Early vascular ageing (EVA) and beyond – accelerated biological development or premature aging in pediatric hypertension

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Early Vascular Ageing (EVA syndrome), accelerated development or premature ageing?

- Primary hypertension and cardiovascular disease is associated with features of ageing of vascular tree – from aorta to capillaries.

- The hallmark of EVA is increased stiffness of arteries

- However, primary hypertension is not only arterial disease. PH is a syndrome of neuro-immune-metabolic abnormalities associated with faster biological development and hypertension is a clinical sign of these disorders.

- Adolescents with PH present the same neuro-immuno-metabolic abnormalities as adults older by few decades

Nilsson PM et al. 2008

Litwin M et al. 2016
## Features of aging

### Aged man
- Chronological age
- Sarcopenia
- Increased visceral fat mass
- IR/metabolic syndrome/T2DM
- Oxidative stress
- Increased carotid IMT
- Increased arterial stiffness (PWV, central SBP)
- Decreased FMD
- Immune senescence
- Increased sympathetic drive

### Comment
- From biological and evolutionary point of view, chronic diseases of adulthood such as PH and CV disease develop only after achievement of reproductive years and are typical for late adulthood/elderly.
- The basis of both PH and CV disease are alterations in the structure and function of arterial vessels and the most important risk factor for CV disease is age.
- Thus, the development of PH and its complications in the form of CV disease **earlier** than in the adulthood/elderly may be termed as “**premature**” or “**early**”
Methods for assessing vascular disease and arterial stiffness

- Assessment of vascular structure and function is the same as assessment of mortality risk
- Ancient China
- Ancient Greece and Rome
Lessons about the pulse in five books written by Joseph Strutius Oporinus, Basileae 1555 (Basel 1555)

• „Because the artery can withstand and raise bigger or smaller weights, depending on the force, it can be noticed that if in that place one puts a leaf, some skin, a piece of canvas or cloth, it will move up or down”
Pulse wave analysis

Old subject or uremic/diabetic/hypertensive child. High resistance of peripheral arteries and low arterial compliance causes greater left ventricular load.
Pulse wave velocity

- Carotid – femoral
  - elastic, great arteries
  - PWV correlates with the risk of CV event

- Carotid – radial
  - muscular arteries
  - no correlation with CV risk

<table>
<thead>
<tr>
<th>Wiek (lata)</th>
<th>PulsePen (tonometr)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Chłopcy 95. cc [m/s]</td>
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<tr>
<td>7</td>
<td>5,4</td>
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<td>17</td>
<td>6,87</td>
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<tr>
<td>18</td>
<td>7,08</td>
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</tbody>
</table>
Carotid IMT – a measure of arterial age
The prevalence of subclinical arterial injury in adolescents with primary hypertension – cIMT

- Increased carotid IMT in PH in comparison with normotensive controls
- Carotid IMT >95 pc in 28-40% of PH pts
  
  Sorof et al. 2003, Litwin et al. 2004, 2006

- Decreased carotid elasticity in PH pts in comparison with normotensive controls
  
  Litwin et al. 2004

- Systematic review of 28 high-quality pediatric studies - PH is associated with increased carotid IMT.

- However, multiple regression analysis did not find uniform association of cIMT with SBP/DBP

- Is cIMT determined by other factors related with PH?

  Day TG et al. Cardiol Young 2017
The prevalence of subclinical arterial injury in adolescents with primary hypertension – PWV, FMD

- BP is an independent determinant of PWV in preHT youth
- In HT adolescents PWV is associated with exposure to cardiovascular risk factors (obesity, metabolic syndrome, dyslipidemia)
- Synergistic effect of obesity and hypertension on increased PWV

- Decreased FMD in children and adolescents with CV risk factors (obesity, hypertension)
- Synergistic effect of obesity and hypertension on decrease of FMD

*rev in Urbina EM et al. 2018*
Physiological rise of BP starts with pubertal spurt. BP differences between boys and girls – significant rise of BP in boys but not girls (start of growth spurt in Poland ♀- 11,5 ♂- 13,5 year of age) (n = 25,000)

- Prevalence of arterial hypertension in children and adolescents
  (0-18 yrs) is 2.2-5%

  *Chiolero et al. J Hypertens 2007*

  *Nawarycz-Ostrowska et al. Kardiol Pol 2007*

- However, among adolescents (14-18 yrs) prevalence of arterial hypertension is greater and reaches 10-12% (Poland, Warsaw)

  *Derezinski et al. Prog Med 2015*

  *Symonides et al. Arch Med. Sci 2010*

- Boys : girls 4 : 1

- The main form of arterial hypertension in children >10 yrs is primary hypertension (PH)

  *Gupta-Malhorta et al. Am J Hypertens 2015*
EVA or general phenomenon of accelerated biological maturation?

