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# A Pilot Estimation of Ventricular-Arterial Coupling Using a Vascular Screening Device (VaSera®)

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**Background:** Non-invasive cardiovascular assessment has become an alternative to invasive techniques. VaSera®, a vascular screening device, measures arterial stiffness with the cardio-ankle vascular index (CAVI); it also measures cardiophysiological variables of ejection time (ET) and pre-ejection period (PEP). We aimed to apply the parameters obtained by VaSera® to estimate heart function based on left ventricular end-systolic elastance/arterial elastance (Ees/Ea) and to assess the minimal required number of measurements for estimation.

**Methods:** We conducted an experimental laboratory study for healthy volunteers. Using the previously established formula, the Ees/Ea value of each participant was estimated using ET and PEP values measured by VaSera®. The intraclass correlation coefficient (ICC) assessed the minimum required number of measurements. Concordance correlation coefficient (CCC) and Bland and Altman analysis assessed variation of Ees/Ea estimation against the trimmed average.

**Results:** A total of 660 measurements from 132 participants were included. The Ees/Ea estimates from the VaSera® were 1.5 [1.2, 1.9]. The ICC for Ees/Ea was 0.71 (95% confidence interval: 0.65-0.77), suggesting that four measurements were required. The CCC between the trimmed average of Ees/Ea and the mean of four Ees/Ea estimates was 0.99. Bland and Altman analysis showed excellent agreement for the mean of four Ees/Ea estimates and the trimmed average of Ees/Ea.

**Conclusions:** For screening of heart failure, the Ees/Ea estimated using non-invasive vascular-stiffness assessment device would be tolerable and four sequential measurements were required.

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**Key words:** cardiovascular physiology, VaSera®, ventricular function, ventricular-arterial coupling, screening

## Introduction

Several diagnostic and screening examinations for cardiovascular morbidity have been developed[1–3]. Physiological values assessing cardiac function or vascular integrity are usually obtained using gold standard techniques, such as pulmonary artery catheter or arterial cannula[4]; however, these devices are invasive. Given the complications associated with invasive devices[4,5], non-invasive methods are favorable for screening tools[6,7].

VaSera®, a non-invasive vascular screening device, measures arterial stiffness with the cardio-ankle vascular index (CAVI) and stenosis or occlusion of the arteries in the lower limbs with the ankle-brachial index (ABI)[8,9]. Additionally, the device shows cardiovascular parameters such as ejection time (ET) and pre-ejection period (PEP)[1]. Ventricular-arterial coupling (ventricular end-systolic

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elastance/arterial elastance, Ees/Ea) reflects the mechanical and energetic capability of the left ventricle and the efficacy of energetic transfer from the heart to the artery[3,10]. Non-invasive Ees/Ea estimation based on the measured values using VaSera® would be possibly useful[11], albeit not yet confirmed the variation of estimation[3,11]. In this pilot study, we applied the parameters obtained by VaSera® into a formula to estimate Ees/Ea and verify such estimation. Thereafter, we assessed the minimal number of measurements required for the estimation of Ees/Ea and CAVI.

## Materials and Methods

### Participants and Ethical Issues

This study was performed on healthy volunteers between August 2017 and March 2019. These participants were medical students at the University of Fukui. Written informed consent was obtained from all participants. The study protocol was approved by the Research Ethics Committee of the University of Fukui (#20140124).

### Data

Age, sex, body weight, height, and body mass index of the participants were obtained. Using the VaSera® device, heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure, pulse pressure, ET, PEP, ABI, and CAVI were recorded.

The participants lay on their backs for 5 minutes to rest. For measurements using the VaSera® (VS-1500A; Fukuda Denshi Co., Ltd., Japan), the cuffs were applied to the bilateral upper and lower extremities, the electrocardiogram leads were attached to the upper arm, and the phonocardiogram captor was placed on the midsternum. The oscillometric method was used to measure extremity blood pressure[1,12]. The examination was performed between 12:00 and 14:00. The sequences of measurement were initiated five times for each participant by a single rater. The CAVI and cardiovascular parameter values on the right side, among which Ees/Ea has been estimated, were used for the analysis.

