Arterial stiffness index beta and cardio-ankle vascular index inherently depend on blood pressure but can be readily corrected

Arterial stiffness index beta and cardio-ankle vascular index inherently depend on blood pressure but can be readily corrected

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Objectives: Arterial stiffness index β and cardio-ankle vascular index (CAVI) are widely accepted to quantify the intrinsic exponent (β_0) of the blood pressure (BP)-diameter relationship. CAVI and β assume an exponential relationship between pressure (P) and diameter (d). We aim to demonstrate that, under this assumption, β and CAVI as currently implemented are inherently BP-dependent and to provide corrected, BP-independent forms of CAVI and β.

Methods and results: In $P = P_{\mathrm{ref}} e^{\beta_0[(d/d_{\mathrm{ref}})-1]}$, usually reference pressure (P_{ref}) and reference diameter (d_{ref}) are substituted with DBP and diastolic diameter to accommodate measurements. Consequently, the resulting exponent is not equal to the pressure-independent β_0. CAVI does not only suffer from this 'reference pressure' effect, but also from the linear approximation of $(\mathrm{d}P/\mathrm{d}d)$. For example, assuming $\beta_0 = 7$, an increase of SBP/DBP from 110/70 to 170/120 mmHg increased β by 8.1% and CAVI by 14.3%. We derived corrected forms of β and of CAVI (CAVI_0) that indeed did not change with BP and represent the pressure-independent β_0. To substantiate the BP effect on CAVI in a typical follow-up study, we realistically simulated patients ($n = 161$) before and following BP-lowering 'treatment' (assuming no follow-up change in intrinsic β_0 and therefore in actual P–d relationship). Lowering BP from $160 \pm 14/111 \pm 11$ to $120 \pm 15/79 \pm 11$ mmHg ($p < 0.001$) resulted in a significant CAVI decrease (from 8.1 ± 2.0 to 7.7 ± 2.1, $p = 0.008$); CAVI_0 did not change (9.8 ± 2.4 and 9.9 ± 2.6, $p = 0.499$).

Conclusion: β and CAVI as currently implemented are inherently BP-dependent, potentially leading to erroneous conclusions in arterial stiffness trials. BP-independent forms are presented to readily overcome this problem.

Keywords: arterial stiffness, arteriosclerosis, blood pressure correction, carotid compliance, hypertension, pulse wave velocity

Abbreviations: A, artery lumen cross-sectional area; a, b, constants relating $\mathrm{CAVI}_{\mathrm{VS}}$ to CAVI; BP, blood pressure; CAVI, cardio-ankle vascular index as used in this manuscript; CAVI_0, pressure-independent CAVI; $\mathrm{CAVI}_{\mathrm{VS}}$, CAVI in the Fukuda Denshi VaSera device, related to CAVI in our manuscript by $\mathrm{CAVI}_{\mathrm{VS}} = a \times \mathrm{CAVI} + b$; d, artery lumen diameter; d_{ref}, reference diameter; $N(\mu,\sigma)$, independent samples drawn from a normal distribution with mean μ and SD σ; P, blood pressure; P_{d}, DBP; $P_{\mathrm{d,bl,nf}}$, $P_{\mathrm{p,bl,nf}}$, $P_{\mathrm{s,bl,nf}}$, simulated, noise-free baseline DBP, pulse pressure, and SBP; $P_{\mathrm{d,fu,nf}}$, $P_{\mathrm{p,fu,nf}}$, $P_{\mathrm{s,fu,nf}}$, simulated, noise-free follow-up DBP, pulse pressure, and SBP; P_{ref}, reference pressure; P_{s}, SBP; PWV, pulse wave velocity; $\mathrm{PWV}_{\mathrm{bl,nf}}$, $\mathrm{PWV}_{\mathrm{fu,nf}}$, simulated, noise-free PWVs at baseline and follow-up; SDC, supplemental digital content 1; β, stiffness index beta; β_0, intrinsic, pressure-independent stiffness index beta; ρ, blood mass density

INTRODUCTION

Arterial stiffness, as assessed by pulse wave velocity (PWV), is an important independent predictor for cardiovascular disease. PWV, however, is known to depend intrinsically on arterial blood pressure (BP) [1,2]. This BP dependence has led to the search for BP-independent measures of arterial stiffness.