- NHANES II and III: The level at which BP tracks during childhood is related to growth, obesity and the degree of maturation acquired.

- Children whose BP are rising or falling in relation to their peers have body growth and maturation characteristics (bone age, no. of permanent teeth, waist circ.) similar to those who maintain their rank order high or low, respectively.

Lauer RM et al. Hypertension 1984
Tempo of biological maturity and cardiovascular risk

Association of age at menarche with cardiovascular risk factors, vascular structure, and function in adulthood: the Cardiovascular Risk in Young Finns study\textsuperscript{1–3}

Am J Clin Nutr 2008;87:1876–82.

Mika Kivimäki, Debbie A Lawlor, George Davey Smith, Marko Elovaara, Marko Jokela, Liisa Keltikangas-Järvinen, Jussi Vahtera, Leena Taittonen, Markus Juonala, Jorma SA Viikari, and Olli T Raitakari

<table>
<thead>
<tr>
<th>Adulthood outcome</th>
<th>$\beta$</th>
<th>95% CI</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (in kg/m\textsuperscript{2})</td>
<td>-0.81</td>
<td>-1.08, -0.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>-17.77</td>
<td>-24.77, -10.77</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>-0.006</td>
<td>-0.010, -0.002</td>
<td>0.003</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>-1.07</td>
<td>-1.87, -0.28</td>
<td>0.008</td>
</tr>
<tr>
<td>Insulin (mU/L)</td>
<td>-0.600</td>
<td>-0.925, -0.275</td>
<td>0.0003</td>
</tr>
<tr>
<td>Insulin resistance (HOMA index)</td>
<td>-0.155</td>
<td>-0.238, -0.072</td>
<td>0.0003</td>
</tr>
<tr>
<td>Metabolic syndrome\textsuperscript{4}</td>
<td>-0.022</td>
<td>-0.043, -0.001</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Tempo of biological maturation and primary hypertension in adulthood

- Males and females who had passed through peak height velocity earlier had significantly increased risk of elevated BP at the age of 50

_Hulanicka B et al. Econ Hum Bol 2008_

- Rapid linear growth between 8 an 13 years, and especially between 11 and 13 years, predicts elevated adult BP both in boys and girls.

- The greater growth velocity, the more severe hypertension at 50 yrs of age

_Halldorsson TJ et al. Hypertension 2011_
Fels Longitudinal Study – delayed vs accelerated maturation and different exposure to CV risk factors in adulthood.

Late maturation – lower exposure to CV risk factors

Early maturation – higher exposure to CV risk factors

Sun SS et al. 2009

The earlier age at growth spurt, the higher BP at age of >20 yrs

Sabo RT et al. 2017
Tempo of biological maturation and severity of primary hypertension in childhood/adolescence

• PH in childhood is associated with more advanced biological maturity expressed as difference between bone age (BA) and chronological age (CA) than in BMI-matched normotensive children. Hypertensive children have older BA by 1.5 yrs.

• Hypertensive children with faster biological maturation have more severe hypertension.

Pludowski P et al. Hypertension 2009

Figure 2. Biological maturity expressed as a difference between BA and CA in relation to blood pressure status. Significant differences between normotensive cases and prehypertensive (P=0.006) and hypertensive patients (P=0.0001), as well as between stage-2 hypertensives and prehypertensives (P=0.009).
Primary hypertension in children and adolescents – is it only EVA or rather accelerated maturation and aging?

Disturbed body composition.

• Hypertensive children have decreased lean body mass in relation to body weight in comparison with normotensive children (adjusted both for age, weight and height)

Pludowski et al. Hypertension 2009
Primary hypertension in children and adolescents - metabolic abnormalities.