### Ees/Ea Estimation

To estimate Ees/Ea, we used a framework for clinical application using left ventricular end-systolic pressure (Pes), SBP, DBP, ET, and PEP[3,10]. Using the concept of the pressure-volume relationship, Ees/Ea is algebraically expressed as $Ees/Ea = DBP/Pes\ (1 + k \times ET/PEP) - 1$. DBP, ET, and PEP were measured using the VaSera®. Pes was estimated using the prediction equation developed from the participant sample in the study by Kappus *et al.* as follows[13]: $Pes\ [mmHg] = (0.205 \times SBP) + (0.898 \times DBP) + 0.4214$. The value of k has been reported to correlate with Ees/Ea in animal studies[3,10], and it is approximated as $k = 0.53 \times (Ees/Ea)^{0.51}$. Then, Ees/Ea was derived by Newton's method. Regarding Ees/Ea estimation, participants with at least one negative value of Ees/Ea or > 3 were excluded in order to follow physiological standards in the estimation[14].

### CAVI Values

The CAVI value, which is displayed on the VaSera® device, was assessed using the Bramwell-Hill equation as follows[15]: $CAVI = \ln (SBP/DBP) \times 2\rho/PP \times PWV^2$, where PWV is the pulse wave velocity, PP is the pulse pressure and ρ is the blood density (constant: $1.03 \times 10^3\ kg/m^3$)[1,15], and PWV was calculated as the ratio of the estimated length from the aorta to the ankle (L) divided by the measured time taken for the pulse wave to propagate from the aortic valve to the ankle (T). The estimated length (L) from the height of the participant was calculated using the following formula[16]: $L\ [cm] = 0.77685 \times height\ [cm] - 1.7536$. The measured propagating time for the pulse wave to propagate from the aortic valve to the ankle (T) was determined using the following formula: $T\ [s] = tba + tb$, where tba is the time between the rising point of the brachial pulse wave and ankle pulse wave and tb is the time between the aortic valve opening sound and the rising point of the brachial pulse wave.

### Statistical Analysis

Data are expressed as mean and standard deviation (SD) or median and interquartile range [IQR] for continuous variables. The normality of the distribution of variables was assessed using the Kolmogorov-Smirnov test[17,18]. The paired *t*-test was used to compare each measurement of CAVI and the mean of the other measurements. The repeated measures analysis of variance (ANOVA) and Bonferroni's post-hoc test for CAVI values and Ees/Ea estimates were applied to evaluate the interaction effect and to identify significant measurement differences.

We calculated the intraclass correlation coefficient (ICC) (1, k) to determine the variation in Ees/Ea estimates and CAVI[19]. Then, the minimum required number of measurements was determined from the rounded-up number of k of the following equation: $k = \rho_1(1 - \rho_2)/\ \rho_2(1 - \rho_1)$, where $\rho_1 = 0.9$, which is the target value, and $\rho_2$ is the ICC value obtained[20].

To observe the variation and precision of Ees/Ea estimates or CAVI measurements, we assumed the 40% trimmed average among the five measurements (T-Ees/Ea and T-CAVI, as the hypothetical reference[21,22]. For lin-

ear regression analysis, Deming regressions were performed to obtain the intercept and slope coefficients[23,24]. Lin's concordance correlation coefficient (CCC) was calculated to evaluate the accuracy of the mean of different numbers of Ees/Ea measurements for T-Ees/Ea or T-CAVI. CCC > 0.95 was classified as excellent according to the Partik classification[25]. Bland and Altman plots were used to assess the agreement of Ees/Ea with T-Ees/Ea or CAVI toward T-CAVI. When the differences between Ees/Ea estimates and T-Ees/Ea or between measured CAVI values and T-CAVI were not normally distributed, the bias was assessed as the median, the limits of agreement were assessed as the 2.5th and 97.5th quantiles, and the 95% confidence interval (CI) of the median was calculated using the bootstrapping method[24].

Statistical analyses were performed using MedCalc version 19.6.4 (MedCalc Software, Ostend, Belgium), SPSS version 25 (IBM Corp., Armonk, NY, USA), R version 4.0.4 (The R Project, Vienna, Austria). For all analyses, the level of statistical significance was set at $P < 0.05$.

Table 1 Participants' characteristics (n=166)

| Variables | |
|---|---|
| Male / female | 101 / 65 |
| Age (years) | 24 (3) |
| Weight (kg) | 60.8 (10.8) |
| Height (cm) | 166.8 (8.1) |
| Body mass index (kg/m$^2$) | 21.7 (2.6) |

Variables are presented as n/n or mean (standard deviation).

