



Original Article

Inadequacy of Augmentation Index for Monitoring Arterial Stiffness: Comparison with Arterial Compliance and Other Hemodynamic Variables

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Abstract

Purpose—Augmentation Index (AI_x) is used clinically for monitoring both wave reflections and arterial stiffness, which when increased is a risk factor of cardiovascular mortality and morbidity. We hypothesize that AI_x is not solely related to vascular stiffness as described by arterial compliance and other hemodynamic parameters since AI_x underestimates wave reflections.

Methods—Aortic pressure and flow datasets ($n = 42$) from mongrel dogs were obtained from our experiments and Mendeley Data under various conditions. Arterial compliances based on the Windkessel model (C_t), the stroke volume (SV) to pulse pressure (PP) ratio ($C_v = SV/PP$), and at inflection pressure point (C_{Pi}) were computed. Other relevant hemodynamic factors are also computed.

Results— AI_x was poorly associated with arterial stiffness calculated from C_t ($r = 0.299$, $p = 0.058$) or C_{Pi} ($r = 0.203$, $p = 0.203$), even when adjusted for heart rates. C_t and C_v were monotonically associated. Alterations in inflection pressure (P_i) did not follow the changes in pulse pressure (PP) ($r = 0.475$, $p = 0.002$), and P_i was quantitatively similar to systolic pressure ($r = 0.940$, $p < 0.001$).

Conclusion— AI_x is neither linearly correlated with arterial stiffness, nor with arterial compliance and several cardiac and arterial parameters have to be considered when AI_x is calculated.

Keywords—Arterial compliance, Augmentation index, Vascular stiffness, Inflection pressure, Hemodynamic factors.

INTRODUCTION

Increased arterial stiffness is a dominant risk factor associated with many forms of cardiovascular diseases and their progression.³¹ Variation in arterial stiffness is manifested by structural and functional changes in the blood vessel wall and affects both sexes.²⁵ The variations in arterial stiffness, in turn, change pulse pressure and vascular load to the left ventricle. An increase in vascular stiffness, along with a concomitant increase in pulse wave reflections¹⁸ have been shown to contribute adversely to the severity of hypertension. Systolic hypertension, accompanied by a reduction in diastolic pressure, hence increased overall pulse pressure, expedites other cardiovascular diseases by weakening coronary perfusion.^{28,35} Significantly increased pulse pressure is a hallmark of decreased overall arterial compliance.^{24,44}

Augmentation index (AI_x) has been used as a measure of vascular stiffness in many clinical studies. Gurovich *et al.* showed that refractory angina patients have stiffer arteries and increased afterload compared to a control group.¹³ This, in turn, affected the myocardial oxygen-supply demand due to increased wave reflections and quantified them using the augmentation index. However, Climie *et al.* in studying Type II diabetic patients, concluded that AI_x was not indicative of the large artery stiffness.⁸ Segers *et al.* also used AI_x as one of the global reflection indices to quantify vascular stiffness due to pulse wave reflection in Marfan's syndrome patients.⁴¹

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Similarly, AI_x has been utilized as the stiffness index in end-stage renal disease populations, hypercholesterolemia, intracranial aneurysms, hyperthyroidism, and syncopal attacks.³³ Additionally, other studies have demonstrated a change in vascular stiffness due to aging and hypertension and the respective changes in the augmentation index.^{6,32} We have previously shown that AI_x underestimates wave reflections under different pressure states,¹⁸ and the augmented pressure estimated using the definition of AI_x is lower than the augmented pressure estimated by the pressure wave resolution process developed from the wave reflection theory.²⁴ Reduced estimation of wave reflections results in the reduced estimation of vascular stiffness. Besides, augmented pressure depends on both the magnitude of reflection and the return time of the reflected wave. There is evidence from computational and clinical studies that AI_x is sensitive to changes in low arterial stiffness values, which is affected by the shape of the forward and the reflected waves and in turn by the magnitude of reflection.^{29,53} They also revealed that AI_x is insensitive to changes in high arterial stiffness values. Furthermore, Segers *et al.*⁴² and Westerhof *et al.*⁵² have shown that the inflection time is different from the return time of the reflected wave. Hence, we hypothesized that AI_x was an inadequate, stand-alone clinical marker of arterial stiffness.

