Arterial stiffness: Clinical Usefulness

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at the beginning a disease is easy to cure but difficult to diagnose; but as time passes, not having been treated or recognized at the outset, it becomes easy to diagnose but difficult to cure.

Arterial Biomarkers

- Functional
  - Endothelial Dysfunction
  - Central Hemodynamics-Wave Reflections

- Structural
  - Plaque
  - IMT
  - ABI

Arterial Stiffness
Criteria of a Biomarker

A theoretical basis

High reproducibility

Ease of use

Incremental value

Ability to monitor and guide therapy

R Vasan 2006
Aortic Stiffness

Expert consensus document on arterial stiffness: methodological issues and clinical applications

Stephane Laurent¹*, John Cockcroft², Luc Van Bortel³, Pierre Boutouyrie¹, Cristina Giannattasio⁴, Daniel Hayoz⁵, Bruno Pannier⁶, Charalambos Vlachopoulos⁷, Ian Wilkinson⁸, and Harry Struijker-Boudier⁹ on behalf of the European Network for Non-invasive Investigation of Large Arteries

Incremental value

Ability to monitor and guide therapy
Aortic Stiffness

A theoretical basis

High reproducibility

Ease of use

Incremental value

Ability to monitor and guide therapy
What determines arterial stiffness?
What does arterial stiffness determine?
What determines arterial stiffness?
What does arterial stiffness determine?

Quantitative relationship between gene expression and arterial stiffness


EHJ 2009
What determines arterial stiffness?
What does arterial stiffness determine?

Traditional Risk Factors for CV Disease
- Blood pressure
- Cholesterol
- Diabetes
- Smoking
- Male gender
- Age

Non-Atherosclerotic CV Disease
- White matter lesions
- LVH
- Fibrosis
- Ischemia
- Diastolic heart failure

Aortic Stiffness

Atherosclerosis

Inflammation and Arterial Stiffness

**Acute Infection Model**
Salmonella Typhi Vaccine

**Chronic inflammatory disease**


Maki-Petaja K, et al., Circulation 2006

There is a causative link between acute systemic inflammation and arterial stiffness.
What determines arterial stiffness?

What does arterial stiffness determine?

Aortic stiffness

A theoretical basis

High reproducibility

Ease of use

Incremental value

Ability to monitor and guide therapy
Arterial stiffness measurements are permitted by numerous methods and devices but they differ largely according to their physical basis, simplicity to use and nature of the measured parameter.

Laurent S, et al., EHJ 2007
Aortic stiffness - Evaluation

Pulse Wave Velocity

Carotid-femoral PWV is considered as the ‘gold-standard’ measurement of arterial stiffness.

\[ \text{PWV} = \frac{L}{\text{time (sec)}} \]

- Easy to perform
- Learning curve
- Reproducible
- Not expensive
Aortic stiffness

A theoretical basis

High reproducibility

Ease of use

Incremental value

Ability to monitor and guide therapy
PWV and surrogate end-points
PWV and intermediate endpoints

**Left ventricular geometry/hypertrophy**
- Roman et al Hypertension 2000
- Schillaci et al Hypertension 2007
- Toprak et al Am J Cardiol 2009

**Renal function/Albuminuria/Cystatin C**
- Mule et al J Intern Med 2004
- Gosse et al Am J Hypert 2005
- Schillaci et al Hypertension 2006

**Cognitive impairment/Brain lesions**
- Scutteri et al J Hypert 2005
- Hanon et al Stroke 2005
- Poels et al Stroke 2007
- Waldstein et al Hypertension 2008
- Henskens et al Hypertension 2008
- Elias et al Hypertension 2009
- Triantafyllidi et al Am J Hypert 2009
- Pase et al J Hypert 2010

**Carotid IMT/plaque**
- Van Popele et al Stroke 2001
- Zureik et al J Hypert 2002
# Aortic stiffness and atherosclerosis

