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Independency of the cardio-ankle vascular index from blood pressure at the time of measurement

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In the recent article by Spronck *et al.* [1], the authors concluded that β and cardio-ankle vascular index (CAVI) are inherently blood pressure (BP)-dependent, potentially leading to erroneous conclusions in arterial stiffness trials.

There are some useful insights in the article, and these might contribute to a deeper understanding of the concept of measuring arterial stiffness, but the title of the article and the conclusions reached are ultimately inaccurate and misrepresent the concept of the CAVI. We would like to explain our reasoning behind why we reached this conclusion.

First, as the authors point out, there is a difference between Hayashi's beta (described as β_o in this article) [2] and Kawasaki's beta (β) [3]. Hayashi's beta is based on a reference BP at 100 mmHg, whereas Kawasaki's beta is based on DBP. It is not possible to measure the diameter change around a reference value of 100 mmHg clinically in each patient. Therefore, for practical reasons, Kawasaki's method has been employed. The difference between β and β_o has already been referred to by Kawasaki *et al.* [3]. He reported that this difference is not clinically significant. Kawasaki's β arterial mathematical model has been generally accepted and has prevailed. This is one reason why CAVI was developed based upon Kawasaki's β .

Even though there are differences between β_o and β , both are mathematical models reflecting proper arterial stiffness independently from BP at measurement time. However, in their article, the authors assumed β_o as a 'ground truth' and only demonstrated that β changed with BP in comparison with β_o . They provided no evidence or logical arguments to assess which method is superior to the other.

Therefore, the statement that 'Arterial stiffness index beta inherently depends on blood pressure' is incorrect.

Second, the authors presented the equation cardio-ankle vascular index o ($CAVI_o$) = $2\rho PWV^2/P_d - \ln(P_d/P_{ref})$ [Eq. (9)] and compared it with CAVI using simulation data. They demonstrated that $CAVI_o$ is not dependent on BP, whereas CAVI does change with BP.

CAVI and $CAVI_o$ are based on stiffness index β and a wave equation derived from Newton's second law (Bramwell–Hill's equation in the case of the artery). The difference between CAVI and $CAVI_o$ is that CAVI employs β over a range of diastolic to systolic pressures and $CAVI_o$ employs β at diastolic pressure. Bramwell–Hill's equation is then applied to the β or β_o equation.

We employed SBP and DBP in the measurement of CAVI [4].

$CAVI_o$ uses diastolic pressure as the standard reference value. If the length of the arterial pathway being measured

is short enough, diastolic pressure would not significantly change. However, it is known that diastolic pressure decreases, and systolic pressure increases from the origin of the aorta to the peripheral arteries [5].

Therefore, in case of the long arterial pathway, adoption of one point of DBP only becomes less accurate as a reference value representing the entire length of the pathway. In this way, there is a concern that $CAVI_o$ along a long pathway becomes less accurate. In the case of CAVI, both SBP and DBP are used. Although both methods are mathematically different and each have rational basis, both also have their limitations. The clinical utilities of both equations will be important, and those are presented later.

Third, the authors compiled Table 1 based upon a virtual calculation. At a glance, it seems that the authors tested both arterial stiffness indexes when BP changed, and that $CAVI_o$ did not change, whereas CAVI did change. However, upon closer scrutiny, it seems that the simulation was designed not to change the $CAVI_o$ value between baseline and follow-up, and clinical data were generated using normally distributed random numbers simulating biological variation. As there is a mathematical difference between CAVI and $CAVI_o$, it is natural that CAVI would change in relation to $CAVI_o$, when BP changed.

Therefore, the results of the simulation only showed that there are some differences between CAVI and $CAVI_o$ when BP changes, but no evidence or logic was presented to show which method is more accurate than the other.

No clinical data of any kind were included in this simulation, though the terms 'young subject' and 'older subject' are included in the text, which may cause some misunderstanding.

As for the relationship between CAVI and BP at the time of measurement, the independency of CAVI from BP was confirmed experimentally in man *in vivo* in Shirai *et al.* [6]. In this article, we demonstrated that by administration of metoprolol, β_1 selective blocker, BP decreased, but CAVI did not significantly change, indicating that CAVI is independent from BP at measuring time.

Fourth, we tried to find out the actual difference between both CAVI and $CAVI_o$ in two clinical studies.

At first, we reanalyzed part of the data of the article in Shirai *et al.* [6] as shown in Fig. 1. When metoprolol was administered, BP decreased, and both CAVI and $CAVI_o$ did not change significantly. When doxazosin was administered, BP decreased. At this time, CAVI and $CAVI_o$ decreased in the same way. The tendency of both values was parallel and essentially the same. The significance in statistical analysis was almost the same.