More importantly, increased arterial stiffness is equivalent to reduced arterial compliance, and several seminal studies have considered arterial compliance in clinical diagnosis to quantify vascular load.^{7,23,30,36} Li *et al.*²⁶ and Berger *et al.*³ have shown that arterial compliance is a marker of isolated hypertension. It is vital to quantify stiffness precisely in applications that involve quantification of pulsatile load such as progressive vessel damage and atherogenesis so that both myocardial supply-demand and ventricular-arterial coupling can be assessed accurately. Moreover, confounding factors that affect AI_x must be defined in order to get a clear picture of the pathophysiology in coronary or aortic occlusions.

AI_x is used as a measure of wave reflections and vascular stiffness. In this study, we look at its validity in the assessment of vascular stiffness. Since large artery compliance is clinically recognized as a marker of vascular stiffness, we hypothesize that AI_x is not linearly related to arterial stiffness calculated from both linear Windkessel arterial system model, stroke volume over pulse pressure ratio, and non-linear pressure-dependent compliance methods. Additionally, we investigated whether AI_x is related to other hemodynamic parameters that are dependent on both arterial and cardiac functions.^{14,43}

METHODS

Data Collection

We first collected simultaneously measured aortic pressure and aortic flow data from our previous experiments in mongrel dogs ($n = 6$, average weight = 22 kg). The details of the experiment are reported elsewhere.¹⁹ Briefly, intravenous anesthesia was administered to the dogs with the aid of Nembutal (30 mg/kg) after Rutgers University IACUC approval of the experimental protocol. A left thoracotomy was performed to place an electromagnetic flowmeter in the ascending aorta. The surgical procedure was performed at the fifth intercostal space. A Millar catheter-tip pressure transducer was advanced through the femoral artery to the ascending aortic flow measurement site. After control normotensive aortic pressure and aortic flow signals were measured, 1 mL bolus dose of methoxamine (2–5 mg/mL) was infused to induce hypertension. At steady state, 1 mL bolus dose of nitroprusside (50 μ g/mL) followed to induce vasodilation. Data were digitally stored in a computer at a sampling rate of 100 Hz for further prospective analysis.

In order to examine a broad spectrum of clinically relevant physiologic conditions with substantial blood pressure variations, additional aortic pressure and flow signals were obtained from Mendeley Data (Mendeley Ltd., London, United Kingdom). The details of each dataset have been reported previously.¹⁸ We extracted 2 aortic pressure and aortic flow datasets under vasoconstriction and vasodilation from⁵ while we obtained an aortic pressure-flow dataset pair under normal conditions from.¹² This publication was also used to obtain a dataset under vasoconstriction from angiotensin administration and 2 datasets under vasodilation from hydralazine and nitroprusside administration respectively. Similarly, two aortic pressure-flow datasets were obtained from Ref. 15 under normal conditions, and another set were extracted under vasoconstricted conditions. Besides, we identified four pairs of simultaneous aortic pressure-flow measurements under vasoconstricted and vasodilated conditions (two under each condition).⁵¹ Additionally, aortic pressure aortic flow datasets from hearts paced at 4 different rates were extracted from Ref. 38. Four more aortic pressure-flow measurements were identified from dogs that had been paced after cardiomyoplasty.¹ Our search for more data also resulted in two simultaneous aortic pressure-flow measurement sets under expanded blood volume conditions.^{9,10} One of the datasets also had reference pressure-flow measurements under control conditions, fluid infusion and hemorrhagic conditions.¹⁰ More-

over, we procured aortic pressure-flow datasets under aortic occlusion along with a reference normal pressure-flow measurement pair.²¹ Finally, we extracted an aortic pressure-flow dataset with diastolic oscillations from.¹¹

The datasets included 30 normotensive control, vasoconstricted, vasodilated, pacing, post-cardiomyoplasty, and post-fluid resuscitation datasets. The acquired datasets were digitally resampled to 100 Hz.

