Systolic hypertension in children and adolescents

P Palatini, University of Padova, Italy.

Warsaw, 26 May 2019
8.7.1 Isolated systolic hypertension in the young

was closely associated with smoking. On the basis of current evidence, these young individuals should receive recommendations on lifestyle modification (particularly cessation of smoking); whether they should receive drug treatment is unclear, but they do require longer-term follow-up as many will develop sustained hypertension.
TABLE 1. Classification of hypertension in children and adolescents

<table>
<thead>
<tr>
<th>Category</th>
<th>0–15 years SBP and/or DBP percentile</th>
<th>16 years and older SBP and/or DBP values (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;90th</td>
<td>&lt;130/85</td>
</tr>
<tr>
<td>High-normal</td>
<td>≥90th to &lt;95th percentile</td>
<td>130–139/85–89</td>
</tr>
<tr>
<td>Hypertension</td>
<td>≥95th percentile</td>
<td>≥140/90</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>95th percentile to the 99th percentile and 5 mmHg</td>
<td>140–159/90–99</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>&gt;99th percentile plus 5 mmHg</td>
<td>160–179/100–109</td>
</tr>
<tr>
<td>ISH</td>
<td>SBP ≥95th percentile and DBP &lt;90th percentile</td>
<td>≥140/&lt;90</td>
</tr>
</tbody>
</table>

Increasing prevalence of hypertension (HTN) in children and adolescents has become a significant public health issue driving a considerable amount of research. Aspects discussed in this document include the challenges in the definition of HTN in 16 year olds, the clinical significance of isolated systolic HTN in youth, the importance of out of office and central blood pressure measurement, new risk factors for HTN, methods to assess vascular phenotypes, clustering of cardiovascular risk factors and treatment strategies among others. The recommendations of the present document synthesize a considerable amount of scientific data and clinical experience and represent the consensus of experts.
Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents

Joseph T. Flynn, MD, MS, FAAP, David C. Kaelber, MD, PhD, MPH, FAAP, FACP, FACMI, Carissa M. Baker-Smith, MD, MS, MPH, FAAP, FAHA, Douglas Blowey, MD, Aaron E. Carroll, MD, MS, FAAP, Stephen R. Daniels, MD, PhD, FAAP, Sarah D. de Ferranti, MD, MPH, FAAP, Janis M. Dionne, MD, FRCP, Bonita Falkner, MD, Susan K. Flinn, MA, Samuel S. Gidding, MD, Celeste Goodwin, Michael G. Leu, MD, MS, MHS, FAAP, Makia E. Powers, MD, MPH, FAAP, Corinna Rea, MD, MPH, FAAP, Joshua Samuels, MD, MPH, FAAP, Madeline Simasek, MD, MSCP, FAAP, Vidhu V. Thaker, MD, FAAP, Elaine M. Urbina, MD, MS, FAAP, SUBCOMMITTEE ON SCREENING AND MANAGEMENT OF HIGH BLOOD PRESSURE IN CHILDREN

PEDIATRICS Volume 140, number 3, September 2017:e20171904
ESH vs AAP guidelines
Implications for ISH diagnosis and management

• ISH considered by ESH but not AAP (measurement of central SBP)
• Different classification of BP categories in children
• AAP calculated the percentiles based only on normal weight children
• Different age cut-off for use of adult values in adolescents, 16 vs 13 ys (new American cut-off!)
• For TOD assessment, AAP recommends measurement of LVM (51 g/m2.7) only

Adapted from Lurbe E et al. J Hypertens 2018;36:1456
Prevalence of ISH
Frequency of Different Types of Hypertension In Youth

ISH: Most common form of hypertension in children, adolescents and young adults. (In children and adolescents 1.6 to 11.9%)

- Sorof J et al. J. Paediatrics 2002
- McEniery C et al. Hypertension 2005
- Chiolero A et al. J Hypertension 2007
- Saladini F et al Am J Hypertension 2009
- Lurbe E et al. J Hypertension 2016
- Cheung EI et al. Pediatrics 2017
- Karatzi et al. Atherosclerosis 2017
Prevalence of ISH in general French working population (IHPAF study n=27,783)

Adapted from: Mallion J-M et al. J Hum Hypertens 2003; 17: 93–100
Prevalence of ISH among 1141 hypertensive participants from the HARVEST

BP Trajectories
From childhood to adulthood
Trajectories of Systolic BP and Pulse Pressure


Franklin et al. *Circulation*. 1997;96:308-315
Tracking of Blood Pressure

A Meta-analysis of 50 cohort studies

Chen X & Wang Y, Circulation 2008;117:3171
BP Measurement in the young age
There is some concern about the use of oscillometric BPM in children and adolescents.