As shown by Hayashi *et al.* [3], the relationship between arterial pressure and diameter can be described by an exponential function in the physiological range (Fig. 1a). Throughout the present article, this exponential relationship between arterial pressure and diameter with pressure-independent exponent β_0 is assumed as a 'ground truth' on which all other derivations are based. Of note, this article has no intention to prove the validity of this basic assumption.

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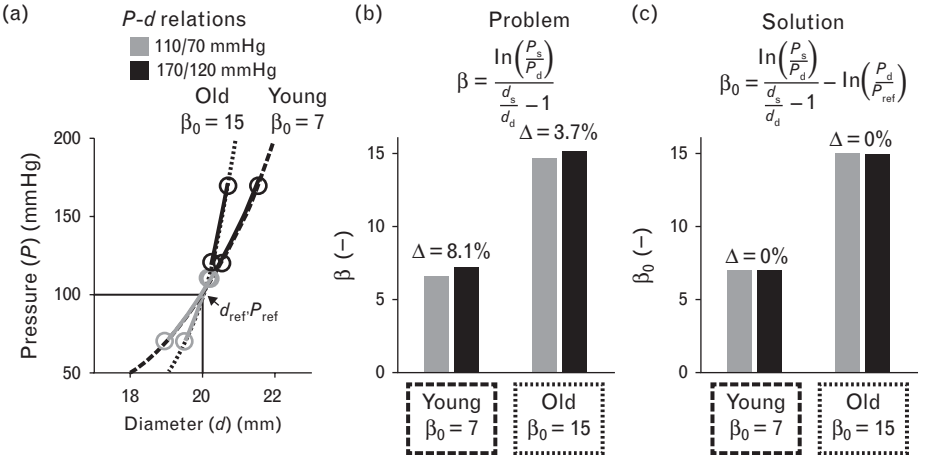

FIGURE 1 Pressure dependence of stiffness index beta (β). (a) Intrinsic relationship between arterial pressure and diameter [Eq. (1)]. Hayashi *et al.* [3] showed that in the physiological pressure range, this relationship is exponential. The exponential nature of this relationship is assumed as a 'ground truth' in this article, serving as the basis for all other derivations. Pressure ranges (SBP/DBP) indicated in this panel are used for calculating stiffness parameters in panels (b) and (c). $P_{ref} = 100$ mmHg is a reference pressure [Eq. (1)]. d_{ref} is the diameter corresponding to the reference pressure. d_{ref} is kept fixed at 20 mm to illustrate solely the effect of a change in β_0 on the pressure-diameter relationship. (b) Measured stiffness index β, as computed from SBP and DBP (P_s, P_d) and diameters (d_s, d_d) on panel (a)'s curves, is blood pressure-dependent. Because the pressure dependence of β can be shown to exist mathematically [Eq. (4)], β can be corrected using $\ln(P_d/P_{ref})$, obtaining the intrinsic, pressure-independent stiffness index beta (β_0, panel c). P_{ref} and d_{ref}, reference blood pressure and diameter corresponding to Eq. (1).

Kawasaki *et al.* [4] proposed a clinically usable stiffness index β that is based on the exponential relationship as demonstrated by Hayashi *et al.* [3]. In the present article, we will demonstrate that β is only an approximation of β_0, and that β is in fact pressure-dependent.

Cardio-ankle vascular index (CAVI) is being increasingly used in small and large population studies [5] and is advocated as a pressure-independent index of arterial stiffness [6]. CAVI is closely related to stiffness index β and is also an approximation of the exponent of the pressure–diameter relationship. Although β is used for local characterization of small artery segments, CAVI is derived as a summary measure for the heart-to-ankle arterial trajectory. CAVI is obtained by measuring PWV and converting it into an index using the Bramwell–Hill equation [1].