## Results

A total of 166 participants were included in the study (**Table 1**). The number of male participants was 60.8%, and the mean age was 24 years.

**Assessment of Ees/Ea Estimation**

Among the total participants, 660 measurements from 132 participants were included for the Ees/Ea estimation. The values of five-time measurements using VaSera® were applied into the Ees/Ea estimation using Hayashi's formula (**Table 2**). The Ees/Ea estimate from the VaSera® was 1.5 [1.2, 1.9].

Intraclass correlation coefficient (ICC) and minimum required number of measurements

Considering Ees/Ea estimates variation, we first calculated the ICC. The ICC (1, *k*) value was 0.71 (95% CI: 0.65-0.77), suggesting a moderate correlation based on a mean rating ($k$ = 5), absolute agreement, and one-way random-effect model[19]. To reach the target value of 0.9, the required number of consecutive measurements was 3.68. Therefore, four measurements were minimally required for the estimation of Ees/Ea.

Linear regression analysis

The T-Ees/Ea was 1.5 [1.2, 1.9]. Linear regression analysis by the Deming method was performed between the mean of different numbers of Ees/Ea estimates and the T-Ees/Ea (**Table 3** and **Fig. 1A**). The regression parameters, such as intercept and slope, tended to be close to 0 and 1, and the CIs narrowed when the number of measurements increased from 1 to 5 (**Fig. 1B**), suggesting that measuring cardiovascular parameters four times or more to estimate Ees/Ea was in line with the precision

Table 2 Left ventricular end-systolic elastance/arterial elastance (Ees/Ea) estimation using consecutive measurements

| | Series of measurements | | | | |
|---|---|---|---|---|---|
| | Once (first measurement applied) | Twice (first and second measurements applied) | Three times (first, second, and third measurements applied) | Four times (first, second, third, and fourth measurements applied) | Five times (all five measurements applied) |
| SBP (mmHg) | 118.5 (12.8) | 117.8 (12.1) | 117.2 (11.9) | 117.0 (11.7) | 116.8 (11.7) |
| DBP (mmHg) | 70.8 (7.2) | 70.6 (6.9) | 70.4 (6.8) | 70.2 (6.6) | 70.3 (6.5) |
| ET (ms) | 309.4 (15.6) | 309.4 (15.3) | 309.5 (15.2) | 309.5 (15.2) | 309.4 (15) |
| PEP (ms) | 95.0 (12.3) | 95.5 (11.4) | 95.8 (11.3) | 96.4 (11.3) | 96.4 (11.3) |
| Pes (mmHg) | 88.3 (8.5) | 87.9 (8.1) | 87.7 (8) | 87.5 (7.8) | 87.5 (7.7) |
| k# | 0.6637 (0.1155) | 0.6602 (0.1060) | 0.6592 (0.1021) | 0.6542 (0.10117) | 0.6546 (0.1003) |
| Ees/Ea (mmHg-mL$^{-1}$)# | 1.6 [1.1, 1.9] | 1.6 [1.2, 1.9] | 1.5 [1.2, 1.9] | 1.5 [1.2, 1.9] | 1.5 [1.2, 1.9] |

Variables are presented as mean (standard deviation), and Ees/Ea variables are presented as median [interquartile range]. #Pes = (0.205 × SBP) + (0.898 × DBP) + 0.4214; Ees/Ea = DBP/Pes (1 + k × ET/PEP) – 1; k = 0.53 × (Ees/Ea) $^{0.51}$. DBP, diastolic blood pressure; Ees/Ea, ventricular end-systolic elastance/arterial elastance; ET, ejection time; PEP, pre-ejection period; Pes, left ventricular end systolic pressure; SBP, systolic blood pressure.

