Childhood Blood Pressure Matters

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Outline

• Effects of High BP in Adults
• Effects of High BP in Childhood
  • Development of hypertensive TOD
  • Tracking of BP from childhood to adulthood
  • Adult cardiovascular disease
Effects of High BP in Adults

- Cut-points used to define BP thresholds and classification in adults are based on “hard” CV end-points:
  - Myocardial infarction
  - Stroke
  - End-stage renal disease

Early Death
HTN is a Leading Cause of Death Worldwide

The 10 leading causes of death in the world
2012

- **Ischaemic heart disease**: 7.4 million
- **Stroke**: 6.7 million
- **COPD**: 3.1 million
- **Lower respiratory inf...**: 3.1 million
- **Trachea bronchus, lun...**: 1.6 million
- **HIV/AIDS**: 1.5 million
- **Diarrhoeal diseases**: 1.5 million
- **Diabetes mellitus**: 1.5 million
- **Road injury**: 1.3 million
- **Hypertensive...**: 1.1 million
BP Level, Stroke and MI

High BP & Risk of ESRD

Klag et al., NEJM 1996; 334:13
High BP & Risk of ESRD

Hsu et al., Arch Intern Med 2005;165:923
What About the Effects of High BP in the Young?

- Hypertension-related events rarely occur in childhood
- Lack of clinical trial data linking BP levels to long-term outcome
  - USPSTF evidence review
USPSTF Statement, 2013

• “The USPSTF found no direct evidence that routine BP measurement accurately identifies children and adolescents who are at increased risk for cardiovascular disease in adulthood and inadequate evidence that routine BP measurement accurately identifies children and adolescents who are at increased risk for adult hypertension or other intermediate measures of adult cardiovascular disease.”

Moyer et al., Ann Intern Med 2013; 159:61
What About the Effects of High BP in the Young?

- Hypertension-related events rarely occur in childhood
- Lack of clinical trial data linking BP levels to long-term outcome
  - USPSTF evidence review
- Therefore other types of data must be examined to ascertain the effects of high BP in youth
  - Cross-sectional studies
  - Tracking studies
  - Observational cohort studies
Hypertensive TOD in Children

• Left ventricular hypertrophy
• Increased carotid intimal-medial thickness
• Increased vascular stiffness
• Cognitive deficits
• Renal damage
Left Ventricular Hypertrophy

• Many studies have shown that LVH occurs commonly in hypertensive children:
  • Zahka, 1981: LV mass 45% greater in teens with mild HTN compared to normotensives
  • Daniels, 1990: 38% of teens with BP > 90%tile had LV mass >95%tile
  • Hanevold, 2004: 30% of patients from IPHA centers had LVH
  • Brady, 2008: 41% of newly diagnosed with primary HTN had LVH
Left Ventricular Hypertrophy

- Study of effects of BP and BMI in 301 AA teens
- BP level and BMI had additive effects on LVH
- LVH most common in obese hypertensives
- LVMI and prevalence of LVH increased with increasing BP level
- ↑ LV mass appeared at BP levels <90th percentile

Falkner et al., J Pediatr 2013; 162:94
Carotid intimal-medial thickness

- Study of ambulatory BP and cIMT in 28 children with primary HTN, matched by age, sex and BMI to 28 normotensive children
- cIMT higher in the hypertensive group
- cIMT correlated with SBP on ABPM

Lande et al., Hypertension 2006;48:1
Pulse Wave Velocity vs. Mean SBP on ABPM

Mean Wake SBP (mmHg)

SHIP-AHOY Study (Unpublished)
Adverse Cognitive Effects of High BP

- Children with BP >90\textsuperscript{th} percentile in NHANES III had decreased performance on several cognitive tests, notably Digit Span
- In a single-center study, hypertensive children had worse executive function than controls and more internalizing behaviors
- Children with sustained HTN on ABPM were more likely to be diagnosed with a learning disability and to be treated for ADHD

Lande et al., J Clin Hypertens 2012; 14:353
Proteinuria in Children with Pre-hypertension

Proteinuria

Lubrano et al., Pediatr Nephrol 2009; 24:823
Blood Pressure Tracking


- “Thus, blood pressure measured during adolescence predicts…the course of blood pressure and the frequency with which hypertension develops in adults.”
BP Tracking: Muscatine Study

- 2445 subjects examined longitudinally at age 7-18\text{y} and again at age 20-30\text{y}
  - Children with BP > 90\text{th }\%\text{tile on any single measurement were 2.4x more likely than expected to have an adult BP > 90\text{th }\%\text{tile}}
- 959 subjects with 3 or more BP measurements
  - 24\% with 2 or more SBP > 90\text{th }\%\text{tile had adult SBP > 90\text{th }\%\text{tile}}
- Normal childhood BP resulted in a reduced risk of adult HTN

Lauer and Clarke, Pediatrics 1989; 84:633
Progression to HTN among Israeli Adolescents