In the present article, we will:

1. Show that β, as commonly calculated in biomedical literature, is not equal to the actual, intrinsic stiffness index of the pressure–diameter relationship (β_0) but instead varies with BP.
2. Show that the BP dependence of β can be corrected for, yielding a formula to obtain the true, intrinsic stiffness index β_0 from the same measurements.
3. Show that CAVI, which essentially is a form of stiffness index β, is also BP dependent.
4. Show that a straightforward modification of the formula for calculating CAVI yields a pressure-independent version, that is, $CAVI_0$.
5. Illustrate the scientific and clinical relevance of our analysis and proposed corrected β_0 and $CAVI_0$ formulas.

METHODS

Behaviour of the arterial wall: intrinsic stiffness index beta

Hayashi *et al.* [3] showed experimentally that, in the physiological BP range, arterial pressure (P) and diameter (d) relate exponentially:

$$P = P_{ref} e^{\beta_0[(d/d_{ref})-1]}. \quad (1)$$

Throughout this article, this equation serves as our 'ground truth'. β_0 in this relationship is an intrinsic, pressure-independent measure of arterial stiffness. Note the use of P_{ref} (a 'reference' or 'standard' pressure) in this equation. d_{ref} is the diameter corresponding to the reference pressure. Figure 1a shows two pressure–diameter relationships obtained using Eq. (1) at $\beta_0 = 7$ and 15. Each curve corresponds to one β_0 value. $P_{ref} = 100$ mmHg was used throughout the present study [3].

Assessment of arterial wall mechanics: measured stiffness index beta

Stiffness index β as commonly reported is calculated using a slightly different equation than Eq. (1):

$$P_s = P_d e^{\beta[(d_s/d_d)-1]}, \quad (2)$$

in which P_s, d_s, P_d, and d_d denote SBP and DBP and diameters, respectively. Note the following differences between Eqs. (1) and (2): (i) reference pressure and diameter have been changed to DBP and diameter; (ii) instantaneous variable pressure has been changed to SBP; and (iii) intrinsic stiffness index β_0 has been changed to measured stiffness β.

Eq. (2) can be rearranged to obtain the commonly used expression for β:

$$\beta = \frac{\ln(P_s/P_d)}{(d_s/d_d) - 1}. \quad (3)$$

If this equation is used to quantify β in an exponentially-distending wall [Eq. (1)] with a given $\beta_0 = 7$ and $P_{ref} = 100$ mmHg, calculated βs will be dependent on the

pressure ranges (Fig. 1b). This can be understood as follows.

Pressure dependence of measured stiffness index β

Suppose that two pressure–diameter points are measured on the intrinsic pressure–diameter relationship [Eq. (1)]: a systolic (P_s,d_s) and a diastolic (P_d,d_d) point. From Eq. (3) and rearranging the result [Supplemental digital content 1 (SDC), http://links.lww.com/HJH/A682], we obtain

$$\beta = \beta_0 + \ln\left(\frac{P_d}{P_{ref}}\right). \quad (4)$$

This equation shows that β, the measured stiffness index, differs from the intrinsic stiffness index β_0, by an amount of $\ln(P_d/P_{ref})$. This also implies that we can readily obtain the intrinsic, pressure-independent stiffness index β_0 by rearranging Eq. (4):

$$\beta_0 = \beta - \ln\left(\frac{P_d}{P_{ref}}\right). \quad (5)$$

Note that if P_d is equal to P_{ref}, $\ln(P_d/P_{ref}) = 0$, and β_0 equals β. However, in general, this is not the case.

Substituting the initial expression for β [Eq. (3)] into Eq. (5) yields

$$\beta_0 = \frac{\ln(P_s/P_d)}{(d_s/d_d) - 1} - \ln\left(\frac{P_d}{P_{ref}}\right), \quad (6)$$

which is a formulation that can be used to obtain the intrinsic, pressure-independent stiffness index β_0 from measured SBP and DBP and diameters.

The value of reference pressure

The previous sections demonstrate that the pressure (either P_d or P_{ref}) that is used to multiply the exponential function influences the value of β or β_0 that is obtained. It is important to realize that a value of β_0 *corresponds to* a P_{ref} value. Therefore, one should choose one, *fixed* P_{ref} value for *all* patients in a study, to be able to compare the β_0 values among these patients. The numerical value of P_{ref} that is chosen is a matter of standardization or consensus. P_{ref} does *not* represent a physiological pressure. Different values of P_{ref} (and the corresponding d_{ref}) lead to different values of β_0. However, the *P*–*d* curves that are described using these different combinations of $P_{ref}/d_{ref}/\beta_0$ perfectly and analytically overlap. Therefore, P_{ref} values should be taken *equal* between studies (irrespective of the patient cohort studied), if β_0 values are to be compared between those studies. Arbitrarily, in the present study, we have chosen $P_{ref} = 100$ mmHg.

