Reply

3. Kawasaki T, Sasayama S, Yagi S, Asakawa T, Hirai T. Noninvasive assessment of the age related changes in stiffness of major branches of the human arteries. *Cardiovasc Res* 1987; 21:678–687.
4. Shirai K, Hiruta N, Song M, Kurosu T, Suzuki J, Tomaru T, *et al.* Cardio-ankle vascular index (CAVI) as a novel indicator of arterial stiffness: theory, evidence and perspectives. *J Atheroscler Thromb* 2011; 18:924–938.
5. Nichols WW, Avolio AP, Kelly RP, O'Rourke MF. Effects of age and of hypertension on wave travel and reflections. In: O'Rourke MF, Safar M, Dzau V, editors. *Arterial vasodilation: mechanisms and therapy*. London: Edward Arnold; 1993. pp. 23–40.
6. Shirai K, Song M, Suzuki J, Kurosu T, Oyama T, Nagayama D, *et al.* Contradictory effects of β1- and α1-aderenergic receptor blockers on cardio-ankle vascular stiffness index (CAVI) – CAVI independent of blood pressure. *J Atheroscler Thromb* 2011; 18:49–55.
7. Suzuki K, Ishizuka N, Miyashita Y, Shirai K. Epidemiological examination about the standard value and the validity for the standardization as the examination of CAVI (cardio-ankle vascular index) noninvasive blood pressure-independent arteriosclerosis. *Niigata J Med Technol* 2008; 48-1:2–10; (in Japanese).

Journal of Hypertension 2017, 35:1521–1526

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DOI:10.1097/HJH.0000000000001349

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 $P = P_{\mathrm{ref}} e^{\beta_0((d/d_{\mathrm{ref}})-1)}$, 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: $P = P_{\mathrm{d}} e^{\beta((d/d_{\mathrm{d}})-1)}$, 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 $\ln(P/P_{\mathrm{ref}})$ 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 (Do) 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]:

$$\beta_0 = \frac{\ln(P_{\mathrm{s}}/P_{\mathrm{d}})}{(d_{\mathrm{s}}/d_{\mathrm{d}}) - 1} - \ln\left(\frac{P_{\mathrm{d}}}{P_{\mathrm{ref}}}\right). \quad (1)$$

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 $\mathrm{d}P/\mathrm{d}d$ at DBP (P_{d}). This

principle underlies our derivation of $CAVI_0$ and yields the following equation [2]:

$$CAVI_0 = \beta_0 = \frac{PWV^2 \times 2\rho}{P_d} - \ln\left(\frac{P_d}{P_{ref}}\right). \quad (2)$$

Shirai *et al.* correctly observed that there is no SBP term in this equation. This is a logical consequence of the fact that foot-to-foot PWV depends on DBP and not on SBP. Shirai *et al.* argue that because only DBP is used, a change in DBP along the arterial bed due to pulse wave amplification would make $CAVI_0$ less accurate, as $CAVI_0$ is controlled for DBP at only one point in the arterial bed. They argue that the longer the arterial bed and thus the larger the pulse wave amplification, the more inaccurate $CAVI_0$ will become. This is indeed a limitation of using a single reference pressure, although the actual decrease in DBP along the arterial bed is small and is on average 1–3 mmHg [14,15] (although a large interpatient variability exists). If we interpret Shirai *et al.* correctly, they imply that when using both DBP and SBP to linearly estimate dP/dd (as in the original CAVI formula), the increase in SBP will cancel out the decrease in DBP, so that on average, dP/dd will remain equal with pressure amplification.

Apart from the fact that the increase in SBP by far outweighs the decrease in DBP [14,15], there is a more fundamental, logical error in Shirai *et al.*'s reasoning. The foot-to-foot PWV, as employed in CAVI, *physically* does not depend on SBP. Using an equation that pretends PWV to depend on SBP will not change the fact that the actual foot-to-foot PWV is only DBP-dependent. Furthermore, CAVI still uses BP at only one point (the brachial artery) for normalization. Therefore, both CAVI as well as $CAVI_0$ suffer from the changing DBP problem indicated by Shirai *et al.* This problem is not solved by using an approximated version of the Bramwell–Hill equation that uses a diastolic-to-systolic estimation of dP/dd.

Third, Shirai *et al.* raised concerns regarding our use of a virtual population to illustrate the theoretical pressure dependence of $CAVI_0$ and stated that 'it seems that the simulation was designed not to change the $CAVI_0$'. We would like to stress that to generate this virtual population, we only assumed that the exponential pressure–diameter relationship did not change. The goal of this simulation was to investigate whether CAVI and $CAVI_0$ would change with BP at the time of measurement, while the arterial wall would remain intrinsically unchanged (i.e. the exponential *relationship* between pressure and diameter would remain unchanged). Shirai *et al.* stated '... but no evidence or logic was presented to show which method [CAVI or $CAVI_0$] is more accurate than the other'. Again, our 'logic' was the assumption that in a single patient, pressure and diameter are exponentially related and that this *relationship* would not change with pressure lowering.