- Hypertensive children are taller and have a greater BMI than normotensive peers.
  
  *Flynn J, Alderman MH Pediatr Nephrol 2005*

- Metabolic syndrome is 10 times more prevalent among hypertensive adolescents (20%) than in general pediatric population (2%).

  *Litwin M et al. Am J Hypertens 2007*
Primary hypertension in children and adolescents - significantly greater oxidative stress in hypertensive adolescents in comparison with normotensive peers.

<table>
<thead>
<tr>
<th></th>
<th>Primary hypertension (n = 30)</th>
<th>Control (n = 30)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male), n (%)</td>
<td>19 (63.3%)</td>
<td>17 (43.3%)</td>
<td>0.598</td>
</tr>
<tr>
<td>Age (years)</td>
<td>14.8 ± 1.9</td>
<td>14.3 ± 1.7</td>
<td>0.710</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>18.3 ± 1.94</td>
<td>18.2 ± 1.18</td>
<td>0.240</td>
</tr>
<tr>
<td>BMI-SDS</td>
<td>-0.98 ± 0.83</td>
<td>-0.9 ± 0.87</td>
<td>0.401</td>
</tr>
<tr>
<td>Family history</td>
<td>14 (46.7%)</td>
<td>5 (16.7%)</td>
<td>0.012*</td>
</tr>
<tr>
<td>Office SBP (mmHg)</td>
<td>149.1 ± 9.65</td>
<td>105.5 ± 9.03</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Office SBP-SDS</td>
<td>3.69 ± 1.12</td>
<td>-0.35 ± 0.85</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Office DBP (mmHg)</td>
<td>98.8 ± 9.62</td>
<td>67.5 ± 8.48</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Office DBP-SDS</td>
<td>2.98 ± 0.76</td>
<td>0.30 ± 0.72</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Native thiol (µmol/l)</td>
<td>350.5 ± 55</td>
<td>428.8 ± 43.6</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Total thiol (µmol/l)</td>
<td>402.5 ± 56.7</td>
<td>471.2 ± 47.3</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Disulphide (µmol/l)</td>
<td>26.0 ± 6.7</td>
<td>21.8 ± 5.6</td>
<td>0.019*</td>
</tr>
<tr>
<td>Disulphide/native thiol (%)</td>
<td>7.5 ± 2.2%</td>
<td>4.9 ± 1.4%</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Disulphide/total thiol (%)</td>
<td>6.5 ± 1.6%</td>
<td>4.4 ± 1.2%</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Native thiol/total thiol (%)</td>
<td>86.9 ± 3.3%</td>
<td>91 ± 2.4%</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

Cakici EK et al. Pediatr Nephrol 2018

Activation of innate immune system in children with primary hypertension – association with metabolic abnormalities and visceral obesity

Increased serum concentrations of MIP-1β and RANTES in hypertensive children in comparison with normotensive controls

The greater number of metabolic abnormalities, the greater immune activity.

The greater immune activity and lower adiponectin concentrations, the greater cIMT.

Litwin M et al. Pediatr Nephrol 2010
Accelerated aging of immune system in hypertension – evidence from studies in adults.

19 hypertensive pts (51.6 yrs) vs 19 normotensive controls (51.5 yrs)

Increased number of CD8 T lymphocytes with markers of immune senescence (CD57+/CD28null)

Youn J-C et al. Hypertension 2013

Hypertensive adults – 52 yrs.
Greater number of T cells bearing 45RO – a marker of activation and senescence.

Itani HA et al. Hypertension 2016
Accelerated maturation/aging of immune system in primary hypertension – evidence from pediatric studies.

45RO molecule is a marker of memory cells. The greater number and intensity of RO45 molecules, the greater number of memory cells. The older man, the greater number of memory cells.