Cardio-ankle vascular index

Stiffness index β [Eq. (3)], which is a function of pressures (P_d and P_s) and diameters (d_d and d_s), can also be expressed as a function of pressures and PWV. This is accomplished by combining Eq. (3) with a simplified version of the Bramwell–Hill equation (SDC Eq. S10) [1]. When PWV in this equation is determined from the heart-to-ankle arterial bed, the resulting quantity (in fact a β index) is termed CAVI:

$$\mathrm{CAVI} = \ln\left(\frac{P_s}{P_d}\right) \times \frac{\mathrm{PWV}^2 \times 2\rho}{P_s - P_d}. \quad (7)$$

PWV from the heart to the ankle is obtained using a combination of the phonocardiography, electrocardiography, and brachial and ankle cuff measurements [6].

For the same reasons outlined in the previous section (the use of DBP instead of a reference BP), CAVI is pressure dependent. However, CAVI also depends on BP for another reason, as explained below.

The derivation of CAVI [6] is based on a simplified version of the Bramwell–Hill equation (Fig. 2b), in which the derivative of pressure to diameter (dP/dd) is replaced by a linear approximation over the DBP-to-SBP range. This approximation introduces an error in the obtained CAVI value. The magnitude of this error can be quantified using the true PWV, that is, the PWV based on the true (dP/dd) in the diastolic point (SDC Eq. S11). Using this PWV to calculate CAVI by means of Eq. (7) yields

$$\mathrm{CAVI} = \left[\beta_0 + \ln\left(\frac{P_d}{P_{ref}}\right)\right] \times \ln\left(\frac{P_s}{P_d}\right) \times \frac{P_d}{P_s - P_d}. \quad (8)$$

The extra terms beside β_0 on the right-hand side of this equation indicate the pressure dependence of CAVI (Fig. 2c).

Finding a pressure-independent cardio-ankle vascular index

A pressure-independent CAVI formula should provide an index equivalent to the intrinsic stiffness index β_0. Such an index can be derived by squaring and rearranging the relationship between true PWV (obtained from the exact, analytic derivative of the *P*–*d* relationship) and β_0 (SDC Eq. S13):

$$\mathrm{CAVI}_0 = \beta_0 = \frac{\mathrm{PWV}^2 \times 2\rho}{P_d} - \ln\left(\frac{P_d}{P_{ref}}\right). \quad (9)$$

This equation can be used to obtain the pressure-independent CAVI_0 from PWV, ρ, and P_d (Fig. 2d).

Simulations

Residual blood pressure dependence of stiffness index β and cardio-ankle vascular index

To quantify the BP dependence of stiffness index β, we calculated β [Eq. (4)] at two clearly distinct BP ranges [normotensive 110/70 mmHg (SBP/DBP) and hypertensive 170/120 mmHg]. We did so for two values of intrinsic stiffness: $\beta_0 = 7$ and $\beta_0 = 15$, corresponding to a normal young patient and an older patient with a stiffened artery, respectively. The reference diameter (d_{ref}) was kept constant at 20 mm. The quantitative effect of BP on CAVI was determined for the same BP ranges and β_0 values [Eq. (8)].

