVADIS-arterial stiffness study

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Methods for large artery stiffness measurement

**Local stiffness**

**Applanation tonometry**

**Echotracking**

\[ \text{Dist} = \frac{DV}{DP \cdot V} \]

**Young’s elastic modulus**

\[ E_{inc} = 3 \left[ 1 + \frac{LCSA}{WCSA} \right] \frac{1}{Dist} \]

**Aortic stiffness**

Aortic pulse wave velocity

\[ PWV = \frac{\Delta L}{\Delta t} = \sqrt{\frac{dP}{\rho \cdot dV}} \approx \sqrt{\frac{1}{\text{DIST}}} \]
Understanding of Cerebrovascular diseases by a cardiologist-pharmacologist

Stroke
  - Ischemia
    - Embolic
      - Heart
      - Cervical arteries
    - Dissection
      - Plaques
      - Aorta
  - Hemorrhagic
    - Aorta
    - Cervical arteries

Neuro-degenerative disease
  - Alzheimer
  - Vascular dementia
    - Leucoaraiosis
Cerebral arterioles remodelling: experimental evidences

- Vascular hypertrophy of cerebral arterioles is related more closely to pulse pressure than to mean pressure.
- Distensibility of pial arterioles is higher in SHRSP than in WKY.
- Reduction of pial arteriolar pressure:
  - prevents cerebral vascular hypertrophy
  - attenuates increases in passive distensibility of cerebral arterioles in SHRSP.
- ACEi but not direct vasodilators prevent pulse pressure-induced remodeling of pial arterioles.
- Endothelial dysfunction is related to increased central pulse pressure.

Pulse-wave encephalopathy:
Unifying link between neurodegenerative diseases and arterial stiffness

- Leucoaraiosis
  - ↑ arterial pulsatility
  - ↓ cerebrospinal compliance
  - fibrosis of periventricular veins

Bateman, Neuroradiology 2002
Feugeas Magnetic resonance imaging 2005
High blood pressure (SBP) is the major determinant of white matter lesions

- 10 European cohorts, 1805 non-demented patients (65-75 years)

<table>
<thead>
<tr>
<th>Severe White Matter Lesions</th>
<th>No Hypertension (n=814)</th>
<th>Hypertension (n=811)</th>
<th>Hypertension Treatment Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n=811)</td>
<td>Untreated (n=267)</td>
<td>Treated Successfully (n=336)</td>
</tr>
<tr>
<td>Periventricular</td>
<td>1.0 (ref)</td>
<td>1.5 (1.0-2.2)</td>
<td>1.4 (1.0-2.0)</td>
</tr>
<tr>
<td>Subcortical</td>
<td>1.0 (ref)</td>
<td>1.1 (0.8-1.7)</td>
<td>1.3 (0.9-1.8)</td>
</tr>
</tbody>
</table>

Van Dijk, Hypertension 2004
Effect of BP lowering on cerebral white matter lesions in patients with stroke: a PROGRESS substudy

- WML dependent on SBP at baseline

43% new high grade WMH

<table>
<thead>
<tr>
<th></th>
<th>Total (n=192)</th>
<th>Placebo (n=103)</th>
<th>Active (n=89)</th>
<th>P Value, Model 1*</th>
<th>P Value, Model 2†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident WMH, n (%)</td>
<td>24 (13)</td>
<td>16 (16)</td>
<td>8 (9)</td>
<td>0.17</td>
<td>0.10</td>
</tr>
<tr>
<td>Mean volume of incident WMH, mm³ (SE)</td>
<td>1.8 (0.5)</td>
<td>2.0 (0.7)</td>
<td>0.4 (0.8)</td>
<td>0.012</td>
<td>0.009</td>
</tr>
<tr>
<td>Volume of incident WMH by initial grade of WMH, mm³ (SE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No WMH</td>
<td>0.05 (0.8)</td>
<td>0</td>
<td>0.09 (0.8)</td>
<td>0.76</td>
<td>0.81</td>
</tr>
<tr>
<td>Mild to moderate WMH</td>
<td>1.2 (1.2)</td>
<td>1.3 (1.0)</td>
<td>0.9 (1.0)</td>
<td>0.58</td>
<td>0.71</td>
</tr>
<tr>
<td>Severe WMH</td>
<td>6.5 (2.0)</td>
<td>7.6 (1.0)</td>
<td>0</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Dufouil C, Circulation 2005
Arterial stiffness and cognitive decline