- 27,000 Israeli adolescents 17-18 y/o followed to age 42y
- Repeated BP measurements available every 3-5y
- Incidence of new HTN cases increased according to baseline BP level
- Hazard ratio for development of HTN for group with highest baseline BP was 2.5 for boys and 2.31 for girls

Tirosh et al, Hypertension 2010; 56:203
Risk of Adult HTN by Childhood BP level – Fels Longitudinal Study

Prediction of Adult HTN and MetS by Childhood SBP

- Analysis of data on childhood BP and relationship to adult HTN and MetS in ~500 participants in the Fels Longitudinal Study
- Participants with elevated childhood BP values had increased risk of HTN and MetS at ≥30 years of age
  - RR of HTN: 1.5-3.8 for boys, 1.5-4.7 for girls
  - RR MetS: 1.1-1.8 for boys, 1.2-5.6 for girls
- Relative risks increased with higher number of elevated BP values in childhood

Prediction of Adult HTN and MetS by Childhood SBP

- HTN →
- MetS →

## TABLE 5
Odds Ratios for Hypertension and Metabolic Syndrome at ≥30 Years of Age (Adjusted for Adult Age and Childhood BMI), Given a Systolic Blood Pressure Exceeding Criterion Values at a Single Examination in Childhood

<table>
<thead>
<tr>
<th>EBP (Yes/No)</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–7 y</td>
<td>3.8 (1.5–9.7)(^a)</td>
<td>4.5 (1.1–17.7)(^a)</td>
<td></td>
</tr>
<tr>
<td>8–13 y</td>
<td>3.5 (1.5–8.3)(^a)</td>
<td>2.7 (1.0–7.1)(^a)</td>
<td></td>
</tr>
<tr>
<td>14–18 y</td>
<td>1.1 (0.5–2.4)</td>
<td>3.8 (1.2–12.7)(^a)</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolic syndrome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–7 y</td>
<td>1.6 (0.6–3.9)</td>
<td>3.1 (1.0–9.7)(^a)</td>
<td></td>
</tr>
<tr>
<td>8–13 y</td>
<td>2.6 (1.1–5.9)(^a)</td>
<td>2.2 (1.0–5.2)(^a)</td>
<td></td>
</tr>
<tr>
<td>14–18 y</td>
<td>1.2 (0.6–2.6)</td>
<td>1.5 (0.6–3.7)</td>
<td></td>
</tr>
</tbody>
</table>

EBP indicates elevated blood pressure at a single examination in childhood that exceeded age- and gender-specific criteria established in part 1; hypertension, systolic blood pressure of >130 mm Hg and/or diastolic blood pressure of >85 mm Hg.

\(^a\) Value is significant at \(P < .05\).
Childrenhood HTN and HTN in Adulthood: i3c Consortium

- Used data from 5035 individuals in 6/7 cohorts included in i3c who had childhood BP measurements and completed questionnaire about HTN at mean age of 46.7y
- Examined tracking of BP over time and whether high BP in childhood was associated with adult HTN
- Correlations between childhood BP and later BP decreased over time but remained significant
- Increase in frequency of adult HTN by BP change group
- Those w/adult HTN more likely to have high BP and adiposity by 10y and abnormal lipids at 16y

Urbina et al. Hypertension 2019;73:1224
Figure 1. Spearman correlation coefficients for blood pressure (BP) between age groups (P<0.0001). DBP indicates diastolic BP; and SBP, systolic BP.
Childhood HTN and HTN in Adulthood: i3c Consortium

Urbina et al. Hypertension 2019;73:1224
Relationship Between Childhood BP and Adult cIMT

- Cardiovascular Risk in Young Finns Study
- Measured CV risk factors including BP in 2200 individuals at ages 3-18 and cIMT 21 years later
- cIMT in adulthood was associated with both childhood and adult SBP
- Increasing number of CV risk factors in teens (12-18y) was significantly associated with adult cIMT; weaker relationship between CV risk factors at ages 3-9y and adult cIMT

Raitakari et al, JAMA 2003; 290:2277
## Table 4. Multivariable Model of the Relationships Between Risk Variables Measured at Ages 12-18 Years and Common Carotid Artery Intima-Media ThicknessMeasured 21 Years Later (n = 1170)*

<table>
<thead>
<tr>
<th>Risk Variable</th>
<th>Regression Coefficient†</th>
<th>SE</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>0.023</td>
<td>0.006</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.002</td>
<td>0.001</td>
<td>.24</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.010</td>
<td>0.003</td>
<td>.001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.009</td>
<td>0.003</td>
<td>.007</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.013</td>
<td>0.003</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking (no/yes)</td>
<td>0.016</td>
<td>0.007</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviation: LDL-C, low-density lipoprotein cholesterol.
*Mean age at time of first measurement, 14.9 (SD, 2.4) years.
†Expressed in millimeters for a 1-unit change in age (year) and a 1-SD change in other continuous variables and for the presence or absence of smoking.
Effect of Child & Adult BP on Subclinical Atherosclerosis: i3C Consortium

