



**contact**

Paul Herijgers

[Paul.Herijgers@uzleuven.be](mailto:Paul.Herijgers@uzleuven.be)

tel. +32 16 34 46 21

fax +32 16 34 46 16

uw bericht van

uw kenmerk

ons kenmerk

Leuven

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**campus Gasthuisberg**

Herestraat 49

B - 3000 Leuven

tel. +32 16 34 42 60

fax +32 16 34 46 16

## Evaluation of the manuscript submitted by Jitka Kucerova Seidlerova

### General remarks:

#### Reviewer 1:

This thesis entitled interactive influences of environmental and genetic factors on the properties of large arteries in relation to sodium handling aimed at the potential relationship between properties of large arteries, renal sodium handling and candidate genes encoding renin-angiotensin-aldosterone system and adducin. This project is part of the large international EPOGH study.

This thesis addresses several important issues: the potential differences in arterial properties/mainly arterial stiffness/ in normotensive offspring of parents with or without hypertension. Normotensive offspring of hypertensive parents had altered large artery properties compared to normotensive offspring of normotensive parents. The major determinant of these differences was high blood pressure.

This thesis contains also original data concerning the heritability and familial aggregation of various indexes of arterial stiffness. The authors found significant correlation between genetic background and aortic stiffness. Higher fractional sodium reabsorption in the distal nephron is associated with higher compliance and distensibility of femoral artery, while higher proximal sodium reabsorption leads to the opposite results. These results are in concordance with the pathophysiological view of the influence of high sodium intake on arterial properties/blood pressure. In addition to that, these results correspond to the findings in some secondary form of hypertension/primary aldo/.

The authors concentrated also on the potential association between arterial properties and genes encoding alpha-adducin (ADD). Brachial artery properties were related to ADD3 polymorphism. Interaction between ADD and angiotensin converting enzyme in relation to arterial properties was also studied. Brachial diameter was increased in ACE CG haplotype homozygotes compared with non-carriers.

The total evaluation of the thesis from my site is extremely positive.

#### Reviewer 2:

This PhD thesis is of a very high quality. The text is very well written and has a clear structure. Data have been analyzed in depth with, as far as I can judge, most appropriate

statistical approach. Discussions are to-the-point and conclusions are clear with attention for potential limitations. Most chapters have been published in high-ranked peer-reviewed journals in the domain of Hypertension research. I only have a few comments mainly related to the introduction chapter. The candidate can be given unconditional permission for the public defense.

**Reviewer 3:**

The PhD thesis is a compilation of 5 full papers already published in international peer reviewed journals. Therefore it is fair to say that the quality of the work has already been evaluated by the international community of scientists active in the field of hypertension.

**Reviewer 4:**

The work represents a comprehensive analysis of the environmental and genetic factors of aspects of hypertension. It is relatively uniform, i.e. the individual chapters deal with distinct aspects of a broad analysis

**Major comments:**

**Reviewer 1:**

The thesis is well and clearly written, the methodology used is sufficient and appropriate. Most of the results were obtained on the relatively large group of subjects in different European countries which increases the quality and reproducibility of the work. Also statistical approach is based on appropriate tests.

All thesis has 175 pages and its structure is based on the already published results in peer-reviewed international journals / 5 publication of dr. Seidlerova as a first author and 4 publication as a co-author who significantly contributed to the published results. All these 9 articles were published in journals with high impact factor, which makes all review process more easy.

**Reviewer 2:**

- (i) Why did you not (also) use the carotid tonometry recordings to assess central AIx
- (ii) How did you calibrate the radial, carotid and femoral tonometer waveforms to assess local PP? This should be added to the intro section.

**Reviewer 4:**

The thesis is composed of published material, and thus the work has undergone extensive peer review already. No major comments.

**Minor comments:**

**Reviewer 2:**

Page 3: I would suggest to retitle section 1.1.1 as Pulse Wave Velocity is not really discussed in this section.

Page 4-5: a decrease in distensibility/compliance does not automatically lead to an increase in systolic blood pressure. It is only through a concomitant increase in resistance that systolic blood pressure rises (see eg. Elzinga and Westerhof, Circ Res 1973; Segers et al., Hypertension 2000)

1.1.2, line 3: replace "exerted" by "induced"

Top of page 5 "distensibility is a determinant of the pulsatile stress on the vessel wall": I would rephrase this section. The distension of the vessel is a kinematic property, rather than a mechanical one. The distension (strain) of the vessel is linked with the stresses in the material via its material properties (the constitutive equation). As it is written now, I would interpret this paragraph as having a high distensibility being a bad feature.

Section 1.1.3: I suggest to give the Bramwell-Hill formula linking PWV to the distensibility coefficient.

page 6, 5<sup>th</sup> line from below: outside THE aortic tract

page 7, 12<sup>th</sup> line from below: as THE ratio

page 11, line 2: add references to support this statement

page 11, line 3: PP and AIx are dependent on the speed of both the forward and reflected wave

page 11, 5-3<sup>rd</sup> line from below: I don't think it is correct that smaller body size favours higher systolic pressures. Reason is that also the heart rate is higher in smaller subjects (see e.g. Westerhof N., Cardioscience 1994).

page 12, 2<sup>nd</sup> line from below: "aPWV" instead of "a PWV"

p19, line 2: THE effect

p23: Chapter 4, based on THE ...

p37, bottom: I don't think the definition of AIx is correct (also in subsequent sections).

When expressing it as the ratio of (difference in P1 and P2) and PP, the value is always lower than 100%, which is not the case. I think it is expressed as the ratio of P2 to P1 or as  $(P2-DBP)/(P1-DBP)$ . Please verify.

p38: what was the distance used in aPWV ? Direct carotid-femoral or a corrected distance ?

p43, top panel: y-axis should be DeltaPP

p44,45: what is the "systolic" augmentation index ?

**Reviewer 4:**

A few typo's.

see  
to the jury.