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Reply

Reply to Comments: Using the Cardio-Ankle Vascular Index (CAVI) or the Mathematical Correction Form ($CAVI_0$) in Clinical Practice

Bart Spronck [1,2], Alexander Jurko [3], Michal Mestanik [4,5], Alberto P. Avolio [6] and Ingrid Tonhajzerova [4,5,*]

1 Department of Biomedical Engineering, CARIM School for Cardiovascular Diseases, Maastricht University, 6229ER Maastricht, The Netherlands; b.spronck@maastrichtuniversity.nl
2 Department of Biomedical Engineering, School of Engineering & Applied Science, Yale University, New Haven, CT 06511, USA
3 Pediatric Cardiology Martin, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, 03601 Martin, Slovakia; ltvsro@gmail.com
4 Department of Physiology, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, 03601 Martin, Slovakia; mestanik@jfmed.uniba.sk
5 Biomedical Center Martin, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, 03601 Martin, Slovakia
6 Department of Biomedical Sciences, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, NSW 2019, Australia; alberto.avolio@mq.edu.au
* Correspondence: tonhajzerova@jfmed.uniba.sk or ingridtonhajzerova@gmail.com; Tel.: +421-43-2633-425

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We read with great interest Alizargar et al.'s comment on our recent review on biomarkers in cervical cancer and human papillomavirus infection [1,2]. In their comment, they raise important questions and concerns about using cardio-ankle vascular index (CAVI) and $CAVI_0$ [3,4]. We would like to take this opportunity to elaborate our considerations in deriving $CAVI_0$, and to point out some potential misconceptions on the corrections that CAVI and $CAVI_0$ do and do *not* perform.

Due to the nonlinear elastic behavior of the artery wall, a higher blood pressure results in a higher pulse wave velocity (PWV) at the time of measurement [5–7]. It is this inherent blood pressure dependency that both CAVI and $CAVI_0$ aim to correct for. Notably, different individuals with different blood pressures may show a different PWV due to (1) pressure dependency of PWV, and/or (2) intrinsic ("actual") differences in arterial stiffness [8]. CAVI and $CAVI_0$ only correct—and should only correct—for the first effect. Differences in intrinsic arterial stiffness between individuals, e.g., due to hypertensive remodeling, age, obesity, etc., *should* be reflected in CAVI/$CAVI_0$, thus allowing for the use of CAVI and $CAVI_0$ to study the effect of such phenomena on arterial stiffness. After all, if a stiffness index did not vary with any of those phenomena, there would be no use in measuring it, and it would not predict any outcome.

In a recent study, Shirai et al. compared CAVI and $CAVI_0$ in a large population of normotensive and hypertensive individuals [9]. While the use of large populations should be greatly applauded, all analyses presented in their study are cross-sectional, that is, in each individual, CAVI/$CAVI_0$ was measured only once. Therefore, relations with blood pressure observed in such a study will reflect both intrinsic (nonlinear elasticity; within-subject) blood pressure dependency and between-subject differences in intrinsic arterial stiffness. As elaborated in the previous paragraph, CAVI and $CAVI_0$ are only meant to correct the former and *not* the latter effect. It is clear, therefore, that cross-sectional studies, while very useful to study population patterns and to derive reference values, cannot be used to assess the performance of CAVI and $CAVI_0$ in correcting for the intrinsic blood pressure dependency of PWV [8]. Such studies simply contain both effects mixed together, without a way to disentangle them.

Alizargar et al. point out that Shirai et al. observed a negative, "inexplicable" correlation between $CAVI_0$ and diastolic blood pressure (DBP) in healthy individuals, which Shirai et al. then used as a reason to label $CAVI_0$ as "inappropriate" [1,9]. Again, this correlation is cross-sectional, and indicates (statistically) that subjects with a higher $CAVI_0$ on average have a lower DBP. This could be explained as follows. Subjects with (intrinsically) stiffer arteries typically have a larger pulse pressure than subjects with less stiff arteries. As these subjects were classified as healthy (i.e., not hypertensive), their systolic blood pressure was probably approximately normotensive. The DBP of the individuals with stiffer arteries, however, could well have been lower than that of those with less stiff arteries, which potentially explains the negative cross-sectional correlation between $CAVI_0$ and DBP as observed by Shirai et al.