With both ESH and AAP Guidelines, HTN should always be confirmed by the auscultatory BPM.

According to the AAP guidelines, forearm and wrist BPM should be avoided.
Bland and Altman plot measuring the agreement between mercury and wrist oscillometric blood pressure in 120 Adolescents

Menezes AMB et al, Arq Bras Cardiol 2010; 94(3):345-349
Office Systolic BP vs Home Systolic BP in the normotensive and hypertensive participants of the Tecumseh study

Adapted from Julius S et al. J Hypertens 1991;9:77-84
Prevalence of WCH and MH among young (8-18 years) overweight and obese patients

Adapted from Lurbe E et al. Journal of Hypertension 2016, 34:1389–1395
Systolic White Coat Effect* in the HARVEST Participants by Hypertension subtype

*Age-and-sex-adjusted

Adapted from Palatini P et al, J Hypertens. 2018;36:1810
### 2016 ESH Guidelines: Recommendations for 24-hour ambulatory BP measurements

#### During the process of diagnosis

Confirm hypertension with ABPM before starting antihypertensive drug treatment in order to avoid treatment of white coat hypertension

#### Hypertensive response during the treadmill test

#### Discrepancy between office BP and home BP

#### During antihypertensive drug treatment

Evaluate for apparent drug-resistant hypertension

Assessment of BP control in children with target organ damage

Symptoms of hypotension

#### Clinical trials

#### Other clinical conditions

Autonomic dysfunction

Suspicion of catecholamine-secreting tumours

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*Lurbe et al. J Hypertens 2016;34:1887-1920*
Pathogenetic mechanisms
Isolated Systolic Hypertension in Young People Is Not Spurious and Should Be Treated

**Pro Side of the Argument**

Carmel M. McEniery, Stanley S. Franklin, John R. Cockcroft, Ian B. Wilkinson

*Hypertension* 2016;68:269-275

**Con Side of the Argument**

Empar Lurbe, Josep Redon

*Hypertension* 2016;68:276-280
“ISH” in Youth assessed with peripheral and central BPM
An Innocent Condition Called “spurious HTN”

Michael F O’Rourke MD DSc (Syd)
Emeritus Professor of Medicine, UNSW, VCCRI
Sydney, Australia
“Spurious” systolic hypertension Hypothesis (Six ISHs 14-23 years)

Normotensive

“Spurius” systolic hypertensive

Essential hypertensive

Adji, O'Rourke, Avolio. Unpublished data

Sydney data

McEniery et al. Hypertension 2008;45:1476-82


GTF

Systolic Pressure (mmHg)

age (years)
Hyperkinetic Hypothesis
(Tecumseh study, mean age = 32.3 years)

Cardiac index

<table>
<thead>
<tr>
<th>l/m²/min</th>
<th>All normotensives</th>
<th>Normokinetic Hypertensives</th>
<th>Hyperkinetic Hypertensives</th>
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<tbody>
<tr>
<td>2.3</td>
<td></td>
<td></td>
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<tr>
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<tr>
<td>3.0</td>
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<td>3.1</td>
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</table>

Heart rate

<table>
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<th>Hyperkinetic Hypertensives</th>
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<tr>
<td>82</td>
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</table>

Plasma norepinephrine

<table>
<thead>
<tr>
<th>Pg/ml</th>
<th>All normotensives</th>
<th>Normokinetic Hypertensives</th>
<th>Hyperkinetic Hypertensives</th>
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<tbody>
<tr>
<td>0</td>
<td></td>
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</tr>
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<td>350</td>
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</tbody>
</table>

Adapted from Julius S et al. J Hypertens 1991;9:77-84
Heart rate and stroke volume as determinants of high Pulse Pressure in the HARVEST study (mean age = 33 ys)

- p for HR tertiles < 0.001*
- p for stroke-volume tertiles < 0.001*
- p for interaction = n.s.*

*Data adjusted for age ad sex

Contribution of stroke volume and PWV to pulse pressure (ENIGMA Study: 1008 subjects, mean age = 20 years)