Next, we reanalyzed the epidemiologic data reported by Suzuki *et al.* [7]. The number of patients was 3665 in the healthy group and 4988 in the hypertensive group. Patients were also divided by sex and age (elderly or working age). CAVI and $CAVI_o$ values of the hypertensive group were significantly higher than those in the healthy group in all sex and age categories (Fig. 2). The significance in statistical analysis of both indexes was the same.

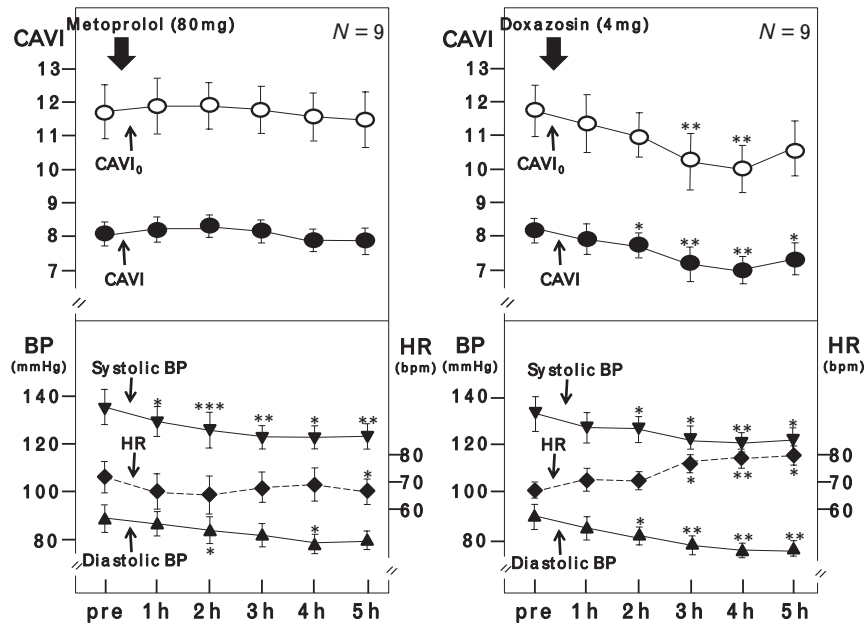


FIGURE 1 The comparison between cardio-ankle vascular index and cardio-ankle vascular index o during administration of metoprolol and doxazosin. Data are presented as the mean \pm standard error. Paired *t* test was used to compare preadministration and postadministration value. **P* < 0.05, ***P* < 0.01, ****P* < 0.001. BP, blood pressure; CAVI, cardio-ankle vascular index; CAVI₀, cardio-ankle vascular index o; HR, heart rate.

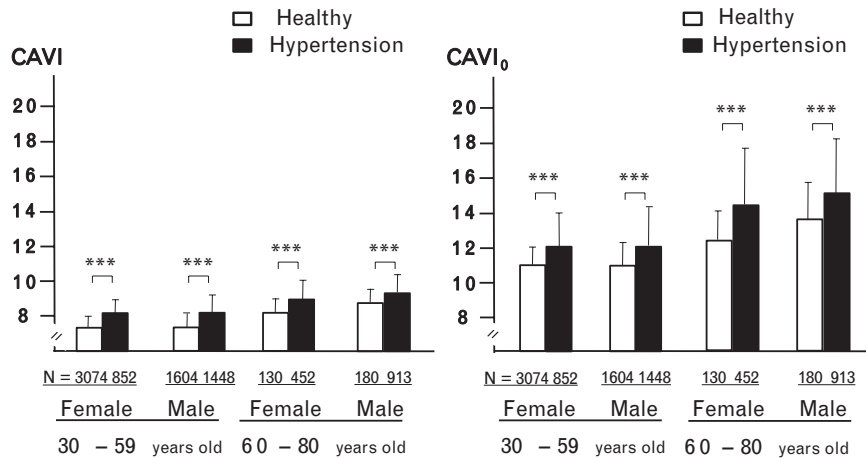


FIGURE 2 The comparison between cardio-ankle vascular index and cardio-ankle vascular index o in a hypertensive group and a healthy group. Data are presented as the mean \pm SD. Unpaired Student's *t* test was used in comparisons with two groups. **P* < 0.001. CAVI, cardio-ankle vascular index; CAVI₀, cardio-ankle vascular index o.

These results suggested that the claim that the existing implementation of CAVI could lead to erroneous conclusions in arterial stiffness trials is not at all the case.

In summary, the beta theory-derived index, which the authors presented in Eq. (9), is elegantly presented and has some merit in mathematical terms. However, the equation used by CAVI is perfectly valid as a tool for measuring arterial stiffness in a real-world setting.

