Review

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# Five years of cardio-ankle vascular index (CAVI) and $CAVI_0$: how close are we to a pressure-independent index of arterial stiffness?

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Pulse wave velocity, a common metric of arterial stiffness, is an established predictor for cardiovascular events and mortality. However, its intrinsic pressure-dependency complicates the discrimination of acute and chronic impacts of increased blood pressure on arterial stiffness. Cardio-ankle vascular index (CAVI) represented a significant step towards the development of a pressure-independent arterial stiffness metric. However, some potential limitations of CAVI might render this arterial stiffness metric less pressure-independent than originally thought. For this reason, we later introduced $CAVI_0$. Nevertheless, advantages of one approach over the other are left debated. This review aims to shed light on the pressure (in)dependency of both CAVI and $CAVI_0$. By critically reviewing results from studies reporting both CAVI and $CAVI_0$ and using simple analytical methods, we show that $CAVI_0$ may enhance the pressure-independent assessment of arterial stiffness, especially in the presence of large inter-individual differences in blood pressure.

**Keywords:** arterial stiffness, cardio-ankle vascular index, $CAVI_0$, pressure-dependency, pulse wave velocity

**Abbreviations:** $\rho$, blood density; $\beta$, Kawasaki's stiffness index beta; $\beta_0$, Hayashi's normalized stiffness index beta; *a* and *b*, scaling coefficients to transform $CAVI_{uns}$ into CAVI; *A*, lumen cross-sectional area; BP, blood pressure; CAVI, cardio-ankle vascular index; $CAVI_0$, modified CAVI; $CAVI_{uns}$, unscaled CAVI; *D*, diameter; $D_d$, diastolic diameter; $D_{ref}$, reference diameter; $D_s$, systolic diameter; haPWV, heart-to-ankle PWV; *L*, heart-to-ankle arterial pathway length; L-CAVI, left CAVI; L-haPWV, left haPWV; MBP, mean blood pressure; *P*, pressure; $P_{haPWV}$, haPWV-relevant pressure; $P_m$, mid pressure calculated as arithmetic mean of SBP and DBP; $P_{ref}$, reference pressure; PWV, pulse wave velocity; R-CAVI, right CAVI; R-haPWV, right haPWV; tb, time difference between the second heart sound and the dicrotic notch of the brachial pressure waveform; tba, time difference between the foot of the brachial and ankle pressure waveforms

## BACKGROUND

Arterial stiffness measures based on pulse wave velocity (PWV) have become established predictors for cardiovascular disease and mortality [1,2]. However, the highly nonlinear mechanical behaviour of the arterial wall makes arterial stiffness and related metrics intrinsically dependent on blood pressure (BP) [3–8]. This aspect of arterial wall mechanics complicates the use of PWV in clinical practice, as inter-individual or inter-clinical-group arterial stiffness differences may be caused by either actual differences in arterial structure and mechanics, differences in BP level at the time of measurement, or, most likely, a combination of the two. Most clinical studies address this issue by using statistical methods and including BP as confounding factor [9–11]. Although this approach has proven effective in population studies, it is not patient-specific and, therefore, is not applicable in daily clinical practice. Furthermore and more fundamentally, statistical blood pressure correction of PWV may lead to overcorrection and may, for example, conceal intrinsic hypertensive remodeling [12].

Researchers have devised different methods for person-specific pressure-normalization of PWV [4,13,14] that would allow converting the measured PWV to that at a reference pressure ($P_{ref}$), thus discerning between actual stiffness differences among people and those induced by pressure. Hayashi *et al.* [5] introduced an approach based on the observation that, in the physiological range of pressure, the pressure—diameter (*P*–*D*) relationship of arteries strongly

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resembles an exponential function and proposed the following exponential tube law

$$P(D) = P_{ref} \cdot e^{\beta_0\left(\frac{D}{D_{ref}} - 1\right)}, \tag{1}$$

where $P$ is the arterial pressure, $D$ is the luminal diameter, $P_{ref}$ is a reference pressure, $D_{ref}$ is the corresponding reference diameter (from Eq. 1, $P(D_{ref}) = P_{ref}$), and $\beta_0$ is an exponential gain. An interesting feature of Eq. 1 is that the same *P-D* relationship can be obtained by different combinations of $P_{ref}$ (and consequently $D_{ref}$) and $\beta_0$ (Fig. 1), so that $\beta_0$ is intrinsically dependent on the choice of $P_{ref}$. However, when $P_{ref}$ is fixed to a constant value and Eq. 1 is used to fit the *P-D* relationships of different individuals, $\beta_0$ becomes a pressure-normalized index of arterial stiffness. 'Pressure-normalized' here means that, while $\beta_0$ is still pressure-dependent (i.e. dependent on the choice of $P_{ref}$), using a fixed $P_{ref}$ guarantees that inter-individual differences in $\beta_0$ are unaffected by inter-individual differences in BP at the time of measurement. Notably, $\beta_0$ is not a PWV measure – $\beta_0$ defines arterial stiffening with increasing pressure.

The exponential tube law introduced by Hayashi paved the way for the development of methods allowing for the patient-specific pressure-normalization of PWV. In 2006, Shirai *et al.* [15] introduced cardio-ankle vascular index (CAVI), followed in 2017 by the introduction of CAVI$_0$ by our group [16]. Both CAVI and CAVI$_0$ aim to provide a pressure-independent arterial stiffness index, similar to Hayashi's $\beta_0$; however, now representing the entire heart-to-ankle arterial bed. Researchers have used both CAVI and CAVI$_0$ to investigate arterial stiffness independently of BP, and the advantages of one technique over the other are still subject of debate. This review aims to address this debate by analysing the current scientific evidence in support of the two metrics. It will first provide an overview of the theoretical background, then summarize all the studies where both CAVI and CAVI$_0$ were used to normalize PWV, and finally discuss their findings in light of the unresolved questions concerning the two metrics.

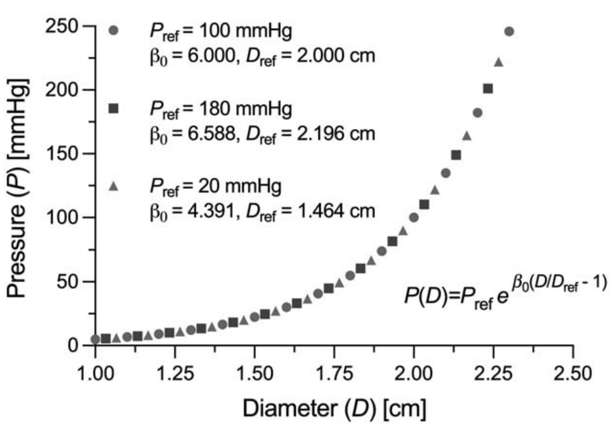


**FIGURE 1** Examples of identical exponential pressure–diameter relationships (Eq. 1) calculated using different combinations of the reference pressure $P_{ref}$ (and corresponding reference diameter $D_{ref}$) and stiffness parameter $\beta_0$.