Shirai *et al.* referred to a previous study in which 'the independency of CAVI from blood pressure was confirmed experimentally in man *in vivo*' [16]. In this study, Shirai *et al.* showed that by administration of metoprolol (a β_1 receptor selective blocker), BP decreased, but CAVI did not change significantly. We would like to stress that this study was performed in only 12 patients, without any form of power calculation. Therefore, the fact that CAVI was not found to change significantly in this study does not prove that CAVI is indeed BP-independent. This study will be discussed further in the fourth point below.

Fourth, we would like to commend Shirai *et al.* for implementing the $CAVI_0$ equation and using it on data obtained from clinical studies. Shirai *et al.* reanalyzed the aforementioned metoprolol data [16] and found that the results derived by implementing $CAVI_0$ did not change their conclusions drawn using CAVI. It has to be noted that Shirai *et al.*'s reanalysis was performed for nine patients [1], whereas the original study contained 12 patients [16]. A reason for omitting three patients for the calculation of CAVI and $CAVI_0$ was not given. In the reanalysis, both CAVI and $CAVI_0$ did not change significantly with changes in BP. Continuing Shirai *et al.*'s line of reasoning as introduced in the third point, this would mean that both CAVI and $CAVI_0$ are pressure-independent measures of arterial stiffness. However, in the third point, Shirai *et al.* also stated that 'As there is a mathematical difference between CAVI and $CAVI_0$, it is natural that CAVI would change in relation to $CAVI_0$, when blood pressure changed ...'. In short, in the third point, Shirai *et al.* stated that it is logical that CAVI and $CAVI_0$ are different, but in the fourth point, they failed to show any difference statistically and implied that CAVI and $CAVI_0$ lead to equivalent results. The only one logical explanation for this paradoxical observation seems to be the lack of statistical power in the dataset used. If this is the case, we expect that a study, such as the metoprolol study [16], would eventually show statistically significant pressure dependence of CAVI when performed in a larger cohort. Whether this also holds *in practice* is impossible to tell at this point.

Finally, Shirai *et al.* reanalyzed data from a large study by Suzuki *et al.* [17] and found that CAVI and $CAVI_0$ values were significantly different between hypertensive and normotensive patients. Specifically, they stated that 'The significance in statistical analysis of both indexes was the same'. It is from this finding that they concluded that our 'claim that the existing implementation of CAVI could lead to erroneous conclusions in arterial stiffness trials, is not at all the case'. First, we would like to emphasize our use of the conditional expression 'could' in this case. Second, the fact that both CAVI and $CAVI_0$ are statistically significantly ($P < 0.001$) different *between normotensive and hypertensive patients* does not provide any insight into the difference *between CAVI and $CAVI_0$*. Visually, it seems from Fig. 2 in Shirai *et al.*'s [1] correspondence that $CAVI_0$ shows larger differences between normotensive and hypertensive patients in the old subgroup than in the young one. This pattern seems not visible in CAVI. However, no attempt seems to have been made to actually *quantify* such CAVI–$CAVI_0$ differences in this analysis.

We appreciate the detailed response by Shirai *et al.* to our study, allowing us to clarify that we acknowledge the significant value that CAVI can bring to assessment of vascular function. We also acknowledge that the differences between CAVI and $CAVI_0$ are not of a very large magnitude; however, as already emphasized by Segers [5], the order of magnitude of the change in CAVI in our simulation study is of the same order of magnitude as

reported in actual intervention studies [18], underpinning our point that under certain circumstances, CAVI could lead to erroneous conclusions in arterial stiffness trials. This could be readily mitigated by incorporating our proposed method of correction.

Our article showed that *in specific cases* (i.e. a large enough study population and a large enough change in BP) and *under the assumption of* an exponential pressure–diameter relationship, CAVI could lead to erroneous conclusions of statistical significance.

Although the errors in deriving CAVI may not always emerge as statistically significant, they (theoretically) lead to systematic errors in *all* CAVI values, including those obtained in individual patients. The fact that CAVI and $CAVI_0$ did not lead to (statistically) different conclusions in the examples by Shirai *et al.* [1] neither proves nor disproves this point, but only suggests that the practical numerical difference between CAVI and $CAVI_0$ may be small. However, the statement by Shirai *et al.* that 'there is no possibility that CAVI could lead to erroneous conclusions in arterial stiffness trials' is clearly unfounded.