Influence of SV and aortic PWV on peripheral PP

Scatterplot of SV versus aortic PWV

\[ \begin{align*}
\text{Pulse Pressure (mmHg)} \\
\text{Quartiles of SV} & \quad \text{Quartiles of PWV} \\
\end{align*} \]

\[ \begin{align*}
\text{Stroke Volume (mL)} \\
\text{PWV (m/sec)} \\
\end{align*} \]

\[ \begin{align*}
\blacktriangle \text{ ISH (n=93)} \\
\times \text{ Normotensives (n=722)} \\
\end{align*} \]

McEniery CM et al, Hypertension 2005;46:221
PWV across the spectrum of BP conditions in 593 overweight or obese children and adolescents

Adapted from Lurbe et al. J Hypertens 2016;34:1389-1395
Central SBP in People with Optimal BP vs ISH in Young Adults

Pulse Pressure Amplification in Young Adults
ENIGMA Study

McEniery C et al, Hypertension 2016;68:269
Excess Body Weight

↑ SALT INTAKE

↑ SNS

↑ Salt-sensitivity

INSULIN RESISTANCE

↑ RAAS

LOW-GRADE INFLAMMATION

VSMC/EC dysfunction
ECM alterations
Endothelial dysfunction

↑ Arterial Stiffness

Isolated Systolic Hypertension

Palatini P et al, J Hypertens 2018;36:1222-1236
“ISH” in Youth
A Heterogeneous Condition!

Determinants of ISH

• Young age
• Male gender
• Athletic participation
• High stroke volume
• White-coat reaction

• Smoking
• Arterial stiffness
• Obesity
• Metabolic syndr.

Adapted from Palatini P et al, J Hypertens 2018;36:1222-1236
Prognosis of ISH in the young
Hazard ratios (95%CI) for hypertension needing treatment according to hypertension subtype identified with ABPM (HARVEST Study, 7-year follow-up)

Data adjusted for age, gender, body mass index, 24h heart rate, parental history for hypertension, lifestyle factors, serum glucose and total cholesterol.

Data from Palatini P et al, J Hypertens. 2018 Sep;36(9):1810
Incidence of sustained hypertension according to hypertension subtype and Central BP (HARVEST Study, mean follow-up 9.5 years)

\[ \text{CBP Cutoff} = 120.5 \text{ mmHg} \]

\[ \text{CBP Cutoff} = 125 \text{ mmHg} \]

- Normo
- ISH
- ISH
- SDH

- LowCBP
- HighCBP

\( p=0.022 \)
\( p=0.041 \)
\( p=0.015 \)
\( p=0.020 \)
\( p=\text{ns} \)

- \( p \)-values are adjusted for age, gender, duration of hypertension, family history of hypertension, coffee intake, smoking status, alcohol consumption, degree of physical activity and baseline heart rate.

Saladini F. et al, J Hypertens 2011;29:1311-1319
Cardiovascular mortality according to hypertension subtype in a General Population from the Chicago Heart Association Study

(27,081 subjects, mean age 33.6 years, mean FU 31.1 years)

Yano Y et al. JACC 2015; 65: 327-35
Risk of CVE according to PP and Mean BP tertile in the HARVEST study (mean FU=12.1 years)

Pulse Pressure tertiles

Mean Blood Pressure tertiles

Data adjusted for age and sex

Adapted from Saladini F. et al, Hypertension 2017,70:537
Assessment of children and adolescents with ISH
Aortic stiffness, wave reflection & central BP

Arterial tonometry

- Peripheral pulse wave
- Calibration with brachial BP
- Validated transfer function

Augmentation index (AI)

AI: $\Delta P/PP$

Central (aortic) pulse wave

Central BP (mmHg)

Time (ms)

$P_1, P_2, P$, DB

$PP, \Delta P, Tr$
Central vs Brachial BP And Target Organ Damage. A Meta-analysis

Pearson's R correlation coefficient

- **LVMI**
  - P<0.01
  - 12 studies
  - N=6431
  - Central SBP: 0.3
  - Brachial SBP: 0.26

- **c-IMT**
  - P<0.01
  - 7 studies
  - N=6136
  - Central SBP: 0.27
  - Brachial SBP: 0.23

- **cf-PWV**
  - P<0.01
  - 14 studies
  - N=3699
  - Central SBP: 0.42
  - Brachial SBP: 0.39

- **UAE**
  - P=n.s.
  - 4 studies
  - N=3718
  - Central SBP: 0.22
  - Brachial SBP: 0.22

Kollias A et al, Hypertension. 2016;67:183-190
Establishing reference values for central blood pressure and its amplification in a general healthy population and according to cardiovascular risk factors

Amplification decreased with age and more so in males than in females.