Alizargar et al. also mention that in our initial study, we did not take into account physiological properties of individuals, such as body mass index (BMI) [1,4]. Again, BMI is a cross-sectional property that varies between individuals. CAVI/$CAVI_0$ were never aimed to be BMI-independent. In our initial study, we simulated subjects with differing values of intrinsic stiffness. Such differences could be interpreted as being due to BMI, age, calcification, arteriosclerosis, etc. However, the aim of our study was not to investigate the effects of these particular phenomena; it was merely to illustrate how, in a typical study cohort with (patho)physiological differences in intrinsic stiffness among subjects, blood pressure fluctuations could (theoretically) influence CAVI and $CAVI_0$ measurements.

Calculation of CAVI involves the use of two scale parameters (*a* and *b*) that were recently disclosed to the public [10]. This disclosure allows for an accurate, exact (instead of estimated [11]) conversion from CAVI to $CAVI_0$ [12]. Different combinations of *a*/*b* parameters are used for different CAVI ranges [10], the effects of which were criticized by Ato et al. [13]. Notably, $CAVI_0$ does not use such scale parameters. Considering these criticisms, as well as the CAVI-$CAVI_0$ discussion, Alizargar et al. suggest that normal PWV and stiffness index β may be more reliable indices than the (less established) CAVI and $CAVI_0$ [1]. We agree that PWV indeed is more established, and has the advantage that it is "simpler", or "closer to the measurement", but with the trade-off of being inherently blood pressure dependent. Stiffness index β (termed heart-ankle β or haβ for the heart-to-ankle trajectory), CAVI, and $CAVI_0$ are all much less blood pressure dependent than PWV [4,10,14], and hence, have the potential of being more "intrinsic" metrics of arterial stiffness. Therefore, potentially, the values of such indices may be more directly interpretable as "arterial stiffness" than PWV values.

To conclude, we would like to re-emphasize that we consider the development and practical application of CAVI, as extensively described by Dr. Shirai and colleagues [3,10], to be innovative and based on sound and robust physiological principles. In our paper and discussion with Dr. Shirai, we aimed to provide additional clarification and suggested improvements by using $CAVI_0$ [4,15–18]. We consider it also important to point out that the difference between statistical corrections based on cross-sectional and longitudinal/repeated measures studies can confound the interpretation of the difference between pressure dependency and intrinsic properties of arterial stiffness.

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Abbreviations

BMI	body mass index
CAVI	cardio-ankle vascular index
$CAVI_0$	cardio-ankle vascular index 0
DBP	diastolic blood pressure
haβ	heart-to-ankle stiffness index β
PWV	pulse wave velocity

