Central Pressures and Prehypertension

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Declaration of Interest 2016-17

Various, please access https://escol.escardio.org/DOI
Central Blood Pressure in PreHypertension

- CV risk in preHTN
- What is CBP? Why do I care?
- Can I change CBP?
- cBP in preHTN
- Conclusions - Gaps in Evidence
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The continuum of BP and cardiovascular mortality

Incidence of heart disease related mortality increases linearly, with BP $>$ 115/75 mmHg

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Central Blood Pressure
Peripheral and central pressures

They are not the same!

The two Fridas, 1939
Central Blood Pressure

- Peripheral BP may overestimate central SP and PP, especially in young subjects.

amplification

Graphs showing pressure and flow measurements at different sites (Asc. aorta, Aorta arch, Abd. aorta, Fem. artery, Sap. artery) for different age groups.
Central pressures more pathophysiologically relevant to organ damage
Central Blood Pressure

- Central PP is strongly associated with brachial blood pressure

Fig. 3  cPP estimated from a linear multivariate regression equation obtained in a population of 868 untreated hypertensive subjects. cPP was measured from radial tonometry calibrated to bSBP/bDBP and a generalized transfer function (SphygmoCor device)

\[
cPP = 25.26 + (\text{brachial pulse pressure} \times 0.749) - (\text{heart rate} \times 0.298) - (\text{height} \times 0.098) + \\
+ (\text{age} \times 0.157) \ (\text{mean arterial pressure} \times 0.097) \ (\text{sex} \times 2.755)
\]

Pucci et al, High Blood Pres Cardiov Prev 2017
Do I have normal / reference values to guide me?
Establishing Reference Values for Central Blood Pressure and Amplification in a General Healthy Population and according to Cardiovascular Risk-Factors

Herbert et al. EHJ 2014
Reference values of CBPs?

Over 70% of individuals with high-normal blood pressure had aortic systolic pressures in common with individuals with stage 1 hypertension

McEniery et al. EJ 2014
Herbert et al. EHJ 2014
Central compared with brachial BP seems to be more strongly associated with most of the investigated indices of preclinical organ damage

Kollias et al Hypertension 2016
Why measure?

To estimate CV risk

**Figure 4** Relative risk (RR) and 95% confidence interval (CI) of clinical events for an 1 standard deviation increase in pulse pressure (top) and systolic pressure (bottom), according to the site of measurement (central vs. brachial). Boxes represent the RRs and lines represent the 95% CI for individual studies. The diamonds and their width represent the pooled RR and the 95% CI, respectively.

Vlachopoulos et al EHJ. 2010
Why measure?

Central PP  1.338 (95% CI 1.236-1.448) vs.  Peripheral PP  1.178 (95% CI 1.091-1.272)

\[ p = 0.017 \]

Protogerou et al.    EHJ letter 2010
Vlachopoulos et al. EHJ reply 2010

Vlachopoulos et al EHJ. 2010
Meta-analysis of CBP and outcomes (individual data)

- Considered alone, brachial and central SBP have similar associations with future CV events

- Associations between central SBP and stroke, after adjustment for brachial SBP, were higher in those aged <61 years than in older individuals (1.83 versus 1.08, p-interaction <0.001)

McEniery et al, ACC 2015
Recommendation for clinical use

The role of vascular biomarkers for primary and secondary prevention

Vlachopoulos et al. Atherosclerosis 2015
European Society of Cardiology/ARTERY - Position Paper

Table 5
Usefulness of vascular biomarkers for primary and secondary CVD prevention.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid ultrasonography</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>Ankle-brachial index</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>Arterial stiffness</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>Carotid-femoral pulse wave velocity</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>Brachial-ankle pulse wave velocity</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td><strong>Central haemodynamics/Wave reflections</strong></td>
<td>IIb</td>
<td></td>
</tr>
<tr>
<td>Endothelial function</td>
<td>III</td>
<td>B</td>
</tr>
<tr>
<td>Flow mediated dilatation</td>
<td>III</td>
<td>B</td>
</tr>
<tr>
<td>Endothelial peripheral arterial tonometry</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>Circulating biomarkers related to vascular wall biology</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>High sensitivity C-reactive protein</td>
<td>IIb</td>
<td>B</td>
</tr>
</tbody>
</table>