Hypertensive children had more memory cells

<table>
<thead>
<tr>
<th>CD45 RO⁺ CD4 (%)</th>
<th>Primary hypertension (N = 68)</th>
<th>Normotensive controls (N = 26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>43.6 ± 10.2</td>
<td>38.6 ± 9.9</td>
<td>p = 0.04</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>CD45 RO⁺ CD8 (%)</th>
<th>25.0 ± 9.1</th>
<th>19.4 ± 6.9</th>
<th>p = 0.008</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD45RA⁺/RO⁺ CD4 ratio</td>
<td>1.3 ± 0.5</td>
<td>1.6 ± 0.8</td>
<td>p = 0.04</td>
</tr>
<tr>
<td>CD45 RA⁺/RO⁺ CD8 ratio</td>
<td>3.6 ± 2</td>
<td>4.6 ± 1.7</td>
<td>p = 0.03</td>
</tr>
</tbody>
</table>

Children with LVH had more older, memory cells than those without LVH

Gackowska L et al. J Hypertens 2018
Accelerated maturation/aging of immune system in primary hypertension – evidence from pediatric studies.

Hypertension was the only predictor, independent of BMI, age and sex, of CD4 and CD8 cells distribution. Hypertensive children had significantly increased pool of T cells bearing activation and senescence markers. Shift towards them correlated with:
- arterial stiffness,
- central BP,
- subclinical arterial injury,
- total peripheral resistance

Gackowska L et al. J Hypertens 2018

| Table 6: Results of quantile regression models: hypertension mutually adjusted for BMI z-score, sex and age; only nonoverlapping confidence intervals for hypertension beta (β) are presented |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Dependent variable (%) | Intercept estimate (95% CI) | Explanatory variables mutually adjusted: β estimate (95% CI) |
| CD4+/CD45RA/-/CCR7- | 22.36 (8.42–28.18) | Hypertension (yes) | BMI z-score | Sex (female) | Age |
| CD4+/CD45RA/+/CCR7+ | 77.28 (71.71–91.45) | -7.55 (–9.17 to 3.52) | 0.52 (–0.70 to 1.83) | -2.44 (–6.21 to 0.59) | -0.33 (–0.51 to 0.53) |
| CD4+/CD45RO/-/CD31+ | 71.99 (55.09–85.24) | 7.64 (3.57–9.18) | -0.51 (–1.83 to 0.39) | 2.39 (0.59–6.41) | 0.36 (–0.53 to 0.45) |
| CD4+/CD45RO/-/CD31+ | 28.00 (15.75–45.64) | -2.61 (–7.57 to 0.61) | 0.53 (–0.63 to 1.45) | 1.23 (–3.26 to 2.99) | 0.34 (–0.57 to 1.37) |
| CD4+/CD45RO/-/CD31+ | 46.18 (19.08–66.85) | -6.46 (–13.38 to 3.32) | -0.33 (–2.13 to 1.06) | 3.79 (0.42–7.21) | 0.76 (–1.03 to 3.36) |
| CD4+/CD45RO/-/CD31+ | 49.65 (33.14–77.16) | 6.35 (2.14–13.81) | 0.89 (–0.85 to 2.13) | -3.04 (–6.74 to 0.48) | -0.57 (–3.27 to 1.17) |
| CD4+/CD45RO+/CD28+ | 95.93 (93.35–100.21) | 1.36 (0.38–3.25) | -0.01 (–0.31 to 0.28) | -0.52 (–1.79 to 0.14) | 0.16 (–0.24 to 0.25) |
| CD4+/CD45RA/-/CD31+ | 29.54 (–2.80 to 38.80) | -3.97 (–6.62 to 0.03) | 0.72 (–2.05 to 1.88) | 0.53 (–3.38 to 9.1) | -0.68 (–1.36 to 1.22) |

<table>
<thead>
<tr>
<th>Correlation</th>
<th>r</th>
<th>p</th>
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<tbody>
<tr>
<td>CD4/CD4RA/A31- vs PWV vs AoBP</td>
<td>0.329</td>
<td>0.02</td>
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<td></td>
<td>0.352</td>
<td>0.008</td>
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<tr>
<td>CD4/CD4RA/28+ vs PWV</td>
<td>-0.301</td>
<td>0.03</td>
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<tr>
<td>CD4/CD4RO vs WCSA vs WCSA-SDS vs TPR</td>
<td>0.403</td>
<td>0.04</td>
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<tr>
<td></td>
<td>0.453</td>
<td>0.001</td>
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<tr>
<td></td>
<td>0.284</td>
<td>0.02</td>
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<tr>
<td>CD8/CD8RO/31- vs AoBP</td>
<td>0.335</td>
<td>0.02</td>
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<tr>
<td>CD8/CD8RO/A31+ vs LCSD vs AoBP</td>
<td>0.294</td>
<td>0.03</td>
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<tr>
<td></td>
<td>0.387</td>
<td>0.006</td>
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<td></td>
<td>0.326</td>
<td>0.02</td>
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<tr>
<td>CD4/CD4/31+ vs AoBP</td>
<td>-0.343</td>
<td>0.01</td>
</tr>
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</table>
Ageing vs primary hypertension in childhood/adolescence