## Cardio-ankle vascular index

Following the work of Hayashi *et al.* [5] and with the intent of establishing a pressure-independent PWV metric, in 2006, Shirai *et al.* [15] introduced CAVI. With reference to Eq. 1, Shirai and colleagues set $P_{ref}$ to the individual-specific DBP (Eq. 2), as previously proposed by Kawasaki *et al.* [17]:

$$P(D) = \mathrm{DBP} \cdot e^{\beta\left(\frac{D}{D_d} - 1\right)}, \tag{2}$$

where $D_d$ is the arterial diastolic diameter and $\beta$ is the value of $\beta_0$ when $P_{ref}$ is set to the individual-specific DBP. The Bramwell–Hill equation (Eq. 3) [18] is an established equation linking arterial distensibility to local PWV:

$$\mathrm{PWV} = \sqrt{\frac{A \cdot \mathrm{d}P}{\rho \cdot \mathrm{d}A}} = \sqrt{\frac{D \cdot \mathrm{d}P}{2\rho \cdot \mathrm{d}D}}, \tag{3}$$

which is approximated as

$$\mathrm{PWV} \approx \sqrt{\frac{D_s(\mathrm{SBP} - \mathrm{DBP})}{2\rho(D_s - D_d)}}, \tag{4}$$

where $D_s$ is the arterial systolic diameter, and $\rho$ is the blood mass density. Combining Eqs. 2 and 4, leads to a quadratic relationship between $\beta$ and PWV:

$$\beta \approx \ln\left(\frac{\mathrm{SBP}}{\mathrm{DBP}}\right) \cdot \frac{\mathrm{PWV}^2 \cdot 2\rho}{\mathrm{SBP} - \mathrm{DBP}} = \mathrm{CAVI}_{uns}, \tag{5}$$

where CAVI$_{uns}$ is the unscaled CAVI. Later, Shirai [19] provided an analytical demonstration that Eq. 5 can be approximately simplified to

$$\mathrm{CAVI}_{uns} \approx \frac{\mathrm{PWV}^2 \cdot 2\rho}{P_m}, \tag{6}$$

where $P_m$, the mid pressure, is the arithmetic mean of SBP and DBP [$P_m$ = (SBP + DBP)/2)]. $P_m$ should not be confused with the mean BP (MBP or MAP, mean arterial pressure) which is the average pressure over a cardiac cycle.

Shirai *et al.* replaced the local PWV in Eq. 5 with the heart-to-ankle PWV (haPWV), that is, a regional PWV calculated over the arterial pathway connecting the aortic valve and the end of the anterior tibial artery (ankle), hence, extending the application of the local exponential *P-D* modelling approach to large regions of the arterial tree. The methodology employed for the measurement of haPWV by the commercial VaSera device (VS 1500, Fukuda Denshi Co., Japan) is represented in Fig. 2. Briefly, haPWV is calculated as $L/(\mathrm{tb} + \mathrm{tba})$, where $L$ is the heart-to-ankle arterial pathway length and the sum of tb and tba constitutes the heart-to-ankle transit time (Fig. 2). tb is the time difference between the second heart sound (i.e. closure of the aortic valve) and the dicrotic notch of the brachial pressure waveform, and tba is the time difference between the feet of the brachial and ankle pressure waveforms. It is worth considering that tb and tba take as reference two