Data were processed to have one heartbeat in length by identifying two consecutive global minima in the pressure signal using a simple linear search algorithm. Resampling and further calculations were performed on a 2.6 GHz Intel i5 processor using MATLAB 2017b (The Mathworks Inc., Natick, Massachusetts, USA). Pulse Pressure (PP) was calculated as the difference between systolic pressure (P_s) and diastolic pressure (P_d). The ejection period (EP) was calculated from the flow waveform. Mean arterial pressure (P_m) was calculated from:

$$P_m = \frac{\int_0^T P(t) dt}{T} \quad (1)$$

where T is the cardiac period

Augmentation Index (AI_x) Calculation

We chose to use the peak flow to identify inflection point of the pressure waveform, since both aortic pressure and flow signals were available. This methodology had the added benefit of precisely identifying the inflection pressure that also avoided the ambiguity induced by the pressure derivative method. The aortic pressure at identified peak flow rate was defined as the inflection pressure (P_i). AI_x was then calculated from the following equation:

$$AI_x = \frac{P_s - P_i}{PP} \quad (2)$$

The calculated AI_x was then normalized to heart rate, as based on a linear regression model¹⁸ that we had developed for our dataset. The normalized AI_x was calculated by normalizing our AI_x data to a heart rate of 100 bpm using the following empirical equation:

$$AI_x = 0.4147 - 0.0017 \times HR \quad (3)$$

Arterial Compliance (C) Calculation

Since stiffness is the inverse of compliance, vascular stiffness was calculated as the reciprocal of arterial compliance. Arterial compliance was calculated using three different methods shown below.

Stroke Volume to Pulse Pressure Ratio Method

A clinically popular method to estimate arterial compliance is based on the fundamental definition of arterial compliance,

$$C = \frac{dV}{dP} \quad (4)$$

Thus, arterial compliance C_v was calculated as the ratio of the volume ejected by the left ventricle, or stroke volume (SV), to the distending pressure in the aorta or the pulse pressure (PP):

$$C_v = \frac{SV}{PP} \quad (5)$$

SV was calculated as the result of trapezoidal numerical integration of the flow signal.

Diastolic Pressure Decay Based on the Windkessel Method

Another popular method to obtain arterial compliance C_t was based on the linear Windkessel model in which the arterial compliance is assumed to be constant over the entire cardiac period. This method assumes the exponential decay of diastolic aortic pressure decay time constant, τ ($= R_s C_t$), and their relationship is described in the following equation.

$$C_t = \frac{t_d}{R_s \ln \frac{P_{es}}{P_d}} \quad (6)$$

where t_d is the diastolic period, R_s is the peripheral resistance or the ratio of mean aortic pressure to mean aortic flow, P_{es} is the end-systolic aortic pressure and P_d is the diastolic aortic pressure.

Non-linear Compliance Method

A pressure-dependent compliance estimation technique has been proposed by Li, and we have reported a detailed analysis of the methodology elsewhere.¹⁹ This method provides information about the arterial compliance variation throughout the cardiac cycle. Briefly, non-linear compliance estimation involves the use of a modified three-element Windkessel model, and non-linear compliance was defined with the following equation:

$$C(P) = a \exp^{bP(t)} \quad (7)$$

where a and b are empirical constants, $P(t)$ is the peripheral pressure estimated by the Windkessel model. The estimation algorithm involves an iterative substitution of a range of values for the parameters a and b in order to solve the Windkessel model equation

that predicts aortic pressure numerically. The set of a and b values that led to the lowest root mean square error (rms) between the actual and the predicted aortic pressures was chosen as the coefficients of the Eq. (7). Arterial compliance calculated at the aortic pressure inflection point (C_{Pi}) was used for further analysis, since this technique yields a compliance waveform rather than a single constant value.

Stroke Work Calculation

Stroke work or external mechanical work of the left ventricle was calculated from the integral of the product of the pressure and the flow signals overtime and the cardiac period by utilizing the following equation¹⁷:

$$SW = \int_0^T P(t)Q(t)dt \quad (8)$$

where $P(t)$ and $Q(t)$ are the aortic pressure and the aortic flow signals, and T is the cardiac period.

