Preventing Early Vascular Ageing (EVA) and its hemodynamic changes

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Age and cardiovascular disease

- Age - a greater risk factor than traditional risk factors
- Age-related changes in vascular structure and function, in association with metabolic disturbances, are likely to be responsible for increased cardiovascular risk

Increasing Age

Increased exposure to risk factors

Changes in the vessel wall

Increase in CAD, Hypertension, CHF, stroke

O´Rourke, Safar, Dzau. Vascular Med 2010
“A man is as old as his arteries”

Thomas Sydenham 1624 – 1689
“The English Hippocrates”
Chronological v Biological Ageing
Left hand image represents twins who looked younger for their age (average perceived age 64, range 57-69) than those represented by right hand image (average perceived age 74, range 70-78 years). The older looking twin had more risk factors, shorter telomeres and a worse prognosis during follow-up.

The life course of human subjects
Life course across generations

Vigeland Statue Park, Oslo, Norway
Birth weight and adult disease

**low birth weight (LBW)**

- hypertension
- type 2 diabetes
- hyperlipidaemia
- insulin resistance
- metabolic syndrome
- vascular dysfunction
- coronary heart disease (CHD)
- osteoporosis
- depression and other psychopathologies

LBW: caused by impaired fetal growth or preterm delivery
CVD risk in Russia
Different levels of understanding

• Genetic factors
• Early life programming
• Influences in adolescence
• Adult lifestyle
• Working and living conditions
• Social stress
• Quality of health care
• Cultural factors
Growing up in the Soviet Union
Arterial ageing and stiffening

What is vascular ageing?

- Arterial stiffening (elastin↓, collagen↑), increased pulse pressure (PP) and pulse wave velocity (PWV) when >12 m/s is risk
- Glycation of vessel wall proteins (AGE)
- Endothelial dysfunction
- Decreased NO production, oxidative stress
- Local and perivascular inflammation (CRP, IL)
- Capillary rarefaction and dysfunction
- Telomere shortening (attrition)

*Increased in hypertension in diabetes!*
Sphygmocor for PWV and Augmentation Index
Arteriograph for central pressure and arterial stiffness
Pulse Wave Velocity
& Augmentation Index
Uses Arterial tonometer (radial)
Carotid pressure waveform is recorded by applanation tonometry
The Impact of the Early Wave Reflection

- This earlier return to the heart of the reflected pressure wave (due to stiffening of the arteries) changes the aortic root pressure waveform, … with 3 key clinical implications
  - Central pulse pressure increases ... **increasing risk of stroke and renal failure**
  - LV Load increases... **increasing LV mass**, and accelerating progress towards LV hypertrophy and heart failure
  - Coronary artery perfusion pressure in diastole reduces.... **increasing risk of myocardial ischemia**
Measurement of carotid-femoral PWV with the foot to foot method

Normal values for pulse wave velocity average according to age (1455 healthy NT subjects)

NT = normotensives (out of a total 16,867 subjects from 8 European countries)
Meta-analysis on individual data: independent predictive value of aortic stiffness for CV events (16,358 subjects)

Y Ben Schlomo et al. ARTERY 11, Oct 2011
JACC 2013, accepted

14 studies including 16,358 subjects with 1700 combined CVD events.

z-scores of log transformed cf-PWV (pooled SD = 3.3m/s).

Higher predictive value in younger subjects: (p-value for trend = 0.0095).
Vascular and brain ageing - cognitive decline

normal

atrophy

microvascular lesion
Arterial stiffness as an independent predictor of longitudinal changes in cognitive function in the older individual
Angelo Scuteri\textsuperscript{a}, Manfredi Tesauro\textsuperscript{b}, Sergio Appolloni\textsuperscript{a}, Francesca Preziosi\textsuperscript{a}, Anna Maria Brancati\textsuperscript{a} and Massimo Volpe\textsuperscript{c,d}
Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility – Reykjavik Study

Gary F. Mitchell,¹ Mark A. van Buchem,² Sigurdur Sigurdsson,³ John D. Gotal,¹ Maria K. Jonsdottir,⁴⁵ Ólafur Kjartansson,³ Melissa Garcia,⁵ Thor Aspelund,³⁶ Tamara B. Harris,⁵ Vilmundur Gudnason³⁶ and Lenore J. Launer⁵

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⁶ Faculty of Medicine, University of Iceland, 101 Reykjavik, Iceland
Figure 2 Prevalence of subcortical infarctions according to sex-specific tertiles of aortic stiffness measures in participants with no prior history of clinical stroke or transient ischaemic attack. PWV = pulse wave velocity.
Pathophysiology of EVA

Poorly identified CV risk factors
(infection-inflammation, oxidative stress, low birth weight, genetics, fetal programming, telomere length, increased sympathetic activity…)

Well identified CV risk factors
(gender, BP, lipids, smoking, diabetes)