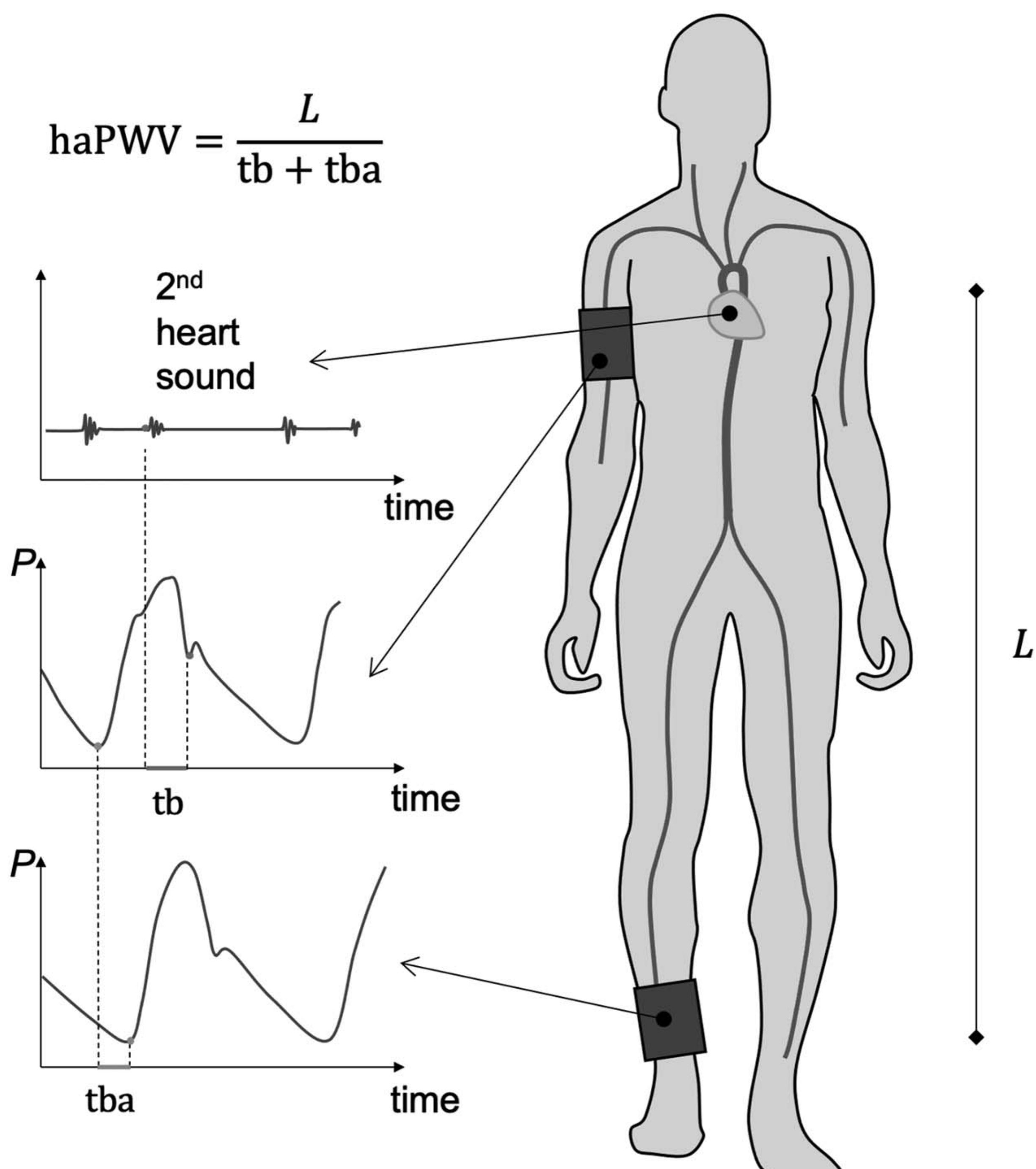


**FIGURE 2** Schematic representation of the algorithm used in the calculation of the heart-to-ankle pulse wave velocity, which is the basis of both cardio-ankle vascular index and $CAVI_0$. The heart-to-ankle transit time is determined as the sum of the transit time between the second heart sound, corresponding to the closure of the aortic valve, and the dicrotic notch in the brachial artery pressure (*P*) waveform (tb), and the time difference between the feet of the brachial and ankle pressure waveforms (tba). $CAVI_0$, modified cardio-ankle vascular index. *L* denotes the length of the heart-to-ankle arterial trajectory.

different points within the cardiac cycle: the dicrotic notch and the foot of the wave, respectively. The VaSera device allows for the estimation of the right haPWV (R-haPWV) using the pressure waveforms of the right arm and right ankle as well as of the left haPWV (L-haPWV) where the right ankle is substituted by the left one (i.e. still the right brachial pressure is used) [20,21]. CAVI is finally calculated by transforming $CAVI_{uns}$ using:

$$\mathrm{CAVI} = a \cdot \mathrm{CAVI}_{uns} + b\ . \tag{7}$$

It is worth noting that $a$ and $b$ are not the same for all values of $CAVI_{uns}$. Eq. 7 is, in fact, a three-piecewise linear function, where $a$ and $b$ are 0.85 and 0.695 when $CAVI_{uns} < 7.34875$, 0.658 and 2.103 when $7.34875 \leq CAVI_{uns} < 10.30372$, and 0.432 and 4.441 when $CAVI_{uns} \geq 10.30372$, respectively [21,22]. This transformation is performed to ensure that the age trend of CAVI quantitatively resembles that of the Hasegawa PWV [23], a commonly used PWV metric in Japan at the time of the development of CAVI [21]. Following the body side-specific haPWV, right (R-CAVI) and left CAVI (L-CAVI) are obtained when R-haPWV and L-haPWV, respectively, are substituted for PWV in Eq. 5.

## Modified cardio-ankle vascular index

Although CAVI has been considered for more than 15 years as a pressure-independent index of arterial stiffness, in 2017, we published a work [16] that analytically suggested a residual pressure dependency of CAVI. Our demonstration is based on two observations.

First, as mentioned above, Shirai's derivation of CAVI is based on the simplified exponential function proposed by Kawasaki (Eq. 2). Therefore, contrarily to $\beta_0$ (Eq. 1), $\beta$ is not pressure-normalized and depends on the individual specific DBP [24]. It can be shown that $\beta$ and $\beta_0$ are linked by the following relationship:

$$\beta_0 = \beta - \ln\left(\frac{\mathrm{DBP}}{P_{\mathrm{ref}}}\right). \quad (8)$$

Figure 3 shows the magnitude of the difference between the pressure-dependent $\beta$ and the pressure-normalized $\beta_0$ as a function of the ratio $\mathrm{DBP}/P_{\mathrm{ref}}$, providing an example of how this difference can affect the inter-individual comparison between clinical groups with inherent differences in DBP.

Second, the derivation of the CAVI formula uses a simplified version of the Bramwell–Hill equation (Eq. 4) where a linear approximation over the DBP-to-SBP range (see Eqs. 3 and 4 and Appendix 1, http://links.lww.com/HJH/B719) is used as an estimate of the infinitesimal $dP/dD$. Similarly, the approximation introduced in Eq. 6 is accurate only over infinitesimally small pressure intervals, hence using $P_m$ as the arithmetic mean of SBP and DBP will inevitably introduce inaccuracies in the estimation of $\beta$.

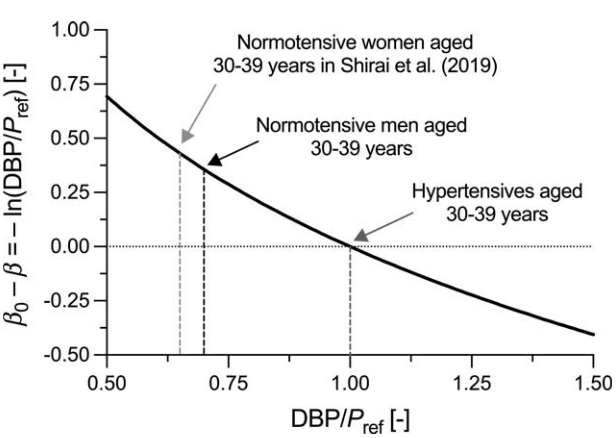


**FIGURE 3** Graphical representation of the magnitude of the logarithmic term that differentiates between stiffness index $\beta$ and $\beta_0$ as a function of the ratio between DBP and reference pressure ($P_{\mathrm{ref}}$). Note that this $\beta_0 - \beta$ difference represents one of the two differences between cardio-ankle vascular index (CAVI) and modified cardio-ankle vascular index ($CAVI_0$) (the other difference being the use of an approximated vs. infinitesimal derivative of the pressure–diameter relationship). Arrows indicate examples, taken from data in [39], of how omitting the logarithmic term can affect the comparison between clinical groups.