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Population</th>
<th>Parameter</th>
<th>Finding</th>
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</thead>
<tbody>
<tr>
<td>Stefanadis</td>
<td>1987</td>
<td>Pts with CAD or not</td>
<td>Aortic distensibility</td>
<td>Lower in CAD pts</td>
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<tr>
<td>Hirai</td>
<td>1989</td>
<td>Pts with CAD or not</td>
<td>Abd Aortic and carotid stiffness index</td>
<td>Higher in CAD pts (especially in those with 3VD)</td>
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<tr>
<td>Stefanadis</td>
<td>1990</td>
<td>Pts with CAD or not</td>
<td>Aortic distensibility</td>
<td>Lower in CAD pts</td>
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<tr>
<td>Dart</td>
<td>1991</td>
<td>Pts with CAD and high cholesterol on not</td>
<td>Aortic arch stiffness index</td>
<td>Steeper increase with age in CAD patients</td>
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<tr>
<td>Cameron</td>
<td>1995</td>
<td>Pts with CAD or not</td>
<td>Systemic arterial compliance</td>
<td>Lower in CAD pts</td>
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<tr>
<td>Gatzka</td>
<td>1998</td>
<td>Pts with CAD or not</td>
<td>Aortic stiffness</td>
<td>Higher in CAD pts</td>
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<tr>
<td>Waddell</td>
<td>2001</td>
<td>Pts with CAD or not</td>
<td>cfPWV</td>
<td>Higher in CAD pts</td>
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<tr>
<td>van Popele</td>
<td>2001</td>
<td>Individuals &gt;60 y.o.</td>
<td>cfPWV</td>
<td>Higher in pts with carotid or aortic plaques, or PAD</td>
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<tr>
<td>McLeod</td>
<td>2004</td>
<td>Pts with suspected CAD</td>
<td>cfPWV and crPWV</td>
<td>Correlated with the extend of coronary plaques</td>
</tr>
<tr>
<td>Hope</td>
<td>2007</td>
<td>Pts with suspected CAD</td>
<td>cfPWV</td>
<td>Correlated with the presence and extend of CAD</td>
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<tr>
<td>Koji</td>
<td>2007</td>
<td>Pts with suspected CAD</td>
<td>baPWV</td>
<td>Higher in CAD pts</td>
</tr>
<tr>
<td>Roman</td>
<td>2007</td>
<td>General</td>
<td>Central pulse pressure</td>
<td>Higher in carotid plaques</td>
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<tr>
<td>Okujama</td>
<td>2008</td>
<td>pts with suspected CAD</td>
<td>Desc Ao stiffness index</td>
<td>Higher in CAD pts</td>
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<tr>
<td>Claridge</td>
<td>2009</td>
<td>pts with PAD or not</td>
<td>Elastic modulus</td>
<td>Higher in PAD pts</td>
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<tr>
<td>Amoh-Tonto</td>
<td>2009</td>
<td>pts with PAD</td>
<td>baPWV</td>
<td>Correlated with the functional status</td>
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</table>
PWV and hard end-points
Arterial stiffness & prognosis
From specific to broader groups
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Arterial stiffness & prognosis
From specific to broader groups
Arterial stiffness & prognosis / End-stage renal disease (ESRD)

PWV $\uparrow$ 1m/s $\Rightarrow$ all-cause mortality $\uparrow$ 39%

*Circulation* 1998
Arterial stiffness & prognosis
From specific to broader groups
PWV is an independent predictor of all-cause and cardiovascular mortality

Arterial stiffness & prognosis / CAD +/- LV dysfunction

Risk of events at FU
Higher tertile: 44%
Lower tertile: 5.6%

Aortic stiffness was the strongest predictor of progression to any end-point

Arterial stiffness & prognosis
From specific to broader groups
Higher aortic stiffness is associated with increased risk for a first cardiovascular event.