Mechanical and chemical stress

Large artery damage
arterial stiffening

Large/small artery cross-talk

EVA
Inadequate repair mechanism

Small artery damage
wall/lumen ratio and rarefaction

Target organ damage
- Myocardial ischemia
- Reduction in GFR
- Microalbuminuria
- White matter lesions
- Cognitive decline

Nilsson PM, et al J Hypertens 2013
Haemodynamic Ageing Syndrome (HAS)

- **Age-related changes in brachial BP**
  - isolated systolic hypertension (ISH)
  - elevated pulse pressure (PP)
- **Age-related changes in central BP**
  - Increased central systolic BP and PP
- **Increased BP variability**
  - Linked to arterial stiffness
- **Decreased heart rate variability**
  - Linked to arterial stiffness
- **Impaired endothelial function**
  - Less vasodilation
- **Impaired baroreceptor function, orthostatic hypotension**
  - Linked to arterial stiffness
EVA and HAS

Age-related morphological changes in the arterial wall and its haemodynamic consequences
N= 3362

Genetics
Genome-wide \(-\log_{10} P\)-value plots and effects for significant loci related to BP

**Summary of GWAS for PWV in the SardiNIA study cohort with controls from the Amish population (n= 1828)**

**Conclusion:** A genome-wide association study identified a SNP in the *COL4A1* gene that was significantly associated with PWV in 2 populations. Collagen type 4 is the major structural component of basement membranes, suggesting that previously unrecognized cell-matrix interactions may exert an important role in regulating arterial stiffness.

Telomeres at the end of the DNA helix
Telomere structure: an overview

- Telomeres are the ends of chromosomes
- Human telomeres consist of TTAGGGG repeats
- Function is to protect the ends of chromosomes from fusion or damage

Nobel Prize in 2009
The “Telomere” Hypothesis of CAD

• Those individuals born with shorter telomeres may be at increased risk of CAD

• In addition to individual genes, a more global structural property of the genetic material may explain the familial basis of CAD

• Conventional risk factors for CAD may act partly via their effect on telomere biology

• Variation in telomere length may, at least in part, provide an explanation for the variability in both susceptibility to & age of onset of CAD

Samani NJ & P van der Harst Heart 2009
Telomere length in healthy offspring of subjects with and without CAD

S Brouilette et al.  Heart 2008
Telomeres and Risk of Premature MI Study

- 203 patients with myocardial infarction before the age of 50 years
- 180 age-gender matched controls without history of CHD
- Measurement of leucocyte mean telomere length (LTL)
- Adjustment for age, gender, acquired and biochemical risk factors

Brouilette et al ATVB 2003
Telomere shortening in premature MI
203 MI cases and 180 matched controls

Brouilette et al. ATVB 2003
Risk of MI is progressively higher with shorter telomere length

![Graph showing Odds Ratio against Quartile of telomere length with asterisks indicating statistical significance.](image-url)

Brouilette et al., ATVB, 2003.
Telomere length, CHD events and benefits from statin treatment in the WOSCOPS trial

<table>
<thead>
<tr>
<th>Tertile</th>
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<th>Statin</th>
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<td>3</td>
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</tbody>
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Brouilette *et al.* Lancet 2007
Telomere length in vascular cells in CAD

Endothelial cells

VSMCs

Ogami et al. ATVB 2004

Data are displayed as $-\log_{10}(P$ values) against chromosomal location for the 2,362,330 SNPs that were tested. The dotted line represents a genome-wide level of significance at $P = 5 \times 10^{-8}$. Loci that showed an association at this level are plotted in red.

Forest plot showing the **effect of telomere length on CAD risk obtained for each SNP** using a risk score analysis for each SNP. Effect sizes are plotted with 95% confidence intervals. The overall estimate is from a fixed-effects meta-analysis over all SNPs, where the odds ratio (OR) relates to the change in CAD risk for a S.D. change in telomere length.

Time course of *Early Vascular Ageing* (EVA) and possible intervention by *Aggressive Decrease of Atherosclerosis Modifiers* (ADAM) in CVD risk patients

Period of early detection and successful regression

Nilsson PM, Laurent S. *et al.* Hypertension 2009
Inverse correlation between omega-3 fatty acid intake and telomere attrition rate

Farzaneh-Far R et al. JAMA 2010
Proposed scheme for the mechanisms by which caloric restriction and the caloric restriction mimetic resveratrol confers vasoprotection
Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

Look AHEAD

Hazard ratio, 0.95 (95% CI, 0.80–1.09)  
P=0.51

The Look AHEAD Research Group. NEJM June 24, 2013
Summary

• Early life programming is of importance for shaping susceptibility to some chronic diseases in adult life

• *Environmental* (nutrition, smoking, stress), *obstetric* (placenta), *genetic* (maternal) and *epigenetic* factors are of importance for fetal growth and organ development

• Arterial stiffness (arteriosclerosis) precedes atherosclerosis, plaque formation and clinical events

• Early vascular ageing (EVA) could be influenced by less elastin content in the arterial wall in former IUGR babies

PN 2013