To overcome the limitations and correct the residual pressure dependency of CAVI, we proposed $CAVI_0$ [16], based on $\beta_0$ and on the calculation of the exact derivative $dP/dD$ at diastolic pressure:

$$CAVI_0 = \frac{2\rho \cdot \mathrm{PWV}^2}{\mathrm{DBP}} - \ln\left(\frac{\mathrm{DBP}}{P_{\mathrm{ref}}}\right). \quad (9)$$

Note that, if the chosen PWV is purely diastolic (e.g. foot-to-foot PWVs), the first term in Eq. 9 equals $\beta$, so that $CAVI_0 = \beta_0$ (Eq. 8). In our previous publications [16,20], we proposed setting $P_{\mathrm{ref}}$ to 100 mmHg. Although $P_{\mathrm{ref}}$ does not represent a physiological pressure, fixing $P_{\mathrm{ref}}$ to a pressure in the physiological range may be advantageous. Choosing $P_{\mathrm{ref}}$ within the physiological range ensures that, on average, patient-specific corrections from $\beta$ to $\beta_0$ are minimized. Furthermore, several studies reporting $CAVI_0$ [25–29] adopted the same choice, thus ensuring direct comparability of $CAVI_0$ values between studies. As mentioned in the Background section, choosing a fixed $P_{\mathrm{ref}}$ makes $\beta_0$ and, consequently, $CAVI_0$ pressure-normalized indices of arterial stiffness but these are still pressure ($P_{\mathrm{ref}}$)-dependent. Therefore, results from studies using different $P_{\mathrm{ref}}$ should not be directly compared (i.e. a conversion using Eq. 8 is needed). It can be shown that $CAVI_0$ relates to CAVI as follows:

$$CAVI_0 = \frac{\mathrm{CAVI} - b}{a} \frac{\left(\frac{\mathrm{SBP}}{\mathrm{DBP}} - 1\right)}{\ln\left(\frac{\mathrm{SBP}}{\mathrm{DBP}}\right)} - \ln\left(\frac{\mathrm{DBP}}{P_{\mathrm{ref}}}\right). \quad (10)$$

We created a conversion tool/calculator to simplifiy this conversion while taking into account the different values of $a$ and $b$ as a function of CAVI [22].

## LITERATURE REVIEW OF STUDIES REPORTING CARDIO-ANKLE VASCULAR INDEX AND MODIFIED CARDIO-ANKLE VASCULAR INDEX

The only inclusion criterium of our literature review was that the study had to report both CAVI and $CAVI_0$ in either the manuscript main text or the data supplement. Our literature search proceeded in two steps: first, given the relatively recent introduction of $CAVI_0$, we reviewed all studies citing the original $CAVI_0$ publications [14,16,20]. This first search led to 14 papers (Table 1). Then, we conducted a second literature search on PubMed, using 'CAVI' and 'stiffness' as search words and excluding all studies published before 2017 – the year $CAVI_0$ was introduced. This second search produced 215 results, which, after application of our inclusion criteria, reduced to the same 14 studies achieved via the first search (Table 1).

The 14 included studies consisted of one computational study, two longitudinal studies on the effect of acute changes in blood pressure on CAVI and $CAVI_0$, three clinical longitudinal studies, and eight clinical cross-

**TABLE 1. Summary of all the studies that reported both cardio-ankle vascular index and modified cardio-ankle vascular index**

| Literature on the comparison between CAVI and $CAVI_0$ | | | |
|---|---|---|---|
| **First author [reference]** | **Type of study** | **Sample size** | |
| Spronck [16] | Computational | N/A (161 in silico) | Provided the analytical basis behind the pressure-dependency of CAVI.<br>Demonstrated computationally the residual pressure-dependency of both $\beta$ (from DBP alone) and CAVI (from both SBP and DBP).<br>Showed computationally that the size of the error produced in CAVI by its pressure dependency is comparable to its intra-individual variability.<br>Showed computationally that $CAVI_0$ is pressure-independent (also see Spronck 2018) [51]. |
| Shirai [30] | Clinical longitudinal | 9 | Both CAVI and $CAVI_0$ did not change significantly after administration of BP lowering metoprolol. |
| Mestanik [25] | Clinical cross-sectional | 140 | Studied differences in CAVI and $CAVI_0$ between normal-weight normotensive ($n=40$), overweight normotensive ($n=30$), overweight white-coat hypertensive ($n=30$), and overweight essential hypertensive ($n=40$) boys.<br>CAVI, but not $CAVI_0$, was significantly higher in overweight white-coat hypertensive than in overweight normotensives.<br>CAVI, but not $CAVI_0$, showed significant correlation with DBP and PP. |
| Mills [42,43] | Clinical longitudinal | 126 | Spironolactone and doxazosin reduced SBP similarly. Changes in CAVI and $CAVI_0$ did not differ between spironolactone and doxazosin treatment groups.<br>Beetroot juice containing nitrate reduced SBP similar to beetroot juice without nitrate. Changes in CAVI and $CAVI_0$ did not differ between groups. |
| Wohlfahrt [26] | Clinical cross-sectional | 2084 | Provided reference values of CAVI and $CAVI_0$ in a white population with no cardiovascular disease.<br>CAVI and $CAVI_0$ showed similar levels of correlation with BP that were much weaker than those of haPWV. |
| Shirai [19] | Clinical cross-sectional | 3591 | $P_m$ showed a higher correlation with haPWV than both DBP and SBP. |
| Tabara [28] | Clinical cross-sectional | 9501 | Close correlation between CAVI and $CAVI_0$.<br>The residual of the regression between CAVI and $CAVI_0$ presented a weak but significant association with SBP. |
| Shirai [39] | Clinical cross-sectional | 8631 | Compared CAVI and $CAVI_0$ in population of 5293 healthy and 3338 hypertensive people.<br>Showed that CAVI shows a positive correlation with DBP, while such correlation is negative for $CAVI_0$.<br>Compared decade-specific differences in CAVI and $CAVI_0$ between controls and hypertensive patients. CAVI was always significantly higher in hypertensive men and women than age-matched controls (except women in their 30s). This was also the case for $CAVI_0$ in people above 50 years, while younger hypertensive people showed comparable, if not lower (women aged 30–39), $CAVI_0$ than age-matched controls.<br>Among SBP, DBP and $P_m$, $P_m$ showed the highest correlation with haPWV in all decade-groups of control people.<br>Adding the reference pressure term $\ln(P_m/P_{ref})$ had negligible, nonsignificant effect on CAVI. |
| Mestanik [28] | Clinical longitudinal | 60 | Studied changes in CAVI and $CAVI_0$ in response to acute blood pressure (BP) changes during cold pressor test.<br>CAVI significantly increased in response to and positively correlated with changes in BP.<br>$CAVI_0$ did not change throughout the test and did not correlate with BP. |
| Czippelova [29] | Clinical cross-sectional | 58 | Both CAVI and $CAVI_0$ were significantly lower in young obese adolescents than age-matched controls.<br>Strong correlation between CAVI and $CAVI_0$ in both obese and normal-weight adolescents. |
| Tonhajzerova [33] | Clinical cross-sectional | 60 | Studied differences in CAVI and $CAVI_0$ between healthy, anorexic, and obese adolescent girls.<br>Similar statistical differences between groups when using CAVI and $CAVI_0$. |
| Kim [32] | Clinical cross-sectional | 85 | Studied differences in CAVI and $CAVI_0$ between women with polycystic ovary syndrome (PCOS) and controls.<br>Results obtained with CAVI and $CAVI_0$ were statistically similar, except for the correlation with age in women with PCOS that was significant in CAVI but not in $CAVI_0$. |
| Itano [40] | Clinical longitudinal | 25 653 | Studied association of CAVI with kidney function in adults without chronic kidney disease.<br>Close correlation between CAVI and $CAVI_0$.<br>Similar results obtained using the two metrics. |
| Spronck [41] | Clinical longitudinal | 156 | Showed that both right CAVI and right $CAVI_0$ but not left CAVI and left $CAVI_0$, predicted heart-failure related end points in a population of 156 individuals.<br>Possible body-side difference in the prediction power of CAVI and $CAVI_0$. |