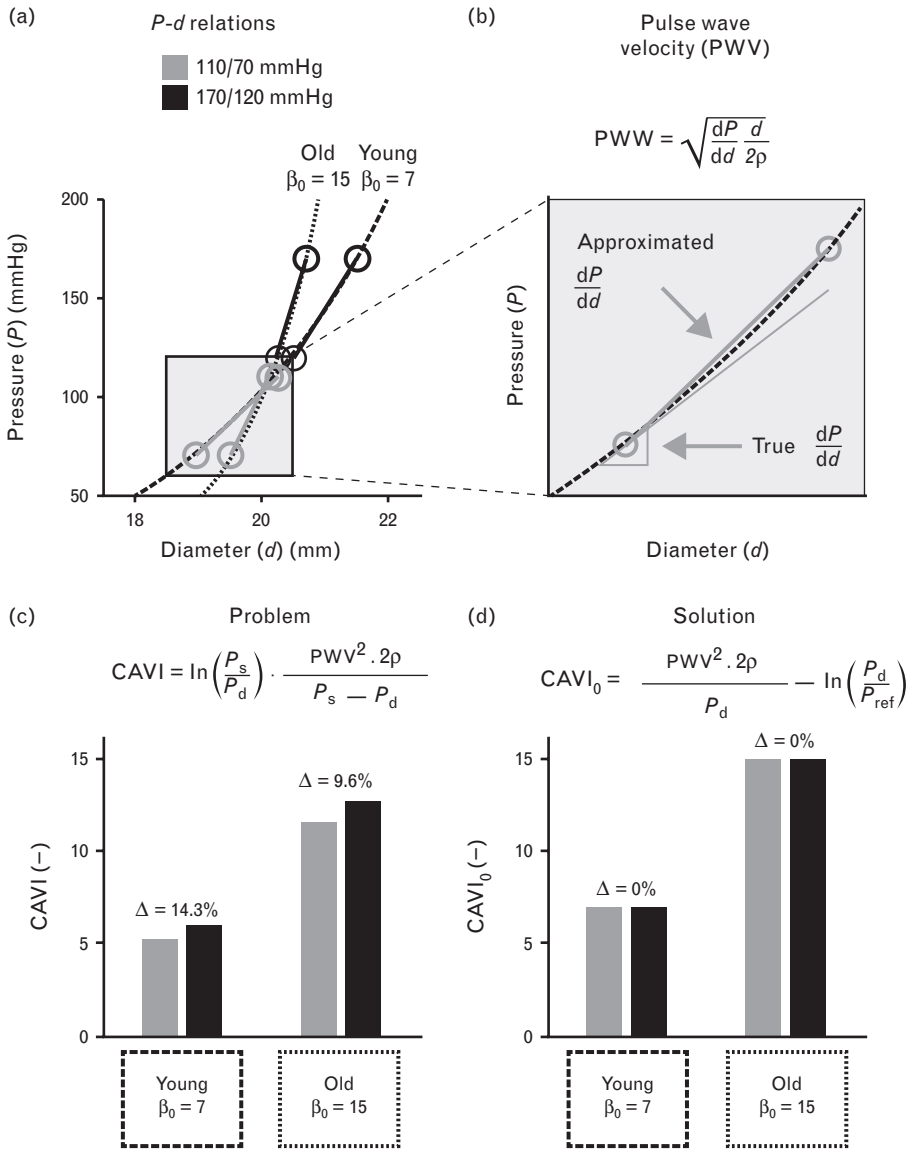

FIGURE 2 Pressure dependence of cardio-ankle vascular index (CAVI). (a) Intrinsic P–d relations [Eq. (1)] and pressure ranges (SBP/DBP) used for calculating cardio-ankle vascular index in panels (c) and (d). $P_{ref} = 100$ mmHg and $d_{ref} = 20$ mm. (b) As CAVI is essentially a form of stiffness index beta, the pressure dependence as shown in Fig. 1 also holds for CAVI. In CAVI, however, there is a second source of pressure dependence, which arises as follows. In the normal CAVI formula, an approximation of the Bramwell–Hill equation is used, effectively substituting $\mathrm{d}P/\mathrm{d}d$ with $\Delta P/\Delta d$. Therefore, if CAVI is determined using measured pulse wave velocity and the standard equation [Eq. (7)] [6], CAVI shows a blood pressure dependence (panel c). (d) As CAVI assumes an exponential pressure–diameter relationship [Eq. (1)], one can analytically determine the true $\mathrm{d}P/\mathrm{d}d$. By using this analytic expression, one can find a pressure-independent formulation of CAVI (CAVI_0). Note the presence of the $\ln(P_d/P_{ref})$ term, which is also present in the corrected form of stiffness index beta [Eq. (6) and Fig. 1c]. P_{ref} and d_{ref}, reference blood pressure and diameter corresponding to Eq. (1).