PWV correlated with MMSE (r=-0.27, p<0.0001)

Hanon, Stroke 2005
Arterial stiffness and further cognitive decline

- Increased arterial stiffness is predictive of further cognitive decline during longitudinal follow-up
Evidence for association between blood pressure and neurodegenerative diseases (Alzheimer, vascular dementia, leucoaraiosis)

• Association with white matter lesions

• Cross-sectional studies: NDD → low blood pressure

• Longitudinal studies: BP at midlife → strongest predictor of NDD

• Treatment of hypertension
  – Prevents progression of white matter lesions
  – Most potent prevention of dementia

• Dufouil C, Lancet Neurol 2005 (review)

• Qiu, Lancet Neurol 2005

• Dufouil C, PROGRESS trial, Circulation 2005


• Tzourio et al, PROGRESS trial, arch intern med 2003
Effect of blood pressure reduction on further incidence of dementia

• SYST-EUR trial
  - risk of dementia by 55%, from 7.4 to 3.3 cases per 1000 patient-years (43 vs 21 cases, P<.001)
  - Adjusted RR of dementia with nitrendipine was 0.38 95% CI [0.23-0.64]; P<.001)

• PROGRESS trial
  - risk of dementia by 34% in patients with recurrent stroke
  - cognitive decline by 19% in whole population and 45% in patients with recurrent strokes
Arterial stiffness, central pressure and cerebrovascular diseases

- Arterial stiffness
- Aortic PP
  - SBP
  - DBP
  - coronary perfusion pressure
  - LVH
  - coronary reserve
- Ischemic cardiomyopathy, arrhythmia, AF
- local PP
  - coronary perfusion pressure
- LVH
- coronary reserve
- Cerebrovascular remodelling
  - Cerebrospinal fluid turnover
  - Venous fibrosis
  - Pulse wave encephalopathy
  - White matter hypersignal
- Carotid atherosclerosis, plaque rupture
- Stroke
  - Leucoaraiosis
  - Alzheimer
  - Vascular dementia

Neurodegenerative diseases
• French prospective cohort study started in 1999 and
  – 3500 non-institutionalized persons aged 65 to 79 years, recruited from the electoral rolls of a French City (Dijon).

The primary aim of the COVADIS study is to evaluate the risk of cognitive impairment and dementia attributable to vascular factors.

  • face-to-face interviews using standardized questionnaires on health-related data
  • blood pressure measurement
  • cognitive testing
  • assessment of vascular risk factors, measurement of biological parameters
  • magnetic resonance imaging (MRI) examinations.
The ancillary COVADIS-ARTERIAL STIFFNESS STUDY

• 2,000 subjects from the COVADIS cohort
  – During the 8-year follow-up (2007-2008)
    • arterial stiffness and central pressure measurements (carotid to femoral pulse wave velocity and pulse wave analysis, respectively; Sphygmocor ®).
  – Arterial measurements will be done only once (2007-2008) into the COVADIS-Arterial stiffness study
  – 2 MRI examinations will be available: the first has been performed in 2003-2004 and the second will be performed in 2010.
  – Objectives:
    • (1) Cross-sectional relationships between arterial stiffness, central pressure with white matter lesions and cognitive status
    • (2) Longitudinal relationships between arterial stiffness and changes in MRI data (new white matter lesions and significant progression of the WML total volume (≥30%) on follow up MRI) and cognitive function will be studied