$\beta$, stiffness index beta, (Eq. 2); $\beta_0$, pressure-normalized index of arterial stiffness (Eq. 1); BP, blood pressure; CAVI, cardio–ankle vascular index; $CAVI_0$, modified cardio–ankle vascular index; haPWV, heart-to-ankle pulse wave velocity; $P_m$, mid pressure; PP, pulse pressure; $P_{ref}$, reference pressure.

sectional studies. The evidence found in these manuscripts will be reported following a study-type rationale rather than a strictly chronological order.

## Computational study

In 2017, alongside the analytical proof of the residual pressure dependency of CAVI and introduction of the adjusted $CAVI_0$ metric, we provided a computational comparison of the two metrics [16]. The computational model chosen assumed, in agreement with Hayashi's findings, an exponential *P–D* relationship (Eq. 1). Simulations showed that $\beta$ showed residual pressure dependency on DBP, CAVI showed dependency on both DBP and SBP and $CAVI_0$ did not show such dependencies. More importantly, the magnitude of the residual pressure-dependency of CAVI was comparable with the intra-individual variability. It is worth noting, however, that in these simulations, PWV was assumed to arise purely from a foot-to-foot estimation, whereas in the VaSera device, part of the estimation is based on the dicrotic notch, where pressure is higher than DBP (see Fig. 2 and Discussion).

## Longitudinal studies on treatment-induced acute changes in blood pressure

Longitudinal studies on the effect of treatment-induced acute changes in BP represent, in our opinion, the ideal setting to study the pressure-(in)dependency of a proposed arterial stiffness metric, as acute changes in BP and stiffness can be monitored simultaneously on a defined group of individuals. However, administration of drugs or manoeuvres to produce acute changes in BP level can potentially affect the vascular tone, thus altering the intrinsic and pressure-independent stiffness of the arterial wall and complicating the evaluation of the pressure dependence of the proposed stiffness metrics.

Shirai *et al.* [30] published a partial reanalysis of previously published data (9 out of 12 individuals from [31]) on the pressure-dependence of CAVI and brachial–ankle PWV (baPWV), extending it to $CAVI_0$. This study uses administration of Metoprolol to decrease BP through decreasing heart rate and ventricular contractility, and Doxazosin to decrease BP by reducing smooth muscle tone. Both drugs produced a significant drop in both SBP and DBP, with consequent decreases in baPWV. On the contrary, both CAVI and $CAVI_0$ remained unchanged after the administration of Metoprolol but significantly decreased with Doxazosin. The authors concluded that both CAVI and $CAVI_0$ proved to be pressure-independent as they were not affected by the BP changes after the administration of Metoprolol. In contrast, Doxazosin likely affected also the vascular tone, thus affecting the intrinsic arterial stiffness. Note, however that the existing methodological differences between CAVI and $CAVI_0$ imply that the two metrics cannot be both pressure-independent. Therefore, this finding suggests that the sample size of this study might have been too small to statistically detect the difference in pressure dependency between the proposed arterial stiffness metrics. Indeed, more recently, Mestanik *et al.* [28] presented preliminary results on changes in CAVI and $CAVI_0$ in response to the cold pressor test and isometric handgrip exercise in 60 healthy adults. Their results showed that CAVI was significantly affected by and showed correlation with changes in BP. Conversely, $CAVI_0$ did not change throughout the test and did not correlate with BP.

## Clinical cross-sectional studies

Most of the articles reporting both CAVI and $CAVI_0$ are clinical, mostly cross-sectional, studies where the two metrics were used to compare arterial stiffness of different clinical groups. Hence, demonstrating the advantages of one method over the other was, in most cases, not the main aim of these works. Furthermore, studying the pressure-(in)dependency of CAVI and $CAVI_0$ using cross-sectional data is problematic. It is known, for example, that people who are exposed to increased levels of arterial pressure tend to have stiffer arteries than healthy normotensive people. Therefore, even pressure-independent arterial stiffness metrics will likely show correlation with BP over the entire population. Most clinical cross-sectional studies reported that results obtained with CAVI and $CAVI_0$ are similar from a statistical standpoint (i.e. statistical differences between the groups included in the studies were comparable when using the two metrics). Wohlfahrt *et al.* [26] reported reference values of CAVI and $CAVI_0$ in a population with no cardiovascular disease and found similar correlations with BP for the two metrics. Kim *et al.* [32] studied differences in CAVI and $CAVI_0$ in Korean women with and without polycystic ovary syndrome and stated that the two methods provided similar statistical results.

Three studies investigated the effect of weight on arterial stiffness in adolescents. Overall, CAVI and $CAVI_0$ agreed in identifying lower values of arterial stiffness in obese and overweight adolescents than age-matched normal-weight healthy people [25,29,33], while increased CAVI and $CAVI_0$ were found in anorexic girls [33], consistent with previous literature on the (inverse) relationship between CAVI and BMI [27,34,35]. Further, Mestanik *et al.* [25] found that differences in both CAVI and $CAVI_0$ between overweight and normal-weight adolescents were no more significant when overweight young people were also hypertensive. Interestingly, however, when using CAVI, also overweight white-coat hypertensive patients appeared to have higher levels of arterial stiffness than overweight normotensive individuals. Such difference was not found when using $CAVI_0$. The authors suggested that the residual pressure-dependency of CAVI could possibly explain this discordant result; as the effects of white-coat hypertension on actual (pressure-independent) arterial stiffness seem marginal [36–38], increased CAVI in this group might reflect their high BP at the time of examination.