- Combines data from multiple cohort studies: Muscatine, Bogalusa, Young Finns, Childhood Determinants of Adult Health, among others
- Examined BP from childhood and adulthood and the risk of elevated adult cIMT (>90th percentile)
- Relative risk of high adult cIMT:
  - Incident HTN: 1.57
  - Persistent HTN: 1.82
  - Resolved HTN: 0.66

Effect of Child & Adult BP on Subclinical Atherosclerosis: i3C Consortium

Prediction of Increased Adult cIMT

- Data from 5925 participants in 6 i3c Consortium cohorts used to determine childhood BP levels predictive of increased adult cIMT (>90\textsuperscript{th} percentile)
- Increased SD of childhood SBP, MAP and PP were associated with increased adult cIMT;
- Various BP components examined for predictive ability – SBP was more predictive than DBP or any other BP component
- Childhood BP cut-points at different ages derived that were predictive of increased adult cIMT

Koskinen et al, Hypertension 2019; 73:335
Prediction of Increased Adult cIMT

Figure. Receiver operating characteristic curves for childhood systolic blood pressure in predicting adult high carotid intima-media thickness, (A) combined in all cohorts, (B) by cohort (BHS indicates Bogalusa Heart study; CDAH, Childhood Determinants of Adult Health study; and YFS, Young Finns study).
## Prediction of Increased Adult cIMT

### Table 2. Associations of Childhood Blood Pressure Measures (Age, Sex, and Study Specific) With High cIMT in Adulthood (Age-, Sex-, and Study-Specific ≥90th Percentile)

<table>
<thead>
<tr>
<th>Blood Pressure Measurement</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>1.24 (1.13–1.37)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic IV</td>
<td>1.07 (0.97–1.17)</td>
<td>0.16</td>
</tr>
<tr>
<td>Diastolic V</td>
<td>1.01 (0.92–1.10)</td>
<td>0.88</td>
</tr>
<tr>
<td>MAP IV*</td>
<td>1.10 (1.07–1.13)</td>
<td>0.006</td>
</tr>
<tr>
<td>MAP V†</td>
<td>1.08 (0.98–1.19)</td>
<td>0.11</td>
</tr>
<tr>
<td>PP IV*</td>
<td>1.15 (1.05–1.27)</td>
<td>0.0027</td>
</tr>
<tr>
<td>PP V†</td>
<td>1.11 (1.08–1.13)</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

*Koskinen et al, Hypertension 2019; 73:335*
BP cut-points – iC3 vs. 2017 AAP CPG

Flynn, Hypertension 2019; 73:296
Long-term Effect of Elevated BP on LVH

• Longitudinal analysis of 1061 individuals in the Bogalusa Heart study with long-term data on BP and BMI
  • Mean follow-up 28 years
• Total BP burden calculated as AUC; LV mass assessed by echocardiography
• Adulthood LVH and LV mass index were significantly associated with higher values of SBP, DBP and BMI in both childhood and adulthood as well as with BP AUC
• Similar associations were found for eccentric LVH and concentric LVH patterns

Lai et al., JACC 2014; 64:1580
Risk of Adult CAD in Iceland

- Retrospective study of 126 adults who had been admitted to hospital as children (median age 15y) between 1950-67
- Median age at follow up 58 years; median duration of follow-up 43 years
- Childhood SBP was significantly correlated with diagnosis of adult CAD
- Childhood SBP >95\textsuperscript{th} percentile also correlated with adult CAD

Ellisdottir et al., Ped Nephrol 2010; 25:323
Childhood CV Risk Factors and Adult CAD

- Retrospective evaluation of 97 participants in Bogalusa Heart Study who died from CV causes
  - Of these, 46 died from CAD (mean age 44.7y)
- Data from childhood and young adult examinations evaluated to determine link between childhood CVRF and death from CAD
- Increased BMI and higher BP starting in childhood were seen in participants who died from CAD
- Longitudinal trends of other CVRF were also worse in those who died compared to those who lived

Adolescent BP and Adult ESRD

- BP measured in 2.6M Israeli army recruits between 16-19 y of age between 1967-2013; ~8000 had hypertension
- Data linked to Israeli ESRD registry, median follow-up 19.6 y
- Overall, 2189 individuals developed ESRD, incidence rate of 3.9/100,000 person-years.
- Among those with HTN
  - Crude hazard ratio for ESRD was 5.07 (95% CI, 3.73-6.88)
  - Adjusted HR for ESRD was 1.98 (95% CI, 1.42-2.77)
  - Association remained significant after removal of those w/severe HTN

Leiba et al., JAMA Intern Med. 2019;179:517
Adolescent BP and Adult ESRD

Leiba et al., JAMA Intern Med. 2019;179:517
Conclusions – Implications of Elevated Childhood BP

- Ample data exist supporting the concept that high BP in childhood is detrimental
- These data include:
  - Cross-sectional studies of hypertensive TOD
  - Tracking studies showing that high childhood BP results in adult HTN
  - Longitudinal cohort studies demonstrating association of high childhood BP with atherosclerosis, LVH and CAD
- **Thus, measurement of BP and detection of HTN in the young have important implications for future CV health**
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