We studied the pressure dependence of CAVI and $CAVI_0$ on a theoretical basis. Whether $CAVI_0$ indeed behaves as theoretically predicted needs to be tested in clinically measured values. This equally holds for CAVI, in which BP (in)dependence has only been tested in an exploratory set of 12 patients [16].

Nonetheless, in deriving CAVI, two simplification steps are made (first and second points) that could be questioned in terms of the laws of physics. Derivation of $CAVI_0$ does not require these steps, yet eventually results in an index with similar ease of use as CAVI. In this light, we argue that $CAVI_0$ is, at least theoretically, preferable over CAVI.

ACKNOWLEDGEMENTS

The study was supported by an Endeavour Research Fellowship awarded by the Australian Government to B.S.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. 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.
2. Spronck B, Avolio AP, Tan I, Butlin M, Reesink KD, 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.
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.
4. Hayashi K, Handa H, Nagasawa S, Okumura A, Moritake K. Stiffness and elastic behavior of human intracranial and extracranial arteries. *J Biomech* 1980; 13:175–184.
5. Segers P. A lesson in vigilance: pressure dependency of a presumed pressure-independent index of arterial stiffness. *J Hypertens* 2017; 35:33–35.
6. Kawasaki T, Sasayama S, Yagi S, Asakawa T, Hirai T. Non-invasive assessment of the age related changes in stiffness of major branches of the human arteries. *Cardiovasc Res* 1987; 21:678–687.
7. Bramwell JC, Hill AV. The velocity of the pulse wave in man. *Proc R Soc Lond B Biol Sci* 1922; 93:298–306.
8. Butlin M. *Structural and functional effects on large artery stiffness: an in-vivo experimental investigation*. Saarbrücken, Germany: VDM Verlag Dr Müller Aktiengesellschaft & Co. KG; 2008.
9. Pedley TJ. *The fluid mechanics of large blood vessels*. Cambridge, UK: Cambridge University Press; 2008.
10. Reneman RS, Meinders JM, Hoeks AP. Noninvasive ultrasound in arterial wall dynamics in humans: what have we learned and what remains to be solved. *Eur Heart J* 2005; 26:960–966.
11. Hermeling E, Hoeks AP, Winkens MH, Waltenberger JL, Reneman RS, Kroon AA, Reesink KD. Noninvasive assessment of arterial stiffness should discriminate between systolic and diastolic pressure ranges. *Hypertension* 2010; 55:124–130.
12. Nichols W, O'Rourke M, Vlachopoulos C. *McDonald's blood flow in arteries: theoretical, experimental and clinical principles*. London, UK: CRC Press; 2011.
13. Gao M, Cheng H-M, Sung S-H, Chen CH, Olivier NB, Mukkamala R. Estimation of pulse transit time as a function of blood pressure using a nonlinear arterial tube-load model. *IEEE Trans Biomed Eng* 2016; [Epub ahead of print].
14. Moore C, Dobson A, Kinagi M, Dillon B. Comparison of blood pressure measured at the arm, ankle and calf. *Anaesthesia* 2008; 63:1327–1331.
15. Salles-Cunha SX, Vincent DG, Towne JB, Bernhard VM. Noninvasive ankle pressure measurements by oscillometry. *Tex Heart Inst J* 1982; 9:349–357.
16. Shirai K, Song M, Suzuki J, Kurosu T, Oyama T, Nagayama D, *et al.* Contradictory effects of β1- and α1-aderenergic receptor blockers on cardio-ankle vascular stiffness index (CAVI) – CAVI independent of blood pressure. *J Atheroscler Thromb* 2011; 18:49–55.
17. Suzuki K, Ishizuka N, Miyashita H, Shirai K. Epidemiological examination about the standard value and the validity for the standardization as the examination of CAVI (cardio-ankle vascular index) noninvasive blood pressure-independent arteriosclerosis. *Niigata J Med Technol* 2008; 48:2–10; (in Japanese).
18. Kurata M, Okura T, Watanabe S, Irita J, Enomoto D, Johtoku M, *et al.* Effects of amlodipine and candesartan on arterial stiffness estimated by cardio-ankle vascular index in patients with essential hypertension: A 24-week study. *Curr Ther Res Clin Exp* 2008; 69:412–422.

Journal of Hypertension 2017, 35:1521–1526

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DOI:10.1097/HJH.0000000000001350

Renal resistive index for resistant hypertension

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In a recent issue of the journal, Kintis *et al.* [1] examined the association of renal haemodynamics with resistant hypertension (RHTN). Specifically, the authors found that patients with RHTN had greater levels of renal resistive index (RRI) compared with patients with controlled hypertension. Based on the findings, they concluded that a greater RRI may help identifying RHTN patients. However, the levels of RRI could have reflected the levels of pulse pressure (PP), the difference between the SBP and DBP readings.