For individuals at intermediate CVD risk, addition of aortic PWV in Framingham Risk Score yielded a net reclassification of 15.7% (p<0.05)
## Aortic PWV as predictor of events (incl. CV)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Population-Sample size</th>
<th>Age (y)</th>
<th>Follow-up duration</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blacher 1999</td>
<td>ESRD (N=241)</td>
<td>51.5±16.3</td>
<td>6 y</td>
<td>Deaths and CV deaths</td>
</tr>
<tr>
<td>Laurent 2001</td>
<td>Hypertension= (N=1,980)</td>
<td>50±13</td>
<td>9.3 y</td>
<td>Deaths and CV deaths</td>
</tr>
<tr>
<td>Meaume 2001</td>
<td>Subjects &gt;70 y (N=141)</td>
<td>87.1±6.6</td>
<td>2.5 y</td>
<td>Deaths and CV deaths</td>
</tr>
<tr>
<td>Shoji 2001</td>
<td>ESRD (N=265)</td>
<td>55.4±10.5</td>
<td>5.3 y</td>
<td>Deaths and CV deaths</td>
</tr>
<tr>
<td>Boutouyrie 2002</td>
<td>Hypertension (N=1,045)</td>
<td>51±12</td>
<td>5.7 y</td>
<td>Coronary events and CV events</td>
</tr>
<tr>
<td>Cruickshank 2002</td>
<td>Diabetes (N=394)</td>
<td>60±10</td>
<td>10.7 y</td>
<td>Deaths</td>
</tr>
<tr>
<td>Blacher 2003</td>
<td>ESRD (N=242)</td>
<td>52±16</td>
<td>6.5 y</td>
<td>Deaths and CV deaths</td>
</tr>
<tr>
<td>Laurent 2003</td>
<td>Hypertension (N=1,715)</td>
<td>51±13</td>
<td>7.9 y</td>
<td>Deaths, CV deaths and stroke deaths</td>
</tr>
<tr>
<td>Pannier 2005</td>
<td>ESRD (N=305)</td>
<td>53.1±16.2</td>
<td>5.8 y</td>
<td>CV deaths</td>
</tr>
<tr>
<td>Shokawa 2005</td>
<td>Ethnic minority (N=492)</td>
<td>63.7±8.8</td>
<td>10 y</td>
<td>Deaths and CV deaths</td>
</tr>
<tr>
<td>Sutton-Tyrrell 2005</td>
<td>Community based old adults (N=2,488)</td>
<td>73.7±2.9</td>
<td>4.6 y</td>
<td>Deaths, CV deaths and CV events</td>
</tr>
<tr>
<td>Mattace-Raso 2006</td>
<td>Community based adults (N=2,835)</td>
<td>71.7±6.7</td>
<td>4.9 y</td>
<td>Deaths and CV deaths</td>
</tr>
<tr>
<td>Willum-Hansen 2006</td>
<td>General population (N=1,678)</td>
<td>40-70</td>
<td>9.4 y</td>
<td>Deaths, CV deaths and CV events</td>
</tr>
<tr>
<td>Choi 2007</td>
<td>chest pain patients (N=497)</td>
<td>57.7±10.1</td>
<td>2.6 y</td>
<td>Deaths, CV deaths and CV events</td>
</tr>
<tr>
<td>Zoungas 2007</td>
<td>ESRD (N=207)</td>
<td>55±13</td>
<td>3.6 y</td>
<td>CV deaths and CV events</td>
</tr>
<tr>
<td>Terai 2008</td>
<td>Hypertension (N=676)</td>
<td>62±12</td>
<td>4.8 y</td>
<td>Deaths and CV events</td>
</tr>
<tr>
<td>Anderson 2009</td>
<td>Non-diabetic general population (N=174)</td>
<td>60±10</td>
<td>19.6 y</td>
<td>Deaths and CV events</td>
</tr>
<tr>
<td>Mitchell 2010</td>
<td>General population (n = 2,232)</td>
<td>63±12</td>
<td>7.8 y</td>
<td>CV events</td>
</tr>
<tr>
<td>Wang 2010</td>
<td>General population (n = 1,272)</td>
<td>52±13</td>
<td>15 y</td>
<td>Deaths and CV deaths</td>
</tr>
<tr>
<td>Verbeke 2010</td>
<td>Dialysis patients (n=1084)</td>
<td>61.9</td>
<td>2 y</td>
<td>Deaths and non fatal CV events</td>
</tr>
</tbody>
</table>
Prediction of Cardiovascular Events and All-Cause Mortality With Arterial Stiffness

A Systematic Review and Meta-Analysis

Charalambos Vlachopoulos, MD, Konstantinos Aznaouridis, MD, Christodoulos Stefanadis, MD

*equal contribution

*equal contribution
Increased aortic stiffness is associated with a 2-fold increase in total CV events, CV mortality, and all-cause mortality.