Table 3 Regression and correlation analyses for left ventricular end-systolic elastance/arterial elastance (Ees/Ea) estimation

| | | Series of measurements | | | | |
|---|---|---|---|---|---|---|
| | | Once (first measurement applied) | Twice (first and second measurements applied) | Three times (first, second, and third measurements applied) | Four times (first, second, third, and fourth measurements applied) | Five times (all five measurements applied) |
| Linear regression analysis (Deming method) | Intercept | –0.22 (–0.40, –0.03) | –0.08 (–0.17, 0.02) | –0.02 (–0.08, 0.04) | –0.01 (–0.05, 0.04) | 0 (–0.02, 0.03) |
| | Slope | 1.18 (1.05, 1.31) | 1.07 (1.01, 1.14) | 1.03 (0.99, 1.08) | 1.01 (0.98, 1.04) | 1 (0.98, 1.02) |
| | R | 0.87 | 0.99 | 0.97 | 0.99 | 0.99 |
| Concordance correlation coefficient | | 0.85 (0.80, 0.89) | 0.93 (0.91, 0.95) | 0.97 (0.95, 0.98) | 0.99 (0.98, 0.99) | 0.99 (0.99, 1.00) |
| Bland and Altman analysis | Bias | 0.04 (–0.02, 0.08)* | 0.03 (0.00, 0.04)* | 0.02 (0.00, 0.04)* | 0.01 (–0.01, 0.02) | 0.01 (0.00, 0.02)* |
| | Limits of agreement | –0.09, 0.20 | –0.03, 0.13 | –0.02, 0.11 | –0.14, 0.16 | –0.01, 0.03 |

The values are presented as mean (95% confidence interval). In the mean of the Ees/Ea estimates using the values of four measurements, neither systematic (0 was within 95% confidence interval of intercept) nor proportional (1 was within 95% confidence interval of slope) differences between Ees/Ea estimates and the 40% trimmed average as the hypothetical reference were shown using the Deming regression method. An excellent concordance correlation coefficient (>0.95) for estimates to the hypothetical reference was shown in more than four measurements. The Bland and Altman plots indicated a non-significant mean bias and narrow limits of agreement for the estimates using more than four measurements compared with the hypothetical reference. *95% confidence intervals were calculated using the bootstrap method.

between the mean estimates of measured values and T-Ees/Ea.

Lin's concordance correlation coefficient (CCC)

Lin's concordance correlation coefficient (CCC) for the estimated Ees/Ea was calculated and compared among the different numbers of measurements (**Table 3**). Using the Partik classification[25], the mean of the estimated Ees/Ea using values measured four times or more gave excellent CCC (> 0.95%) (**Fig. 1C**).

Bland and Altman plot analysis

The Bland and Altman plots of the difference between the different numbers of measurements and T-Ees/Ea were drawn (**Table 2**). The limits of agreement of the mean of four measurements and T-Ees/Ea represented the relevant aligned points without errors, and the mean bias was not significantly different from 0 (**Fig. 1D**).

**Assessment of CAVI Measurements**

All the 830 measurements from 166 participants were included. The CAVI was 5.7 (0.7) and the first CAVI value was slightly higher than the T-CAVI (5.8 (0.7) vs. 5.7 (0.7)).

Intraclass correlation coefficient (ICC) and minimum required number of measurements

The ICC (1, *k*) value was 0.83 (95% CI: 0.80-0.87). This suggested a good correlation based on the mean rating (*k* = 5), absolute agreement, and one-way random-effect model[19]. To reach the target value of 0.9, in the decision formula, the number of consecutive measurements per rater to be taken on each participant was 1.84. Therefore, two measurements of CAVI were minimally required.

Linear regression analysis

Linear regression analysis by the Deming method was performed between the mean of different numbers of measurements and a hypothetical reference, T-CAVI (**Table 4** and **Fig. 2A**). The intercept and slope tended to be close to 0 and 1, and the 95% CIs narrowed when the number of measurements increased from 1 to 5 (**Fig. 2B**). The regression analysis suggested that measuring CAVI twice or more was in line with the precision between the mean of the measured values and T-CAVI.

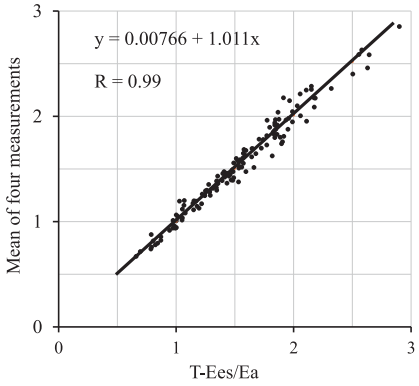
Lin's concordance correlation coefficient (CCC)

Lin's CCC was calculated and compared among the different numbers of measurements (**Table 4**). According to the Partik classification[25], the mean of two or more measurements of CAVI gave an excellent CCC (> 0.95) (**Fig. 2C**).