Shirai and colleagues [39] compared the pressure adjustment provided by CAVI and $CAVI_0$ in a large cohort of normotensive and hypertensive Japanese people. Both metrics showed a significant cross-sectional correlation with SBP in both the hypertensive and normotensive groups, while disagreement between the two techniques was found in terms of relationship with DBP: CAVI showed a significant positive correlation with DBP in the normotensive group only. On the other hand, $CAVI_0$ presented a significant negative correlation with DBP in both groups. Further, while dividing participants in decade age-groups and stratifying by sex, they evaluated differences in CAVI and $CAVI_0$ between hypertensive patients and normotensive individuals. In both men and women, the two metrics indicated higher level of arterial stiffness in hypertensive people aged at least 50 years than in age-matched normotensives. On the contrary, in younger individuals, the results provided by CAVI and $CAVI_0$ did not agree; in men aged 30–39 years and in people of both sexes aged 40–49 years, CAVI was significantly lower in normotensive individuals than in hypertensive patients, while differences in $CAVI_0$ were not significant. Further, in women in their 30 s, $CAVI_0$ was significantly lower in hypertensive patients than normotensive individuals, whereas CAVI did not differ in the two groups. Finally, Shirai and colleagues reported that including the $-\ln(DBP/P_{ref})$ term produced a $1.09 \pm 1.39$ and $3.68 \pm 1.66\%$ increase in the CAVI value provided by the VaSera device in normotensive individuals and hypertensive patients, respectively. The authors suggested that the high dependency of $CAVI_0$ on DBP could explain two unexpected findings: the negative correlation between $CAVI_0$ and DBP and the lower values of $CAVI_0$ found in young hypertensive women compared with age-matched and sex-matched normotensive individuals. Additionally, to advocate for the use of $P_m$ (Eq. 6) over that of DBP (Eq. 9), they reported that the cross-sectional correlation of haPWV with $P_m$ was stronger than its correlation with either SBP or DBP in the healthy normotensive population [19,39], and this was the case also when people were stratified in decade age-groups.

### Clinical longitudinal studies

We found four clinical longitudinal studies where both CAVI and $CAVI_0$ were included in the analysis. Tabara *et al.* [28] studied factors influencing changes in CAVI and $CAVI_0$ between baseline and 5 years' follow-up in the Nagahama study. In agreement with other studies [26,29], the authors found a strong correlation between CAVI and $CAVI_0$. Interestingly, but not unexpectedly, the residuals of the linear regression between the two metrics significantly correlated with SBP. Indeed, CAVI (Eq. 6) estimates $\beta$ from PWV and $\sim P_m$ (depending on both SBP and DBP), whereas, in $CAVI_0$, the $P_m$ is substituted by DBP (Eq. 9), thus explaining why residuals between the two metrics are related to SBP.

Itano *et al.* [40] found that patients with a CAVI of at least 8.1 had an elevated risk of chronic kidney disease events compared with those patients with lower CAVI. Performing the analysis using $CAVI_0$ yielded similar results. We investigated the ability of R-CAVI, L-CAVI, R-$CAVI_0$ and L-$CAVI_0$ of predicting heart failure-related endpoints and found that only R-CAVI and R-$CAVI_0$ had predictive power [41]. Finally, the VaSera trial [42,43] is a double-blinded, parallel, randomized controlled intervention trial evaluating the effect of four interventions (spironolactone, doxazosin, dietary nitrate beetroot juice, and nitrate-free beetroot juice) on arterial stiffness. The authors found that spironolactone and doxazosin had similar effects on SBP, CAVI and $CAVI_0$, as did dietary nitrate beetroot juice and nitrate-free beetroot juice. The interested reader is referred to the original publications for more details.

## DISCUSSION

The development of methods that allow the pressure-normalization of PWV is of crucial clinical importance [12]. The introduction of CAVI in 2006 represented a considerable, though not complete step towards an effective and, possibly more important, convenient way to account for the contribution of pressure to regional (heart-to-ankle) PWV, providing patient-specific corrections. In 2017, we proposed a modified metric, $CAVI_0$, that aimed to improve pressure-independency by targeting two critical points: $\beta$ is based on the individual-specific DBP and is, therefore, intrinsically pressure-dependent, and the use of a linearized Bramwell–Hill equation over the noninfinitesimal DBP-to-SBP pressure range introduces inaccuracies. As advantages of one technique over the other are still subject of debate, this discussion section will be focused on untangling these two points in the light of the scientific evidence reported in the previous paragraphs and with the objective of understanding how close we are to defining a pressure-independent index of arterial stiffness.

The introductory paragraphs explained in detail the difference between Hayashi's $\beta_0$ and Kawasaki's $\beta$. Although both metrics intrinsically depend on the reference pressure chosen to define the exponential *P-D* relationship, $\beta_0$ uses the same $P_{ref}$ for all individuals whereas $\beta$ is based on the individual-specific DBP. Hence, while the first can be considered a pressure-normalized index of arterial stiffness, the second maintains a residual pressure dependency. $\beta$ and $\beta_0$ are linked by a simple equation (Eq. 8), so that $\beta_0$ can easily be calculated from $\beta$ by subtracting $\ln(DBP/P_{ref})$. Shirai and colleagues advocated that subtraction of this term to the standard $\beta$ induces a negligible effect [39,44]. However, a careful analysis indicates that this effect is not negligible when comparing groups with large differences in DBP. Figure 3 shows the magnitude of the logarithmic term as a function of DBP. In the study of Shirai *et al.* [39], DBP ranged from approximately 70–117 mmHg in hypertensive people and from approximately 58–82 mmHg in normotensive individuals. Differences were particularly high in young people (30−39 years), when the average DBP was 100 mmHg in hypertensive individuals (men and women) and approximately 70 and 65 mmHg in normotensive men and women, respectively. Assuming $P_{ref} = 100$ mmHg, the average contribution of the logarithmic term in hypertensive patients aged 30−39 years is null. On the contrary, in normotensive people of the same age-group the average difference between $\beta$ and $\beta_0$ is approximately 0.36 and 0.43 in men and women (Fig. 3), respectively, that translate into $\sim$0.30 and 0.35 in terms of CAVI. It is worth observing that the reported differences in CAVI between groups in this age range were comparable with, if not smaller than, these values. This simple example illustrates how omitting the logarithmic term can lead to potentially significant errors in the evaluation of arterial stiffness and misinterpretation of differences between clinical groups. Indeed, while Shirai and colleagues questioned the validity of $CAVI_0$ on the basis of surprisingly lower average $CAVI_0$ found in young hypertensive women compared with age-matched normotensives, subtracting $\ln(DBP/P_{ref})$ from the normal CAVI, that is, normalizing the pressure-dependent $\beta$ to a fixed $P_{ref}$, seems to provide the same outcome. Furthermore, these errors are calculated using average DBP values; patient-specific errors may be even higher. We do not deny that the average contribution of the logarithmic term in the overall population might be small, especially when inter-individual differences in DBP are relatively small [26,32]. Conversely, this contribution might become nonnegligible when clinical groups are characterized by significantly different pressures [25]. Furthermore, providing a group-based pressure-normalization of PWV is neither the goal of CAVI or $CAVI_0$ as similar corrections can be obtained with established statistical methods. In light of the considerations detailed above and the fact that $\beta_0$ can be easily determined from $\beta$ without the necessity of further measurements, it seems logical and useful to use the proposed methodological adjustment factor.