Vlachopoulos C / Aznaouridis K, and Stefanadis C. JACC 2010
An increase in aortic PWV by 1 m/s corresponded to an age-, sex-, and risk factor–adjusted risk increase of 14%, 15%, and 15% in total CV events, CV mortality, and all-cause mortality, respectively.

Vlachopoulos C / Aznaouridis K, and Stefanadis C. JACC 2010
Aortic PWV as predictor of events

HIGH RISK vs. LOW RISK subjects

The predictive ability of arterial stiffness is higher in subjects with a higher baseline CV risk, such as renal disease

Vlachopoulos C / Aznaouridis K, and Stefanadis C. JACC 2010
Aortic stiffness

A theoretical basis

High reproducibility

Ease of use

Incremental value

Ability to monitor and guide therapy
Can we modify aortic stiffness?
Divergent Effects of Laughter and Mental Stress on Arterial Stiffness and Central Hemodynamics

Charalambos Vlachopoulos, MD, Panagiotis Xaplanteris, MD, Nikolaos Alexopoulos, MD, Konstantinos Aznaouridis, MD, Carmen Vasiliadou, PhD, Katerina Baou, MD, Elli Stefanadi, MD, and Christodoulos Stefanadis, MD
Divergent Effects of Laughter and Mental Stress on Arterial Stiffness and Central Hemodynamics

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Psychosomatic Medicine 2009
Drugs and Arterial Stiffness

Vlachopoulos C et al

Wilkinson I
Does improvement in stiffness mediate an improvement in prognosis?
ESRD pts: Despite similar reduction in MBP, only those who survived reduced aortic pulse wave velocity

## 2007 Guidelines for the Management of Arterial Hypertension

### Table 4  Availability, prognostic value and cost of some markers of organ damage (scored from 0 to 4 pluses)

<table>
<thead>
<tr>
<th>Markers</th>
<th>CV predictive value</th>
<th>Availability</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiography</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Carotid Intima-Media thickness</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Arterial stiffness (Pulse wave velocity)</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

### Subclinical organ damage

- Electrocardiographic LVH (Sokolow-Lyon >38 mm; Cornell >2440 mm²*ms) or:
  - Echocardiographic LVH° (LVMI M ≥ 125 g/m², W ≥ 110 g/m²)
  - Carotid-wall thickening (IMT ≥ 0.9 mm) or plaque
- Carotid-femoral pulse wave velocity >12 m/s
- Ankle/brachial BP index <0.9
- Slight increase in plasma creatinine:
  - M: 115–133 μmol/l (1.3–1.5 mg/dl)
  - W: 107–124 μmol/l (1.2–1.4 mg/dl)
- Low estimated glomerular filtration rate† (<60 ml/min/1.73 m²) or creatinine clearance° (<60 ml/min)
- Microalbuminuria 30–300 mg/24 h or albumin-creatinine ratio: ≥22 (M); or ≥31 (W) mg/g creatinine
Subclinical organ damage (incl. PWV >12 m/s) predicted cardiovascular death independently of SCORE and the combination may improve risk prediction especially in subjects with SCORE 1%-5%.

Sehestedt T, et al EHJ 2009
Ready for implementation into clinical practice?
Reference values for Arterial Stiffness Collaboration

13 European Centers
24,484 (total)/ 11,092 (PWV) subjects
There are convincing reasons why cfPWV as a measure of arterial stiffness should be included in routine clinical assessment of patients at risk for cardiovascular diseases.

Brunner-La Rocca HP Eur Heart J 2010 (Editorial Comment)
PWV: Reference values (children and teenagers)

Reusz G, et al, Hypertension 2010
Lurbe E Hypertension 2010 (editorial commentary)
PWV in clinical practice

Asymptomatic individual

Office-based evaluation
Calculate 10-year probability of CHD

Intermediate (5-10%)
- Family history of early onset CHD
- Metabolic syndrome
- Substantially elevated single risk factor

Low (<5%) with any of the following
- Novel risk factors
- Chronic renal insufficiency

Assess arterial function and structure by ultrasonography and tonometry

No
- Low risk
  - Usual risk reduction therapy

One or both tests abnormal

Yes
- Elevated risk
  - Aggressive risk reduction therapy
Biomarkers: do we see what really matters?
Biomarkers: do we see what we want to see?
Medicine is an art that (...) has principles in action and reasoning in every case

Plato, Gorgias