**Aged man**
- Older
- Sarcopenia
- Increased visceral fat mass
- IR/metabolic syndrome/T2DM
- Oxidative stress
- Increased carotid IMT
- Increased arterial stiffness
- Decreased FMD
- Immune senescence
- Increased sympathetic activity

**Hypertensive adolescent**
- Accelerated maturation
- Decreased ratio of lean mass/BW
- Visceral obesity
- Metabolic syndrome
- Oxidative stress
- Increased carotid IMT
- Increased arterial stiffness
- Decreased FMD
- More mature/memory/senescent T cells
- Increased sympathetic activity
Is rejuvenation of CV system possible?
EVA vs ADAM (aggressive decrease of atherosclerosis modifiers)
Pediatric experience with progeria syndrome.

- 25 pts with Hutchinson-Gilford progeria syndrome
- Farnesyl transferase inhibitor (FTI) for min. 2 years
  
  *Gordon BL et al. PNAS 2012*

  - FTI + statin + bisphosphonate
  - Median f-up – 5.3 years
  - Decrease of IMT
  - Decrease of PWV
  - Increased survival in treated group

*Gordon BL et al. Circulation 2014*
Is rejuvenation of CV system possible?
Pediatric experience with chronic kidney disease (Mönckebergs arteriosclerosis typical for aging)
(ESCAPE Study)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>CKD</th>
<th>Dialysis</th>
<th>Rtx</th>
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<tbody>
<tr>
<td>CCA IMT (mm)</td>
<td>0.39 ± 0.04&lt;sup&gt;c&lt;/sup&gt; -&lt;sup&gt;d&lt;/sup&gt;,&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.44 ± 0.06&lt;sup&gt;b&lt;/sup&gt; -&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.48 ± 0.05&lt;sup&gt;b&lt;/sup&gt; -&lt;sup&gt;c&lt;/sup&gt;,&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.43 ± 0.05&lt;sup&gt;b&lt;/sup&gt;,&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>SDS</td>
<td>0.03 ± 1.0&lt;sup&gt;c&lt;/sup&gt; -&lt;sup&gt;d&lt;/sup&gt;,&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1.3 ± 1.7&lt;sup&gt;b&lt;/sup&gt; -&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3.1 ± 2&lt;sup&gt;b&lt;/sup&gt;,&lt;sup&gt;c&lt;/sup&gt;,&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1.0 ± 1.2&lt;sup&gt;b&lt;/sup&gt;,&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>CCA WCSA (mm²)</td>
<td>6.6 ± 1&lt;sup&gt;c&lt;/sup&gt;,&lt;sup&gt;d&lt;/sup&gt;,&lt;sup&gt;e&lt;/sup&gt;</td>
<td>7.7 ± 1.9&lt;sup&gt;b&lt;/sup&gt;,&lt;sup&gt;d&lt;/sup&gt;</td>
<td>9.2 ± 1.6&lt;sup&gt;b&lt;/sup&gt;,&lt;sup&gt;c&lt;/sup&gt;,&lt;sup&gt;e&lt;/sup&gt;</td>
<td>8.2 ± 1.4&lt;sup&gt;b&lt;/sup&gt;,&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>SDS</td>
<td>0.0 ± 1.0&lt;sup&gt;c&lt;/sup&gt;,&lt;sup&gt;d&lt;/sup&gt;,&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1. ± 1.5&lt;sup&gt;b&lt;/sup&gt;,&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2.6 ± 1.3&lt;sup&gt;b&lt;/sup&gt;,&lt;sup&gt;c&lt;/sup&gt;,&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1.73 ± 1.48&lt;sup&gt;b&lt;/sup&gt;,&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
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Normalization of metabolic milieu and of BP led to significant decrease of carotid IMT after renal transplantation

Litwin M et al. Nephrol Dial Transplant 2008
Is rejuvenation of CV system possible?