The second difference between the CAVI and $CAVI_0$ formulas consists in the calculation of the derivative term in the Bramwell–Hill equation. In CAVI, such derivative is

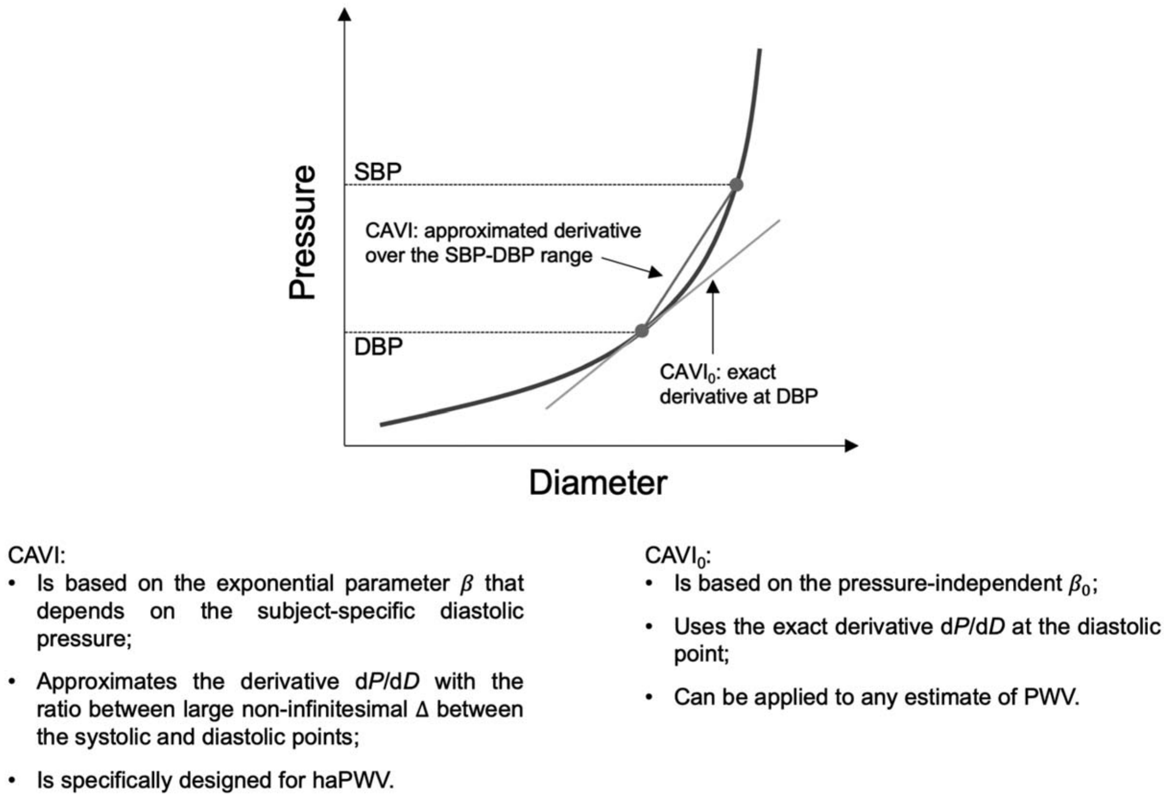


**FIGURE 4** Summary of the methodological differences between cardio-ankle vascular index and modified cardio-ankle vascular index. Cardio-ankle vascular index (CAVI) approximates the derivative term in the Bramwell–Hill equation with differences over the SBP to DBP blood pressure range. Conversely, modified cardio-ankle vascular index ($CAVI_0$) uses the exact derivative at DBP. haPWV, heart to ankle pulse wave velocity.

approximated through a linearization of the exponential *P-D* relationship over the DBP-to-SBP pressure range, whereas in $CAVI_0$, the exact derivative is calculated at diastolic pressure (Fig. 4). As shown previously [19], the linearization used in CAVI is close, although not mathematically equal, to calculating the derivative at the $P_m$. It is worth noting that Eq. 6 can be obtained without approximations if Eq. 2 is redefined with respect to $P_m$ instead of DBP (see Appendix 2, http://links.lww.com/HJH/B719). This suggests that the approximation introduced by Eq. 6 alters the meaning of $CAVI_{uns}$, which no longer approximates Kawasaki's $\beta$ as it arises from a $P_m$-based rather than DBP-based exponential *P-D* relationship (Eq. 2 vs. Eq. A6). Nevertheless, the diatribe between the two methods reduces to determining what is the pressure level at which haPWV is calculated. Before proceeding, it is worth considering that both CAVI and $CAVI_0$ apply a single-exponential *P-D* model to a large region of the arterial tree (heart-to-ankle). Clearly, along this region, both diameter and stiffness vary, and a single unique physical relationship between pressure and diameter is a simplification of reality. Therefore, this diatribe cannot be resolved by solving the inverse problem of determining the pressure at which haPWV is calculated knowing both $\beta$ and haPWV. Hence, the choice of the best method has to be made based on methodological observations.

Shirai and colleagues adduced different justifications for the choice of $P_m$ over DBP [39,44]; the first is based on the observation that, in cross-sectional studies, haPWV shows a higher correlation with $P_m$ than with both SBP and DBP. However, as stated previously, cross-sectional studies can lead to confusing results concerning the dependency of PWV on BP as cross-sectional correlation arises from a combination of acute and chronic effects of BP on PWV. To understand this concept, it is useful to consider that the current guidelines for the diagnosis of hypertension are based on SBP and/or DBP overcoming a predefined threshold (e.g. 140 and 90 mmHg, respectively, in Europe). As hypertension and elevated BP are associated with arterial stiffening, it is likely that people with increased DBP, SBP, or both will have increased PWV. As $P_m$ summarizes both DBP and SBP, it is not surprising that $P_m$, and not DBP or SBP individually, shows the highest correlation with haPWV. In a hypothetical population where some individuals present an elevated SBP but none has elevated DBP, haPWV would likely show higher correlation with SBP than with both $P_m$ and DBP. Therefore, the high cross-sectional correlation of haPWV with $P_m$ is hardly an incontrovertible proof of the fact that haPWV is determined at mid pressure.