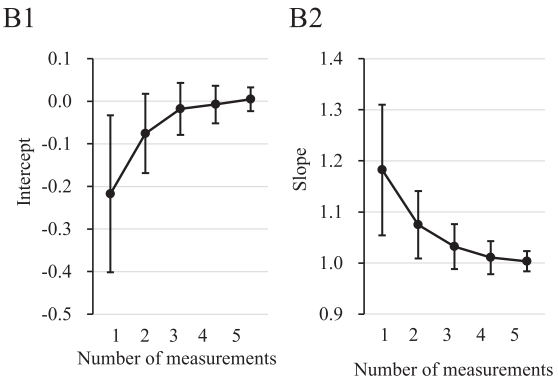
Bland and Altman analysis

The Bland and Altman plots of the difference between the T-CAVI and the mean of different numbers of measurements are shown in **Table 3**. With a 95% CI of median bias covering 0, the limits of agreement of the mean of two measurements and T-CAVI represented the relevant aligned points without errors (**Fig. 2D**).

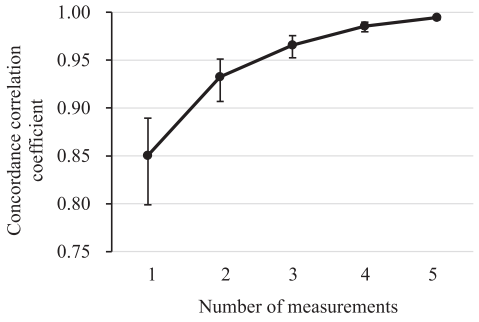
A. Relation of the mean of four measurements for Ees/Ea estimation and T-Ees/Ea.




B. Change in the intercept and slope of the linear regression formula in different numbers of measurements.




C. Change in the concordance correlation coefficient between the mean of the different numbers of measurements for Ees/Ea estimation and T-Ees/Ea.




D. Bland and Altman plots of the mean of the four measurements and T-Ees/Ea.

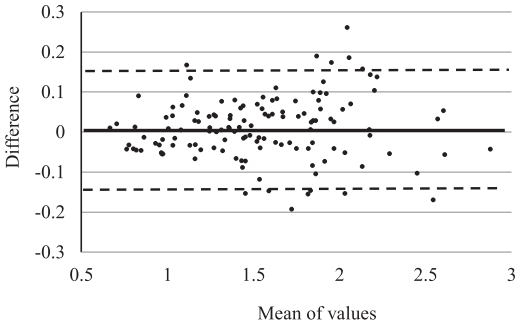



Fig. 1 Relation of different numbers of measurements for Ees/Ea estimation and T-Ees/Ea.
The mean of the estimated Ees/Ea using different numbers of measurements was linearly correlated with T-Ees/Ea. (A) The correlation between the mean of estimated Ees/Ea using four-time measurements and T-CAVI was high (R = 0.99). (B) The intercept (B1) and slope (B2) of the linear regression formula in different numbers of measurements converged to 0 and 1, respectively, and their 95% confidence interval narrowed when the number of measurements was more than four. (C) The concordance correlation coefficient (CCC) between the mean of the estimates using different numbers of measurements and T-Ees/Ea was close to 1 when the number of measurements increased. CCC was classified as excellent in more than four measurements. (D) The Bland and Altman plots of the difference between the mean of estimates using four measurements and T-Ees/Ea showed relevant result with well-aligned points and limits of agreement. Ees/Ea, left ventricular end-systolic elastance/arterial elastance; T-Ees/Ea, trimmed average left ventricular end-systolic elastance/arterial elastance; T-CAVI, trimmed average cardio-ankle vascular index; CCC, concordance correlation coefficient.

## Discussion

Non-invasive screening examinations for cardiovascular function are important. The VaSera® is a non-invasive device that is useful for screening and diagnosing cardiovascular problems due to metabolic syndrome or lifestyle-related diseases[8,9]; in addition, CAVI is correlated with vessel stiffness, known as beta index obtained by transesophageal echocardiography[26]. We hypothesized that the parameters (SBP, DBP, ET, and PEP) obtained by VaSera® could be applied to estimate Ees/Ea. In our study, the formula of Hayashi was used for the Ees/Ea estimation[10]. The formulas included the Pes value, which was a predicted value calculated based on a previous study[13].