Pediatric experience with chronic kidney disease (Mönckebergs arteriosclerosis typical for aging)

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 21)</th>
<th>Study group (n = 22)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>US1</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>11.2 ± 5.1</td>
<td>9.4 ± 3.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>18.3 ± 3.4</td>
<td>20 ± 4.2 (6/2)</td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>142.9 ± 27.5</td>
<td>131.8 ± 20.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>40.6 ± 20.3</td>
<td>36.3 ± 15.9</td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²)</td>
<td>ND</td>
<td>56.1 ± 20.2 (13)††</td>
</tr>
<tr>
<td>cIMT (mm)</td>
<td>0.43 ± 0.03</td>
<td>0.46 ± 0.05*</td>
</tr>
<tr>
<td>CIM (mm²)</td>
<td>7.57 ± 1</td>
<td>8.37 ± 1.24**</td>
</tr>
<tr>
<td>LVMI (g/m².7)</td>
<td>ND</td>
<td>35.8 ± 9.9 (6)‡‡</td>
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<td>SBP (mmHg)</td>
<td>ND</td>
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<td>DBP (mmHg)</td>
<td>ND</td>
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21 children after rtx; 9 year follow up
Stabilization of cIMT over time what means arteriosclerosis regression

Balzano R et al. Pediatr Transplant 2011
Is rejuvenation of CV system possible?
Pediatric experience with obese, pre- and hypertensive children

- 3-months randomized, controlled trial; 44 obese, pre-pubertal children
- exercise vs control group
- significant decrease of BP, IMT, PWV
- increase of FMD

Is rejuvenation of CV system possible?

Pediatric experience with obese, pre- and hypertensive children

Significant improvement of endothelial function, and decrease of IMT – greater with diet + exercise than with diet alone.

Detraining led to worsening of endothelial function – continued training led to further improvement.

Woo KS et al. Circulation 2004
Is rejuvenation of CV system possible – pediatric experience with primary hypertension

- N = 86 (22 girls); 14.1 ±2.4 yrs
- 12 mts treatment based on lifestyle intervention and ACEi/ARB
- 24hABPM
- Left ventricular mass & IMT
- Metabolic abnormalities
- Immune activity

- BP normalization in 70% of pts
- Disappearance of severe left ventricular hypertrophy
- Significant decrease of cIMT
- Prevalence of metabolic syndrome decreased by 50%
- Normalization of elevated hsCRP

- The only independent predictor of decrease of LVM and cIMT was not BP decrease but decrease of visceral fat expressed as decrease of waist circumference and normalization of inflammatory markers.

Litwin M et al. Pediatr Nephrol 2010
Significant decrease of oxidative stress after 12 mts of treatment

Sladowska-Kozlowska J et al.
Pediatr Nephrol 2012
Decrease of visceral fat assessed by MRI and regression of subclinical arterial injury (carotid wall cross-sectional thickness- WCSA) after 12 mts of treatment - the greater decrease of visceral fat the greater decrease of cIMT.

Correlation between decrease of intraperitoneal VAT and regression of carotid Wall Cross Sectional Area (WCSA).

\[ p = 0.002 \]

\[ r = 0.289 \]  
\[ p = 0.04 \]

\[ \Delta \text{WCSA} \]

\[ \Delta \text{IV AT} \]

Niemirksa A et al. Hypertension 2013
EVA vs ADAM
(Aggresive Decrease of Atherosclerosis Modifiers)
Nillson PM et al. Hypertension 2009

Adolescents with primary hypertension present with the main features of EVA such as:
- increased IMT, increased arterial stiffness and disturbed function of endothelium

And accompanied by
• subtle but complex abnormalities typical for aging such as:
  - accelerated biological development
  - disturbed body composition
  - visceral obesity
  - insulin resistance/metabolic syndrome
  - oxidative stress
  - accelerated immune maturation/senescence
  - Increased sympathetic drive
• Limited evidence from clinical trials in children indicates that an early treatment (ADAM) may not only cause normotension but also reverse EVA and normalize metabolic abnormalities