Methodological observation can guide towards educated guesses when the solution to a problem cannot be achieved with strict scientific proof. For instance, as the CAVI and $CAVI_0$ equations to estimate $\beta$ and $\beta_0$ can, in principle, be applied to PWV estimated using any method, the assumption that the DBP is the PWV-relevant pressure level seems reasonable for all the foot-to-foot PWV metrics (e.g. carotid–femoral PWV, brachial–ankle PWV) [44]. Indeed, the reference points used for the calculation of the transit time correspond to the foot of the systolic upstroke when pressure equals DBP. However, as illustrated in Fig. 2, the algorithm used for the determination of haPWV, and thus CAVI/$CAVI_0$ is more complex and entails two time differences calculated at different pressure levels: dicrotic notch for tb and foot for tba. On one side, this algorithm has the advantage of including the ascending aorta in the haPWV arterial pathway, whereas this proximal segment is excluded in the more widely used carotid–femoral PWV. On the other hand, however, the physical meaning of haPWV becomes less tangible, representing an average between a diastolic PWV in the distal aorta and lower limbs' arteries and a PWV at the dicrotic notch pressure for the proximal aorta (Fig. 2). Therefore, DBP probably underestimates the actual pressure at which haPWV is calculated.

Takahashi *et al.* [44] used similar methodological arguments to support the use of $P_m$ over DBP, and stated that as the dicrotic notch is close to SBP, the PWV calculated over tb is approximately the PWV at SBP. Conversely, the PWV calculated over tba is determined at DBP. Therefore, $P_m$, the arithmetic mean between SBP and DBP, would represent the optimal choice for haPWV. However, typical brachial BP waveforms show that the pressure at the dicrotic notch in the brachial artery is approximately $0.55 \times DBP + 0.45 \times SBP$, hence, much closer to MBP or $P_m$ than to SBP [45]. Following the assumption of constant $\beta_0$ in the arterial tree at the basis of CAVI and $CAVI_0$ and knowing the heart-to-brachial and heart-to-ankle arterial path lengths [46], the haPWV-relevant pressure can be estimated to be approximately equal to $0.91 \times DBP + 0.09 \times SBP$ (see Appendix 3, http://links.lww.com/HJH/B719 for full calculations), that is, much closer to DBP than to $P_m$ or to MBP (Fig. 5).

In addition to the previous argument, Shirai *et al.* [30] suggested that $CAVI_0$ is largely dependent on DBP, which may vary along long arterial pathways. However, several studies reported that DBP and MBP are relatively constant along most parts of the arterial tree, whereas SBP significantly increases while moving downstream in the circulation because of pressure amplification [48,49]. It is worth noting that $P_m$ is not equal to MBP and that $P_m$ is strongly dependent on SBP. Therefore, the inaccuracy introduced by regional changes in DBP is deemed to be considerably smaller than that caused by regional differences in SBP, reflecting on $P_m$. In conclusion, although DBP might not be the exact pressure at which haPWV is determined, it likely represents a more accurate approximation of the haPWV-relevant pressure than $P_m$ and has the advantage of being location-independent.

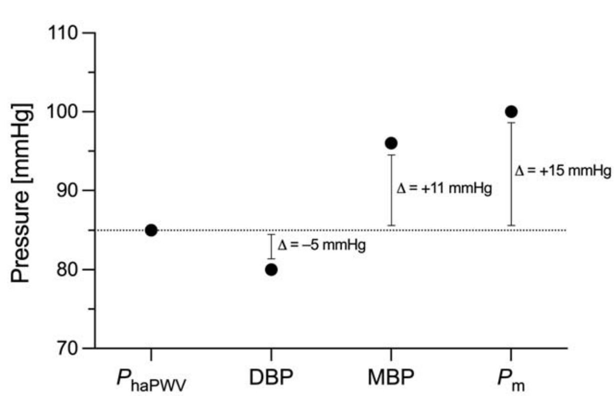


**FIGURE 5** DBP offers a close approximation of $P_{haPWV}$. Numbers presented for a normotensive person with SBP/DBP = 120/80 mmHg. Note that in this example, the difference between $P_m$ and $P_{haPWV}$ is three times the difference between $P_{haPWV}$ and DBP. $P_{haPWV}$, relevant pressure for haPWV (calculation details in Appendix 2, http://links.lww.com/HJH/B719); MBP, mean blood pressure (calculated as $0.4 \times SBP + 0.6 \times DBP$ [47]); $P_m$, mid-blood pressure (arithmetic mean of SBP and MBP).

Notably, haPWV (and hence CAVI/$CAVI_0$) is less influenced by brachial artery stiffness than baPWV. Whereas baPWV directly and negatively depends on brachial artery stiffness, haPWV is only influenced by the brachial artery's stiffness difference between diastolic and dicrotic notch pressures. This subject is further detailed in Appendix 4, http://links.lww.com/HJH/B719.

Finally, Ato [50] raised concerns pertaining to the three-piecewise linear conversion of $\beta$ into CAVI [21]. As conceded by the authors, $\beta$ is an index of arterial stiffness per se, although still pressure-dependent. Although the three-piecewise linear conversion was originally introduced to transform the dimensionless $\beta$ into a PWV-like index that would match the Hasegawa PWV [23], this conversion unnecessarily complicates the relationship between differences in $\beta$ and differences in CAVI. As, nowadays, CAVI is likely more widely used than the Hasegawa PWV, this conversion is no longer necessary and should ideally be avoided.

In conclusion, the introduction of CAVI – based on measurement of heart-ankle PWV – represented a significant step forward by correcting for the pressure-dependency of inter-individual differences in PWV. However, two methodological aspects of CAVI rendered this metric less pressure-independent than initially thought and $CAVI_0$ was then introduced to correct for them by substituting the pressure-dependent $\beta$ with $\beta_0$ and by substituting the approximated derivative in the Bramwell–Hill equation with an exact derivative at the DBP. The advantage of the first correction is clear: the corrective effect of the logarithmic term in $CAVI_0$ is substantial, when the study groups show a large difference in DBP. The second correction is less clear, while it raises the more fundamental question of which 'pressure' governs the pressure-dependency exhibited by the haPWV (Fig. 2). At present, most studies comparing CAVI and $CAVI_0$ have a cross-sectional design (Table 1) and, hence, are not well suited to address this question. The few preliminary longitudinal studies we reviewed have limitations pertaining to parallel effects on pressure as well as arterial tone, with the latter influencing intrinsic arterial stiffness. In the present analysis, we showed that the haPWV-relevant pressure is much more closely approximated by DBP than by $P_m$. Hence, our review supports the utility of $CAVI_0$ as an enhancement of CAVI to improve the pressure-independent assessment of arterial stiffness.


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## Conflicts of interest

There are no conflicts of interest.

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