Reflection Coefficient and Reservoir Pressure Calculation

Reflection Coefficient was estimated after the resolution of the pressure signal into their respective forward (P_f) and backward (P_r) components. The precise estimation technique has been explained elsewhere.¹⁸ Briefly, the Fast Fourier Transform (FFT) algorithm was applied to the pressure, and the flow signals independently first. The average of the ratio of the magnitudes of the pressure harmonics and the flow harmonics between 3 and 10 Hz was estimated as the characteristic impedance of the aorta. The calculated characteristic impedance was then used to resolve the pressure and the flow components with the aid of the following equations.

$$P_f = \frac{P(t) + Q(t)Z_o}{2} \quad (9)$$

$$P_r = \frac{P(t) - Q(t)Z_o}{2} \quad (10)$$

where P_f is the forward pressure wave, P_r is the backward pressure wave, Z_o is the characteristic impedance, and $P(t)$ and $Q(t)$ are the instantaneous pulsatile pressure and the flow signals, respectively.

The reflection coefficient was then calculated as the magnitude of the ratio of the first (principal) harmonic of the Fourier coefficients of the backward pressure wave and the forward pressure wave.

$$\Gamma_1 = \frac{F(P_r)}{F(P_f)} \quad (11)$$

where $F(P_f)$ and $F(P_r)$ are Fourier coefficients of the forward wave and the backward wave, respectively.

From the derivation of reservoir pressure P_{res} according to wave separation analysis, the reservoir pressure is defined by the following equation.²³

$$P_{res} - P = \exp^{-(a+b)t} \int_0^t [aP(t') + bP] \exp^{(a+b)t'} dt' + (P_d - P) \exp^{-(a+b)t} \quad (12)$$

where P_∞ is the asymptotic pressure, P_d is the diastolic pressure at time $t = 0$, b is the reciprocal of the product of arterial resistance, and arterial compliance and a is a constant found by fitting the diastolic period of the pressure signal. This pressure is equivalent to twice the backward pressure that we estimate in the present study, according to a recent review.⁵⁴ The diastolic pressure was subtracted from the backward pressures for further analysis.

Data and Statistical Analyses

AI_x was compared with constant Windkessel compliance C_r , stroke volume/pulse pressure defined compliance, C_v , compliance at inflection pressure point computed from nonlinear pressure dependent compliance model, C_{Pi} , stroke work, SW, principal reflection coefficient, Γ_1 and reservoir pressure, P_{res} .

The collected data, that included both experimental and previously published data, were classified into four groups such as normotensive ($n = 12$), vasoconstriction ($n = 8$), vasodilation ($n = 11$) and pacing ($n = 8$). There were 42 datasets in total. Of the 42, two datasets could not be classified with any of the four groups. Initially, there were 12 datasets in the vasodilated group. However, heart rate normalization of one of the 12 datasets resulted in negative AI_x value. That dataset was omitted from further analysis. Normality was checked for all comparisons using the Lilliefors test with the null hypothesis that datasets were sampled from normally distributed data. This test was chosen because the original mean and standard deviation (SD) were unknown for most datasets. Significant differences for all comparisons were tested using one-way ANOVA along with the Tukey–Kramer for *post-ad-hoc* analysis if normality results were significant. Else, a Kruskal–Wallis test was employed to test all the significant differences along with the Dunn–Sidak method for the *post-ad-hoc* analysis. In order to quantify the strength of relationship, we used Spearman's rank correlation if normality is denied and linear models if normality test results are significant. All statistical hypothesis tests were tested at 95% significance level.

Firstly, normalized augmentation indices with heart rates, and the arterial stiffnesses that were calculated from the non-linear and linear compliances (C_v , C_t) of each group were assessed for normality and significant differences to show how each arterial stiffness calculation method mentioned in section “**Augmentation Index (AI_x) Calculation**” is different from one another. Secondly, we assumed that heart rate normalized AI_x will not follow the changes in arterial stiffness estimated by any of the three methods mentioned in section “**Augmentation Index (AI_x) Calculation**”. In order to test our hypothesis, the strength of relationship between heart rate normalized AI_x and arterial stiffness calculated from the non-linear and the linear compliances (C_v , C_t) was quantified based on normality of the variables. To show the similarity between C_v and C_t , a Bland Altman analysis between the two sets of compliances was performed. Furthermore, a paired t -test was performed between the two sets of compliances to identify significant differences, and the strength of their relationship was quantified based on the normality of the variables. We also analyzed the relationship between the reflection coefficient and normalized AI_x .