Blood pressure dependence of cardio-ankle vascular index in a simulated population study

To gain insight into the magnitude of the BP dependence of CAVI and how this could affect a typical study's results, we computer-simulated a BP-lowering treatment in a population with an average intrinsic stiffness of $\beta_0 = 10$. For a detailed description of the protocol for data generation and randomization, we refer the reader to the SDC.

In short, we simulated a baseline and a follow-up measurement between which BP decreased on average from about 160/110 to 120/80 mmHg. Importantly, we assumed wall behaviour to remain unchanged. That is, with the BP change for each patient, the exponential P–d relationship [Eq. (1)] and, hence, β_0 remained unchanged. DBP, SBP, and PWV values before and following 'treatment' were drawn from normal distributions, simulating biological variation. Subsequently, measurements were simulated by adding normally distributed measurement noise. CAVI and CAVI_0 were calculated from these simulated measurements.

Using the simulated population data, we calculated the sample size at which, for a power of 80% and $\alpha = 0.05$, the BP lowering would lead to a statistically significant change in CAVI. Subsequently, we simulated a study in the number of patients obtained from the sample size calculation to illustrate a typical study's results.

RESULTS

Residual blood pressure dependence of stiffness index β and cardio-ankle vascular index

Figure 1b shows the quantitative effect of BP on stiffness index β. With increasing BP from 110/70 to 170/120 mmHg (SBP/DBP), β increased by 8.1% (from 6.6 to 7.2) in a young individual's artery with $\beta_0 = 7$. In an older individual's artery with $\beta_0 = 15$, β increased by 3.7% (from 14.6 to 15.2).

Pressure dependence of β was markedly smaller than that of PWV. PWV changed to a much larger extent with BP; from 5.4 to 7.4 m/s in the young artery (36% change) and from 8.1 to 10.8 m/s in the older artery (33% change). Stiffness index β as determined using the corrected equation [Eq. (6), yielding β_0] was independent of pressure (Fig. 1c).

Figure 2c shows the quantitative effect of BP on CAVI. With increasing BP from 110/70 to 170/120 mmHg (SBP/DBP), CAVI increased from 5.3 to 6.0 (14.3% increase) in a young individual and from 11.6 to 12.7 (9.6% change) in an older individual. Furthermore, using the standard CAVI formula leads to much lower values for β than the actual, intrinsic β_0s of 7 and 15.

CAVI as determined using the corrected equation [Eq. (9), yielding $CAVI_0$] was independent of pressure (Fig. 2d).

Figure 3 shows how stiffness index β (a) and CAVI (b) depend on DBP and SBP. Comparing Fig. 3a and b, one sees that (i) β only depends on DBP, whereas CAVI depends on DBP and SBP; and that (ii) the BP dependence of CAVI is much larger than that of β (viz., compare the different colour scales of panes a and b). The larger BP dependence of CAVI is caused by the use of an approximated derivative in the CAVI formula (Fig. 2b), in addition to the 'reference pressure' effect that affects both β and CAVI.

Simulated impact of the blood pressure dependence of cardio-ankle vascular index in a population study

For our simulated population, we determined that a sample size of 161 patients would give an 80% chance of finding a statistically significant difference in CAVI due to BP lowering. Table 1 shows the results of a simulated set of measurements in 161 patients. Values throughout are expressed as mean ± SD.

For the lowering of SBP from 160 ± 14 to 120 ± 15 mmHg ($p < 0.001$) and DBP from 110 ± 11 to 79 ± 11 mmHg ($p < 0.001$), PWV significantly decreased from 8.2 ± 1.1 to 6.9 ± 1.0 m/s ($p < 0.001$). CAVI as calculated from the standard equation [Eq. (7)] significantly decreased from 8.1 ± 2.0 to 7.7 ± 2.1 ($p = 0.008$) with lowering BP, as expected for the sample size.

The corrected CAVI as proposed and calculated from Eq. (9) ($CAVI_0$) showed no change with BP ($p = 0.499$).