In the results, the Ees/Ea estimates were 1.5 [1.2, 1.9]. Being closely related to ejection fraction, estimating Ees/Ea using the VaSera® allows the evaluation of the energetic and mechanical efficiency of the left ventricle[27]. As abnormal values of Ees/Ea are particularly related to the ejection fraction, a considerably reduced Ees/Ea is a very

Table 4 Regression and correlation analyses for the cardio-ankle vascular index

| | | Series of measurements | | | | |
|---|---|---|---|---|---|---|
| | | Once (first measurement applied) | Twice (first and second measurements applied) | Three times (first, second, and third measurements applied) | Four times (first, second, third, and fourth measurements applied) | Five times (all five measurements applied) |
| Linear regression analysis (Deming method) | Intercept | –0.51 (–1.00, 0.00) | –0.19 (–0.44, 0.06) | –0.04 (–0.19, 0.11) | –0.08 (–0.17, 0.02) | 0.04 (–0.03, 0.11) |
| | Slope | 1.11 (1.02, 1.19) | 1.04 (1.00, 1.08) | 1.01 (0.98, 1.04) | 1.01 (1.00, 1.03) | 0.99 (0.98, 1.01) |
| | R | 0.92 | 0.97 | 0.99 | 0.99 | 1.00 |
| Concordance correlation coefficient | | 0.90 (0.87, 0.93) | 0.97 (0.96, 0.98) | 0.99 (0.98, 0.99) | 0.99 (0.99, 1.00) | 1.00 (1.00, 1.00) |
| Bland and Altman analysis | Bias | 0.07 (0.03, 0.11)* | 0.02 (–0.02, 0.04)* | 0.00 (0.00, 0.00)* | 0.01 (–0.00, 0.02) | 0.00 (–0.00, 0.01)* |
| | Limits of agreement | –0.04, 0.24 | –0.06, 0.16 | –0.05, 0.08 | –0.14, 0.16 | –0.03, 0.03 |

The values are presented as mean (95% confidence interval). In the mean of two measurements, neither systematic (0 was within 95% confidence interval of intercept) nor proportional (1 was within 95% confidence interval of slope) differences were shown using the Deming regression method. An excellent concordance correlation coefficient was shown with more than two measurements. The Bland and Altman plots indicated a non-significant median bias and narrow limits of agreement between the mean of two measurements and the 40% trimmed average. *95% confidence intervals were calculated using the bootstrap method.

useful sing than when ejection fraction is preserved[28,29]. Additionally, we verified the minimum required number of CAVI measurements using VaSera® and Ees/Ea estimation based on the values obtained by the device. The minimum number of accurate CAVI measurements was two. For the Ees/Ea estimation, four measurements were minimally needed. Moreover, compared with the 40% trimmed average as a hypothetical reference, sequential measurements increase their precision of Ees/Ea estimates, suggesting that Ees/Ea estimates after four measurements were tolerable.

We assessed that four measurements were minimally required for Ees/Ea estimation. The variation in ET and PEP significantly influenced the estimation results. According to the company's comments, the ET and PEP values are displayed as the mean of four-beat measurements. Even with this, the final estimates generated from ET and PEP showed relatively large variations. For this reason, sequential four-time measurements were required for the Ees/Ea estimation.

We showed that the variation among the five measurements of CAVI was small. Statistically, the first measurement of CAVI was high among the five measurements, which is believed to be related to the stress of the participants[30,31]. Although a 5-minute rest period was set before the measurements, stress factors might have influenced arterial stiffness. The slightly high initial value may be linked to anxiety in the sympathetic nervous system and renin-angiotensin system[32,33]. Even with a slight increase in the first measurement of CAVI, we concluded that measuring twice was a minimal requirement for accurate measurements compared with T-CAVI.