Additionally, we analyzed the strength of the relationship between inflection pressure (P_i) and systolic pressure (P_s) and that between P_i and pulse pressure (PP) in order to understand their variations with respect to change in arterial stiffness by finding significant differences and quantifying the relationship strength based on their normality. Variables such as heart rate, ejection period, reservoir pressure, reflection

coefficient, stroke work, and aortic characteristic impedance were identified as the covariates of AI_x . Spearman’s rank correlation was computed to quantify each covariate’s relationship with AI_x .

RESULTS

Results of the normality tests are summarized in Table 1. Heart rate normalized augmentation indices (AI_x) of each group was normally distributed while stiffnesses calculated from stroke volume and pulse pressure ($1/C_v$) and non-linear compliance ($1/C(P)$) of each group were not normally distributed. Table 2 shows the mean and standard deviation of AI_x and the median and interquartile ranges of $1/C_v$ and non-linear compliance $1/C(P)$ for each group. The significant differences among multiple groups are summarized in Table 3. One-way ANOVA was used for AI_x while Kruskal–Wallis test was used for the stiffnesses based on their respective normality results.

AI_x of all the groups were normally distributed while stiffnesses calculated from C_v of all groups were not normally distributed. There was a correlation of 0.299 between the two variables with p -value > 0.05 . This shows that the correlation was not significantly different from zero (See Fig. 1a). Outliers in the stiffness variable were defined as those datapoints that were outside the interquartile range. Removal of outliers did not improve the strength of the relationship between the variables (See Fig. 1b). Similarly, stiffnesses calculated from $C(P)$ of all groups were not normally distributed. The monotonic association between heart rate normalized AI_x and pressure-dependent arterial stiffness showed a weak correlation of 0.203 between the two variables. Outliers were removed from the $1/C(P)$ variable using the interquartile range of $1/C(P)$ and it did not improve the strength of the relationship in this case as well.

The comparison of different clinical methods used to estimate compliances shows that there was a statistically significant monotonic association between C_v ,

TABLE 1. Lilliefors normality test results.

| Group | AI_x | $1/C_v$ | $1/C(P)$ |
|------------------|--------|---------|----------|
| Normal | 0.500 | 0.001 | 0.004 |
| Vasoconstriction | 0.500 | 0.009 | 0.021 |
| Vasodilation | 0.435 | 0.096 | 0.500 |
| Pacing | 0.500 | 0.039 | 0.500 |

p -value < 0.05 rejects the null hypothesis.

TABLE 2. Lilliefors normality test results.

| Group | AI_x | $1/C_v$ | $1/C(P)$ |
|------------------|------------------------|-----------------------------|-----------------------------|
| Normal | Mean: 0.219 Std: 0.092 | Median: 2.800 IQR: 1.133 | Median: 2.527 IQR: 1.620 |
| Vasoconstriction | Mean: 0.269 Std: 0.184 | Median: 2.162 IQR: 7.592 | Median: 2.834 IQR: 9.949 |
| Vasodilation | Mean: 0.157 Std: 0.109 | Median: 1.510 IQR: 1.337 | Median: 0.671 IQR: 0.534 |
| Pacing | Mean: 0.406 Std: 0.323 | Median: 1.050 IQR: 0.947 | Median: 0.856 IQR: 0.572 |

p -value < 0.05 rejects the null hypothesis.

and C_t with $r = 0.841$ and $p < 0.001$ (see Fig. 2). The difference between C_v and C_t were not normally distributed. The Bland-Altman analysis showed a mean offset of -0.383 between C_v and C_t . Kruskal-Wallis test indicated that there were no significant differences ($p = 0.075$) between C_v (Median: $0.457 \text{ mL mmHg}^{-1}$ IQR $0.591 \text{ mL mmHg}^{-1}$) and C_t (Median: $0.693 \text{ mL mmHg}^{-1}$ IQR $1.117 \text{ mL mmHg}^{-1}$).