References

1. Alizargar, J.; Hsieh, N.-C.; Wu, S.-F.V.; Weng, S.-Y. Using the cardio-ankle vascular index (CAVI) or the mathematical correction form (CAVI0) in clinical practice. *Int. J. Mol. Sci.* **2020**, *21*, 2410. [CrossRef] [PubMed]
2. Tonhajzerova, I.; Olexova, L.B.; Jurko, A., Jr.; Spronck, B.; Jurko, T.; Sekaninova, N.; Visnovcova, Z.; Mestanikova, A.; Kudela, E.; Mestanik, M. Novel biomarkers of early atherosclerotic changes for personalised prevention of cardiovascular disease in cervical cancer and human papillomavirus infection. *Int. J. Mol. Sci.* **2019**, *20*, 3720. [CrossRef] [PubMed]
3. Shirai, K.; Utino, J.; Otsuka, K.; Takata, M. A novel blood pressure-independent arterial wall stiffness parameter; cardio-ankle vascular index (CAVI). *J. Atheroscler. Thromb.* **2006**, *13*, 101–107. [CrossRef] [PubMed]
4. Spronck, B.; Avolio, A.P.; Tan, I.; Butlin, M.; Reesink, K.D.; Delhaas, T. Arterial stiffness index beta and cardio-ankle vascular index inherently depend on blood pressure but can be readily corrected. *J. Hypertens.* **2017**, *35*, 98–104. [CrossRef] [PubMed]
5. Bramwell, J.C.; McDowall, R.J.S.; McSwiney, B.A. The variation of arterial elasticity with blood pressure in man (part I). *Proc. R Soc. Lond. B* **1923**, *94*, 450–454.
6. Spronck, B.; Heusinkveld, M.H.; Vanmolkot, F.H.; Roodt, J.O.; Hermeling, E.; Delhaas, T.; Kroon, A.A.; Reesink, K.D. Pressure-dependence of arterial stiffness: Potential clinical implications. *J. Hypertens.* **2015**, *33*, 330–338. [CrossRef] [PubMed]
7. Spronck, B. Stiff vessels approached in a flexible way: Advancing quantification and interpretation of arterial stiffness. *Artery Res.* **2018**, *21*, 63–68. [CrossRef]
8. Spronck, B.; Delhaas, T.; Butlin, M.; Reesink, K.D.; Avolio, A.P. Options for dealing with pressure dependence of pulse wave velocity as a measure of arterial stiffness: An update of cardio-ankle vascular index (CAVI) and CAVI0. *Pulse (Basel)* **2018**, *5*, 106–114. [CrossRef] [PubMed]
9. Shirai, K.; Suzuki, K.; Tsuda, S.; Shimizu, K.; Takata, M.; Yamamoto, T.; Maruyama, M.; Takahashi, K. Comparison of cardio-ankle vascular index (CAVI) and CAVI0 in large healthy and hypertensive populations. *J. Atheroscler. Thromb.* **2019**, *26*, 603–615. [CrossRef] [PubMed]
10. Takahashi, K.; Yamamoto, T.; Tsuda, S.; Okabe, F.; Shimose, T.; Tsuji, Y.; Suzuki, K.; Otsuka, K.; Takata, M.; Shimizu, K.; et al. Coefficients in the CAVI equation and the comparison between CAVI with and without the coefficients using clinical data. *J. Atheroscler. Thromb.* **2019**, *26*, 465–475. [CrossRef] [PubMed]
11. Spronck, B.; Mestanik, M.; Tonhajzerova, I.; Jurko, A.; Jurko, T.; Avolio, A.P.; Butlin, M. Direct means of obtaining CAVI0-a corrected cardio-ankle vascular stiffness index (CAVI)-from conventional CAVI measurements or their underlying variables. *Physiol. Meas.* **2017**, *38*, N128–N137. [CrossRef] [PubMed]
12. Spronck, B.; Mestanik, M.; Tonhajzerova, I.; Jurko, A.; Tan, I.; Butlin, M.; Avolio, A.P. Easy conversion of cardio-ankle vascular index into CAVI0: Influence of scale coefficients. *J. Hypertens.* **2019**, *37*, 1913–1914. [CrossRef] [PubMed]
13. Ato, D. Evaluation of the calculation formulas of the cardio-ankle vascular index used in the japanese apparatus. *Vasc Health Risk Manag.* **2019**, *15*, 395–398. [CrossRef] [PubMed]
14. Shirai, K.; Song, M.; Suzuki, J.; Kurosu, T.; Oyama, T.; Nagayama, D.; Miyashita, Y.; Yamamura, S.; Takahashi, M. Contradictory effects of beta1- and alpha1- aderenergic receptor blockers on cardio-ankle vascular stiffness index (CAVI)–CAVI independent of blood pressure. *J. Atheroscler. Thromb.* **2011**, *18*, 49–55. [CrossRef] [PubMed]
15. Shirai, K.; Shimizu, K.; Takata, M.; Suzuki, K. Independency of the cardio-ankle vascular index from blood pressure at the time of measurement. *J. Hypertens.* **2017**, *35*, 1521–1523. [CrossRef] [PubMed]
16. Spronck, B.; Avolio, A.P.; Tan, I.; Butlin, M.; Reesink, K.D.; Delhaas, T. Reply: Physics cannot be disputed. *J. Hypertens.* **2017**, *35*, 1523–1525. [CrossRef] [PubMed]
17. Shirai, K.; Takata, M.; Takahara, A.; Shimizu, K. Medical science is based on evidence (answer to spronck et al.'s refutation: Physics cannot be disputed). *J. Hypertens.* **2018**, *36*, 958–960. [CrossRef] [PubMed]
18. Spronck, B.; Avolio, A.P.; Tan, I.; Butlin, M.; Reesink, K.D.; Delhaas, T. Reply: Medical science is based on facts and evidence. *J. Hypertens.* **2018**, *36*, 960–962. [CrossRef] [PubMed]