The difference between the two arterial mathematical methods has been shown not to be significant. Even though there is some difference between the two methods, both are mathematical models that represent actual arterial stiffness, and as such, both can be considered valid for use. In practice, there is no possibility that CAVI could lead to erroneous conclusions in arterial stiffness trials.

These results suggest that the title of this article and its conclusions should be amended as they misrepresent the essence and effectiveness of CAVI.

ACKNOWLEDGEMENTS

Conflicts of interest

There are no conflicts of interest.

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Reply: physics cannot be disputed

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We read with interest the comments by Shirai *et al.* [1] on our recent publication in which we studied, on a theoretical basis, the pressure dependence of arterial stiffness index beta and cardio-ankle vascular index (CAVI) [2]. In our article, we demonstrated, given the same assumptions made in deriving CAVI [3], that β and CAVI show a residual dependence on blood pressure (BP). Given these assumptions, we provided corrected stiffness indices (β_0 and $CAVI_0$) that do not show this residual BP dependence [2]. We wish to address the concerns raised by Shirai *et al.* [1], in the context of our theoretical analysis [2].

First, CAVI is based on the assumption that the relationship between arterial pressure (P) and diameter (d) is exponential. Hayashi *et al.* [4] defined this relationship as $P = P_{ref} e^{\beta_0((d/d_{ref})^{-1})}$, with P_{ref} a fixed reference pressure and d_{ref} the corresponding diameter. This relationship was also used by Shirai *et al.* [3] in their article introducing CAVI,

in which they emphasize that β_0 in this relationship ‘... is based on a change in vascular diameter corresponding to arterial pressure variance and does not depend on blood pressure’. However, instead of directly estimating β_0 , they estimated β , which corresponds to a different exponential relationship: $P = P_d e^{\beta((d/d_d)^{-1})}$, where P_d and d_d are *diastolic* (instead of *reference*) pressure and diameter, respectively. This substitution leads to the fact that what should be a (fixed) reference pressure is replaced by an intrinsically variable pressure (DBP). In our article [2], we show that this substitution leads to an intrinsic dependence of β on pressure. Segers [5] acknowledges this effect in his editorial comment and furthermore elegantly visualizes it by plotting $\ln(P/P_{ref})$ versus d/d_{ref} , showing that (Kawasaki’s) β is reference pressure-dependent.

The substitution of P_{ref} and d_{ref} with P_d and d_d was first proposed by Kawasaki *et al.* [6], with the justification that ‘... the diameter (D_0) at standard pressure (100 mmHg) cannot be measured clinically...’. This reasoning, which is repeated by Shirai *et al.* [1] in their letter, is incorrect. In general, only diastolic and systolic diameters can be reliably measured in the clinical setting. Nevertheless, one can still derive an equation to obtain β_0 (corresponding to a true reference pressure) from any two pressure–diameter pairs, *without any simplifications* [2]:

$$\beta_0 = \frac{\ln(P_s/P_d)}{(d_s/d_d) - 1} - \ln\left(\frac{P_d}{P_{ref}}\right). \quad (1)$$

There is no need to substitute P_{ref} and d_{ref} with P_d and d_d as proposed by Kawasaki *et al.* [6]. Performing this substitution introduces unnecessary errors in estimating β . As CAVI is essentially a form of β , these unnecessary errors are also present in CAVI.

Second, Shirai *et al.* correctly state that the Bramwell–Hill relationship is based on Newton’s second law [7]. One of the assumptions required in deriving the Bramwell–Hill relationship is that the changes in vessel cross-sectional area over time are infinitesimally small [8]. Note that the velocity as calculated from the Bramwell–Hill relationship is equivalent to the characteristic wave speed (e.g. p. 74 in Ref. [9]), the speed at which a pressure *disturbance* propagates along the arterial bed. In a healthy arterial system, waves have a typical amplitude of 40 mmHg and yield an arterial wall distension of approximately 10% in diameter [10]. Changes of this magnitude can hardly be termed a disturbance and are not infinitesimally small. Instead, such changes lead to a significant change in vessel cross-sectional area and result in different wave velocities over the cardiac cycle [11]. To overcome this problem of significant changes in cross-sectional area, the foot of the waveform is commonly used as a point of identity on the travelling wave (p. 69 in Nichols *et al.* [12]) when wave speed is measured clinically. The foot is also the point that CAVI uses in determining its underlying pulse wave velocity (PWV). The use of the *diastolic*, foot-to-foot PWV has an important consequence, namely that this PWV is ‘precisely a marker of arterial stiffness at the level of *diastolic* blood pressure’ [13]. In other words, PWV estimated by the foot-to-foot method (as used in CAVI) corresponds to dP/dd at DBP (P_d). This