May be considered
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Central Blood Pressure

Are all drugs equivalent regarding their effect on central aortic pressure?
Central Blood Pressure

Effects of interventions may not be (as) evident in peripheral pressures

Nitrates

Caffeine


Vlachopoulos C, et al. JACC 2004
Lowering central pressures: not all drugs are created equal

The EXPLOR study

**Systolic pressure (mmHg)**

- **Brachial SBP**
  - Mean difference: -1.14 [-4.28 to 1.99], p=NS

- **Aortic SBP**
  - Mean difference: -3.95 [-7.08 to -0.83], p=0.02

- **Baseline**
- **W8**
- **W24**

**Amlodipine+atenolol**

**Amlodipine+valsartan**

Boutouyrie P, et al. Hypertension 2010
Lowering central pressures: not all drugs are created equal

The REASON study

The greater change in LV mass on Perindopril/Indapamide was linked to central and not to brachial blood pressure

<table>
<thead>
<tr>
<th>Adjustment (Adj) with</th>
<th>Left ventricular mass change (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adj mean (Per/Ind) (95% CI)</td>
<td>Adj mean (atenolol) (95% CI)</td>
<td>Adj mean (Per/Ind – atenolol) (95% CI for difference)</td>
</tr>
<tr>
<td>Carotid SBP (Model 1)</td>
<td>−6.6 (−10.2 to −3.0)</td>
<td>−1.4 (−5.7 to +2.8)</td>
<td>−5.17 (−10.88 to +0.53)</td>
</tr>
<tr>
<td>Brachial SBP (Model 2)</td>
<td>−6.2 (−9.9 to −2.5)</td>
<td>−2.0 (−6.4 to +2.4)</td>
<td>−4.19 (−10.00 to +1.62)</td>
</tr>
<tr>
<td>Carotid PP (Model 3)</td>
<td>−7.2 (−10.8 to −3.6)</td>
<td>−0.7 (−4.9 to +3.6)</td>
<td>−6.50 (−12.31 to −0.71)</td>
</tr>
<tr>
<td>Brachial PP (Model 4)</td>
<td>−6.3 (−10.0 to −2.6)</td>
<td>−1.8 (−6.2 to +2.6)</td>
<td>−4.53 % (−10.48 to +1.42)</td>
</tr>
</tbody>
</table>

Central hemodynamics
Clinical Utility
The ASCOT Study

Less events with Amlo/perind, despite similar BP reduction. WHY?

Cardiovascular mortality

Systolic and diastolic blood pressure

Atenolol ± thiazide
(No of events patients: 342)

Amlodipine ± perindopril
(No of events patients: 263)

HR = 0.76 (0.65-0.90) - P=0.0010

Mean difference 2.7 mmHg

Mean difference 1.9 mmHg

Central Blood Pressure

CAFE Study

Brachial SBP
Diff Mean (AUC) = 0.7 (-0.4, 1.7) mm Hg

Central SBP
Diff Mean (AUC) = 4.3 (3.3, 5.4) mm Hg

Atenolol
Atenolol
Amlodipine

Circulation. 2006;113:1213-1225
The angiotensin receptor blocker/neutral endopeptidase inhibitor was significantly more effective at lowering brachial and central aortic systolic and pulse pressures than conventional renin–angiotensin system blockade with an angiotensin receptor blocker.
• Guidance of hypertension management with central BP results in a significantly different therapeutic pathway than conventional cuff BP

• With intervention there was a significant stepwise decrease in daily defined dose

• The central aortic BP group showed a trend for a reduction in LV mass, whereas the usual care group showed a trend for an increase

Sharman, et al. *Hypertension* 2013
Avolio *Hypertension* 2013
**Central Blood Pressure**

Not all created equal

<table>
<thead>
<tr>
<th>Medication</th>
<th>Augmentation index, central SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>↓↓</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>↓↓</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>↓↓</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>↓</td>
</tr>
<tr>
<td>VD β-blockers</td>
<td>↓</td>
</tr>
<tr>
<td>NON VD β-blockers</td>
<td>↑</td>
</tr>
</tbody>
</table>
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Prospective studies conducted to determine whether increased arterial stiffness might be an independent risk factor for the development of hypertension in pts with pre-hypertension.