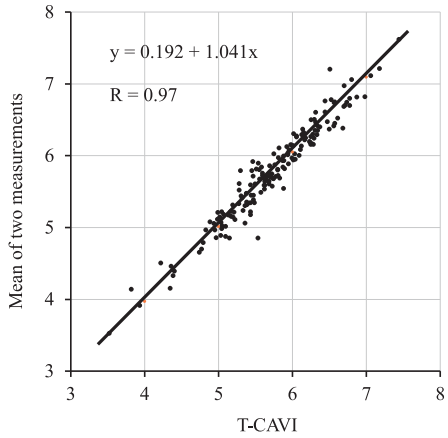
A previous study showed that the ICC value of CAVI using VaSera® was 0.60[8]. In our study, the value was as high as 0.83. The discrepancy could have been caused by the number of raters and the timing of measurements. In our study, one rater performed the measurements sequentially. Moreover, diurnal variation was not considered in case of repeated measurements in a single experiment. In a coordinated examination at a single time point, only two measurements were minimally required when measuring CAVI using VaSera®.

This study had several limitations. First, it was conducted in a laboratory setting at a single institute, where the participants were uniformly young. Hence, our results cannot be generalized for clinical situations. Second, we did not compare the estimated value of Ees/Ea to those obtained from other devices or the values of CAVI; however, the 40% trimmed average value was among the five measurements for Ees/Ea and CAVI.

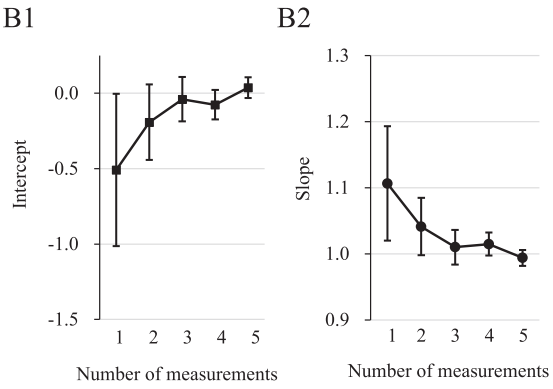
In conclusion, non-invasive Ees/Ea estimation using the VaSera® was tolerable, and its precision increases with sequential measurements. A minimum of two measurements for CAVI and four measurements for Ees/Ea estimation were required.

**Availability of data and materials:** The datasets used and/or analyzed during the current study are available upon request.

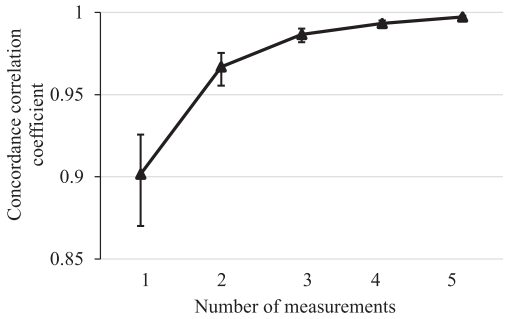
A. Relation of the mean of two measurements of CAVI and T-CAVI.




B. Change in the intercept and slope of the linear regression formula in different numbers of measurements.




C. Change in the concordance correlation coefficient in different numbers of measurements of CAVI and T-CAVI.




D. Bland and Altman plots of the mean of the two measurements and T-CAVI.

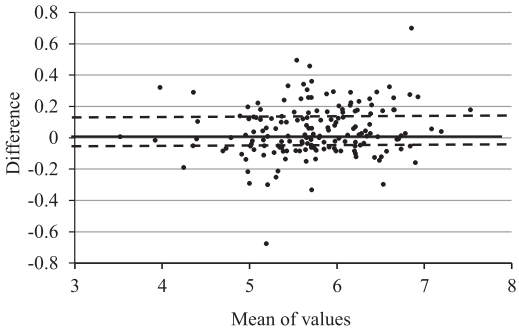



Fig. 2 Relation of the different numbers of measurements of CAVI and T-CAVI.
The mean values of CAVI in the different numbers of measurements were linearly correlated with T-CAVI. (A) The correlation between the mean of two measurements of CAVI and T-CAVI was high (R = 0.97). (B) Considering the linear regression formula, the intercept (B1) and slope (B2) converged to 0 and 1, respectively, and their 95% confidence interval narrowed when the number of measurements was doubled or more. (C) The concordance correlation coefficient (CCC) between the mean of the different numbers of measurements and T-CAVI was close to 1 when the number of measurements increased. CCC was classified as excellent in more than two measurements. (D) The Bland and Altman plots of the difference between the mean of the two measurements and T-CAVI by their mean showed relevant results with well-aligned points and limits of agreements (D). CAVI, left ventricular-arterial coupling; T-CAVI, trimmed average cardio-ankle vascular index; CCC, concordance correlation coefficient.

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