Augmentation indices without normalization were not normally distributed while reflection coefficients were normally distributed. Figure 3 shows the monotonic association between augmentation index (with and without heart normalization) and reflection coefficient. The correlation analysis reveals that the heart rate normalization reduced the strength of relationship

between AI_x and reflection coefficient. The statistical significance also becomes insignificant when normalization is applied to AI_x . The difference between P_i and P_s were not normally distributed. The Bland-Altman analysis showed a mean offset of -7.013 mmHg between P_i and P_s (Fig. 4a). There were no significant differences between the two variables ($p = 0.310$). A comparison between P_i and P_s shows that both the sets of pressure have a significant monotonic association (see Fig. 4b) with a correlation coefficient of 0.940 ($p < 0.001$).

A comparison between inflection pressure and pulse pressure showed that there was a significant monotonic relationship (see Fig 5) with a strength of 0.475 ($p = 0.002$). Table 4 summarizes the covariates of AI_x and their rank correlation coefficients. It can be seen that the heart rate (HR) and the reflection coefficient (Γ_1) were significantly associated with AI_x in our data ($p < 0.05$). Heart rate and stroke work had negative monotonic associations with AI_x . In contrast, the ejection period, the reflection coefficient, and the characteristic aortic impedance had positive associations with AI_x . Additionally, reservoir pressure seems to be not associated with AI_x in our data.

TABLE 3. Results of the significance difference tests.

| Group 1 | Group 2 | AI_x | $1/C_v$ | $1/C(P)$ |
|------------------|------------------|--------|---------|----------|
| Normal | Vasoconstriction | 0.934 | 0.998 | 0.968 |
| Normal | Vasodilation | 0.850 | 0.324 | 0.007 |
| Normal | Pacing | 0.139 | 0.056 | 0.0531 |
| Vasoconstriction | Vasodilation | 0.564 | 0.779 | 0.001 |
| Vasoconstriction | Pacing | 0.459 | 0.270 | 0.012 |
| Vasodilation | Pacing | 0.031 | 0.943 | 0.999 |

p -value < 0.05 shows significant difference.