Increased aortic stiffness predicted development of hypertension in pts with prehypertension.
Effects of Prehypertension on Arterial Stiffness and Wave Reflections

Heart rate-corrected augmentation index

Aortic PWV

45 subjects with prehypertension and an age-matched control group of 40 normotensive individuals

Prehypertension was a significant predictor of aortic PWV and Alx@75

Aortic, but not brachial blood pressure category enhances the ability to identify target organ changes in normotensives

1169 participants, 319 (27%) of whom had a normal/ high-normal BP

Target organ changes assessed with PWV (n=1025), eGFR (n=944), and LVMI (n=690)

Unadjusted and multivariate adjusted indices of target organ changes of prehypertensives with (Yes) or without (No) aortic SBP greater than thresholds (112 mmHg) defined in those with optimal conventional blood pressure values

<table>
<thead>
<tr>
<th>Blood pressure categories</th>
<th>Optimal &lt;120/80</th>
<th>Normal/high-normal ≥120/80 and &lt;140/90 with aortic SBP≥112 mmHg</th>
<th>Hypertensives ≥140/90 or treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure range (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PWV (m/s) (n)</td>
<td>4.83 ± 1.24 (289)</td>
<td>5.07 ± 1.30 (128)</td>
<td>6.12 ± 1.94***,††† (151)</td>
</tr>
<tr>
<td>Estimated GFR (ml/min per 1.73 m²) (n)</td>
<td>128 ± 32 (244)</td>
<td>126 ± 32 (108)</td>
<td>111 ± 26***,††† (149)</td>
</tr>
<tr>
<td>LV mass index (g/m²) (n)</td>
<td>35.5 ± 10.2 (181)</td>
<td>38.2 ± 11.0 (82)</td>
<td>44.0 ± 12.1***,††† (109)</td>
</tr>
<tr>
<td>Multivariate adjusted values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse wave velocity (m/s) (n)</td>
<td>5.89 ± 2.21 (289)</td>
<td>6.09 ± 2.05 (128)</td>
<td>6.30 ± 1.95* (151)</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²) (n)</td>
<td>118 ± 29 (244)</td>
<td>115 ± 27 (108)</td>
<td>108 ± 26**,-,† (104)</td>
</tr>
<tr>
<td>LV mass index (g/m²) (n)</td>
<td>40.0 ± 14.3 (181)</td>
<td>40.7 ± 13.2 (82)</td>
<td>44.5 ± 12.6**,-,† (109)</td>
</tr>
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</table>

As compared to those with an optimal BP, target organ changes were consistently noted in those with a normal/high-normal BP with, but not in those without high aortic SBP values

Booysen et al. Journal of Hypertension 2013, 31:1124-1130
Impact of aortic rather than brachial pulsatile haemodynamics on variations in end-organ measures across the full adult blood pressure range

- In 1307 community participants LVMI, IMT and eGFR were estimated
- Increases in SBP across the full adult BP range, including BP values within normotensive ranges, were associated noted
- However, only in the normotensive participants pulsatile haemodynamic variables (including wave reflection indices) were associated with end-organ damage when corrected for brachial pressure
Relation of central hemodynamics with events in perHTN?
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Central Blood Pressure in preHTN

1. CBP assessment is easy to implement in clinical practice
2. CBP identifies subclinical organ damage and has demonstrated an incremental predictive value for CV events beyond classic risk scores
3. Its value as surrogate end-point remains to be demonstrated by therapeutic intervention trials
4. Patients with preHTN demonstrate increased values of arterial stiffness and central hemodynamic indices
5. Central hemodynamics predict target organ damage in preHTN
6. Arterial stiffness predicts development of HTN in pts with preHTN
7. Whether central hemodynamics retain their predictive value in preHTN is currently unknown