DISCUSSION

CAVI and β assume an exponential relationship between pressure and diameter. In this study, we have demonstrated that, under this assumption and contrary to the often made claim [6], stiffness index β and CAVI are BP dependent. This confirms findings by Lim *et al.* [7], who showed a BP dependence of CAVI in an experimental setting. However, the BP dependence of other artery stiffness parameters, such as PWV [2], is greater than that of β and CAVI.

Using CAVI under the assumption of it being fully BP-independent may confound conclusions, especially in large population studies investigating relatively small changes in CAVI. For example, several studies have reported that arterial stiffness, as measured with CAVI, decreases with BP-lowering medication [5,8]. However, our simulations show that even in a study with relatively few participants ($n = 161$) in which intrinsic wall parameters (β_0) were explicitly kept constant, the BP effect on CAVI may emerge as statistically significant.

In our simulation study, the BP effect on PWV (1.3 m/s) is much larger than the within-patient SD of 0.5 m/s [9]. The BP-induced change of CAVI of 0.4 in our simulation study is of the same order as the CAVI within-patient SD of 0.5 [10]. This comparison underlines the much smaller BP dependence of CAVI when compared with PWV and emphasizes that CAVI as usually implemented may lead to erroneous conclusions.

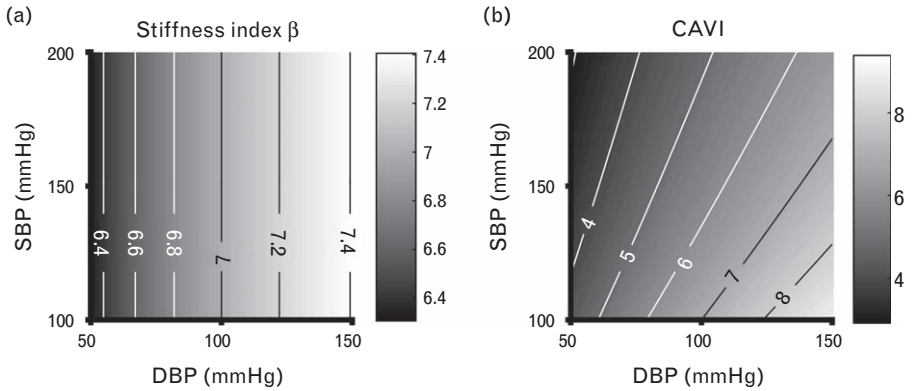

FIGURE 3 Dependence of stiffness index β and cardio-ankle vascular index (CAVI) on DBP and SBP. (a) β depends on DBP because of the 'reference point' effect [cf. the difference between Eqs. (1) and (2)]. (b) The 'reference point' effect also influences CAVI, causing a dependence of CAVI on DBP. CAVI is additionally blood pressure-dependent due to the use of an approximated derivative in the Bramwell–Hill equation (Fig. 2b), also introducing a dependence on SBP. Plots were generated for reference pressure = 100 mmHg and $\beta_0 = 7$ (see text).

TABLE 1. Uncorrected cardio-ankle vascular index leads to misinterpretation

Parameter	Unit	Baseline	Follow-up	*p*
SBP	mmHg	161 ± 14	120 ± 15	<0.001
DBP	mmHg	111 ± 11	79 ± 11	<0.001
PWV	m/s	8.2 ± 1.1	6.9 ± 1.0	<0.001
CAVI	–	8.1 ± 2.0	7.7 ± 2.1	0.008
$CAVI_0$	–	9.8 ± 2.4	9.9 ± 2.6	0.499

Pressure dependence of CAVI in a simulated data set ($n = 161$). Values denote mean ± SD. CAVI, standard, pressure-dependent cardio-ankle vascular index [Eq. (7)]; $CAVI_0$, corrected, pressure-independent cardio-ankle vascular index [Eq. (9)]; *p*, *p* value of two-sided paired *t* test comparing baseline to follow-up values; PWV, pulse wave velocity. Intrinsic stiffness index β_0 was 9.8 ± 1.9, and was equal at baseline and follow-up.

As mentioned in the introduction, Kawasaki *et al.* [4,11] previously derived β from β_0. In their derivation, they correctly mentioned that clinically, it is difficult to measure diameter at a standard pressure of for example, 100 mmHg. After this notice, they simplified Eq. (1) to Eq. (2), thereby neglecting the underlying BP dependence emerging from substituting DBP and *diastolic* diameter for P_{ref} and d_{ref} in Eq. (1).