Data were stratified by gender and age class

10th, 25th, 50th, 75th, and 90th percentiles were provided
Characteristics of overweight or obese children and adolescents with ISH and “normal” central BP

ISH with a cSBP <90\textsuperscript{th} percentile as compared to ≥90\textsuperscript{th} percentile were:

- predominantly \textit{male} (14 out of 18)
- \textit{taller} (168.8±2.6 cm vs 156.2±4.4 cm, p=0.022; respectively)
- \textit{lower} oDBP (65.5±1.3 mmHg vs 71.5±1.0 mmHg, p<0.016; respectively)
- trend for \textit{high amplification} (PP ratio 1.83±0.06 vs 1.65±0.08, p=0.098; respectively).
- No differences were observed in \textit{age, degree of obesity, oSBP, PWV} and no increment of LV mass.

\textit{Lurbe et al. J Hypertens 2016;34:1389-1395}
2016 ESH Guidelines
Criteria to define hypertension-induced organ damage in children

• **Left ventricular hypertrophy**
  – Left ventricular hypertrophy should be defined as LVMI or relative wall thickness (RWT) ≥ 95th percentile by age and gender

• **Carotid intima thickness**
  – cIMT ≥ 95th percentile by age and gender

• **Pulse wave velocity**
  – PWV ≥ 95th percentile by age and gender

• **Kidney**
  – Albuminuria (albumin/creatinine quotient >30mg/g creatinine or >3mg/mmol creatinine); proteinuria (as measured by urinary albumin/creatinine quotient (>300mg/g creatinine or >30mg/mmol creatinine) or by 24 h urinary protein excretion (>200 mg/m²/day)

*Lurbe et al. J Hypertens 2016;34:1887-1920*
Treatment of ISH in the young
Isolated systolic hypertension in Children and Adolescents. 2016 ESH Guidelines

- Detecting white-coat by using 24-hour ABPM
- Recording “low” cSBP, and
- Checking the absence of early organ damage

give grounded support in the decision of not to treat

Adapted from Lurbe et al. J Hypertens 2016;34:1887-1920
Isolated systolic hypertension in the young: a position paper endorsed by the European Society of Hypertension

Paolo Palatini\textsuperscript{a}, Enrico Agabiti Rosei\textsuperscript{b}, Alberto Avolio\textsuperscript{c}, Gregorz Bilo\textsuperscript{d,e}, Edoardo Casiglia\textsuperscript{a}, Lorenzo Ghiadoni\textsuperscript{f}, Cristina Giannattasio\textsuperscript{g}, Guido Grassi\textsuperscript{h}, Bojan Jelakovich\textsuperscript{i}, Stevo Julius\textsuperscript{j}, Giuseppe Mancia\textsuperscript{k}, Carmel M. McEniery\textsuperscript{l}, Michael F. O’Rourke\textsuperscript{m}, Gianfranco Parati\textsuperscript{d,e}, Paolo Pauletto\textsuperscript{a}, Giacomo Pucci\textsuperscript{n,o}, Francesca Saladini\textsuperscript{a}, Pasquale Strazzullo\textsuperscript{p}, Konstantinos Tsioufis\textsuperscript{q}, Ian B. Wilkinson\textsuperscript{l}, and Alberto Zanchetti\textsuperscript{r}

\textit{J Hypertens.} 2018 Jun;36(6):1222-1236
Diagnostic-therapeutic Flow-chart for the young subject with ISH

2018 ESH Consensus document

ISHs
Office ≥ 140 and DBP<90 or SBP ≥ 95th percentile and DBP < 90th percentile*

Out-of-office measurement
ABPM or home BP

If out-of-office measurements confirm
ISH proceed to the next step

Measurement of Central BP

High central BP
Low central BP

Search for target organ damage and risk factors

High risk profile
Consider pharmacological treatment

Low risk profile
Lifestyle changes and close follow-up

Home BP ≤ 135/85 or Daytime < 135/85, Night-time < 120/70
24-h BP < 130 980 **

* Target values for children and adolescents < 16 years of age
** Appropriate threshold levels for children and adolescents < 16 years of age [ESH2016 Guidelines]

J Hypertens. 2018;36(6):1222-1236