Note that CAVI as reported by the VaSera device by Fukuda Denshi, Co. Ltd (Tokyo, Japan) ($CAVI_{VS}$) is a scaled version of CAVI as used in this article: $CAVI_{VS} = a \times CAVI + b$ [6]. The constants *a* and *b* are considered proprietary information by the company and therefore are not publically available. However, as *a* and *b* constants, the BP dependence of CAVI is equally applicable to $CAVI_{VS}$.

The present study relies on the assumption that the in vivo arterial wall pressure–diameter relationship is exponential. The underlying arterial wall mechanics of the exponential behaviour are complex. At lower pressures, mainly elastin bears the load, whereas at higher pressures, this load bearing is gradually shifted to collagen [12,13]. This shift leads to the typical form of the full *P–d* relationship, which, starting from $P = 0$, first shows an *increase* in compliance, then has a maximum, and subsequently decreases with increasing pressure [14]. The maximum compliance, corresponding to an inflection point in the *P–d* relationship, occurs at a pressure of around 45 mmHg in individuals aged 30 years. With increasing age, the pressure at which the maximum compliance occurs decreases and becomes 0 mmHg at the age of 80 [15]. If this full *P–d* relationship with an inflection point is to be described, a single-exponential *P–d* relationship is clearly insufficient; an arctangent-type model may be more suitable in this case [14].

Because young patients have an inflection point at relatively high pressures of ≈45 mmHg, the assumption of a single-exponential relationship may not hold when they are hypotensive. In this case, their low DBPs may be close to their inflection point. However, in all other patients, physiological BPs are normally well above the inflection point. Therefore, a single-exponential relationship provides an appropriate approximation of the true *P–d* relationship.

The exponential shape of the *P–d* relationship as shown *in vitro* by Hayashi *et al.* [3] was confirmed *in vivo* in humans by Stefanadis *et al.* [16]. They reported that 'the pressure–diameter data fitted excellently to the monoexponential function $P = b \times e^{a \times D}$, ($r = 0.97$–$0.99$, $p < 0.001$), ...' in the human aorta, both in normotensive and hypertensive patients. Later studies by these investigators again confirmed this finding [17,18].

The choice of an exponential *P–d* relationship has a pragmatic reason. Models that are more complicated than the single-exponential model cannot be uniquely parameterized using a set of SBP and DBP and two diameters or a PWV. This limits their use to very specific research studies in which the full pressure–diameter relationship is measured, or in which more than two *P–d* points are measured (e.g. by adding an additional dicrotic notch point [19]). In our opinion, this limitation, together with the in-vivo validations by Stefanadis *et al.* [16], makes a strong case for using an exponential model to characterize in vivo arterial *P–d* relationships.

CONCLUSION

CAVI and stiffness index β rely on the assumption of an exponential relationship between pressure and diameter. In this article, we have shown that, under this assumption, stiffness index β and CAVI as commonly implemented depend on BP. This dependence can potentially lead to erroneous conclusions in studies that use β and CAVI to estimate changes in stiffness of the artery wall. We have presented corrected stiffness indices, β_0 and $CAVI_0$, that readily overcome this problem.

Perspectives

The findings presented in this manuscript have direct implications for all studies that incorporate β and/or CAVI measurements. We have shown that due care should be taken in interpreting β and CAVI as strictly pressure-independent measures of arterial stiffness. In a moderately sized study, a BP decrease from a hypertensive to a normotensive range may lead to a significant decrease in CAVI as calculated from the standard equation, merely due to the change in BP. $CAVI_0$, as derived in the present study, does not exhibit this pressure dependence. Our new formulations (β_0 and $CAVI_0$) allow even retrospective data analysis for improved interpretation of arterial stiffness trials. Recently, we have shown that the degree of BP dependence of PWV is clinically relevant [2], and that the BP dependence is apparent from the PWV reference values [20]. Based on the reference values for PWV, and considering the approach proposed in the present article, pressure-independent reference values for $\beta_0/CAVI_0$ could be obtained.

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Conflicts of interest

There are no conflicts of interest.

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