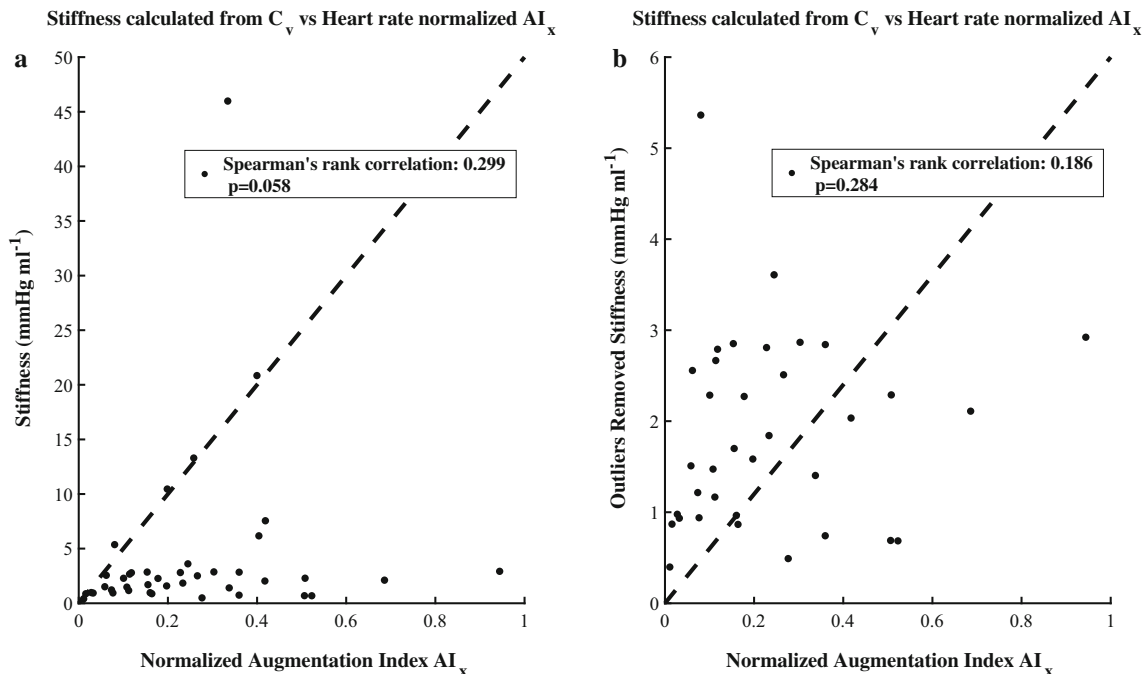


FIGURE 1. (a) Comparison of heart rate normalized augmentation index (AI_x) with Arterial Stiffness calculated from C_v ($1/C_v$), with $C_v = \text{Stroke Volume/Pulse Pressure}$. Observation shows a lack of significant monotonic association between these two indices. The broken line represents the zero-slope line. (b) Comparison of Heart Rate normalized Augmentation Index (AI_x) with Arterial Stiffness from C_v ($1/C_v$), with $C_v = \text{Stroke Volume/Pulse Pressure}$ after removing the outliers in $1/C_v$. Observation shows an insignificant monotonic association between the two variables. The broken line represents the zero-slope line.

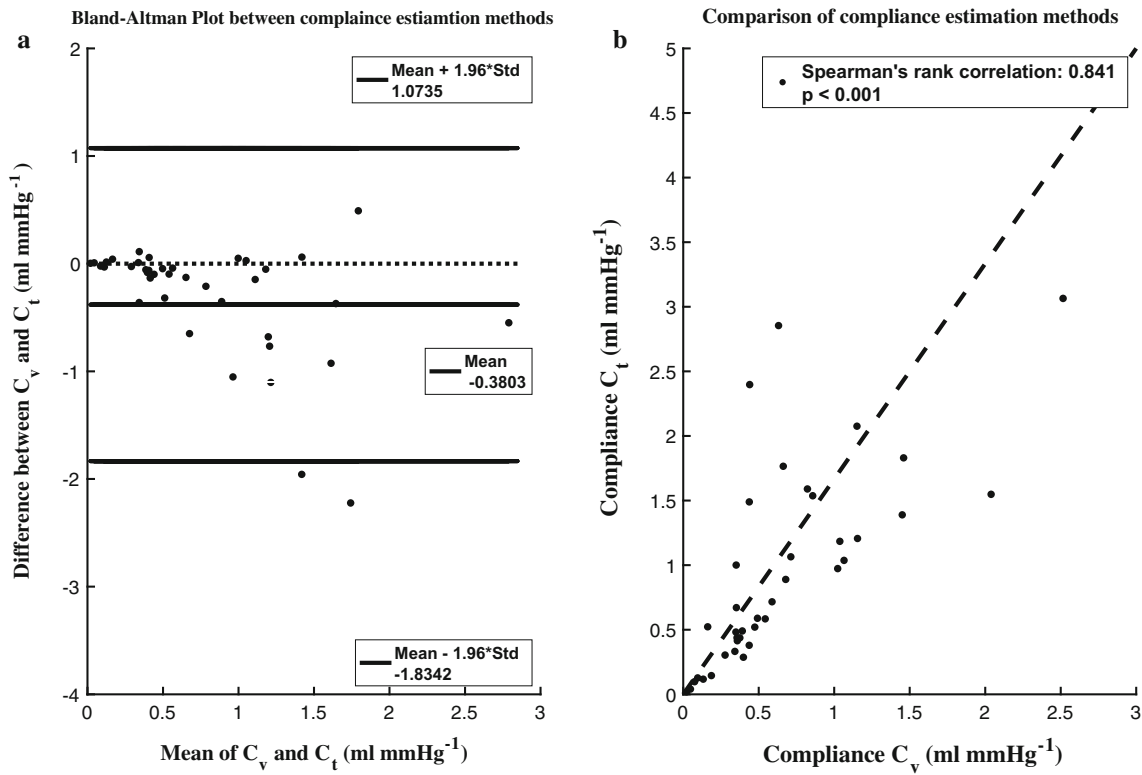


FIGURE 2. (a) Bland Altman plot between Compliance calculated from the Stroke Volume and the Pulse Pressure (C_v) and Compliance calculated from the diastolic aortic pressure (C_t). (b) Comparison of Compliance calculated from the ratio of Stroke Volume to Pulse Pressure (C_v) with Compliance calculated from the diastolic aortic pressure or Windkessel time constant (C_t). The broken line represents the zero-slope line.

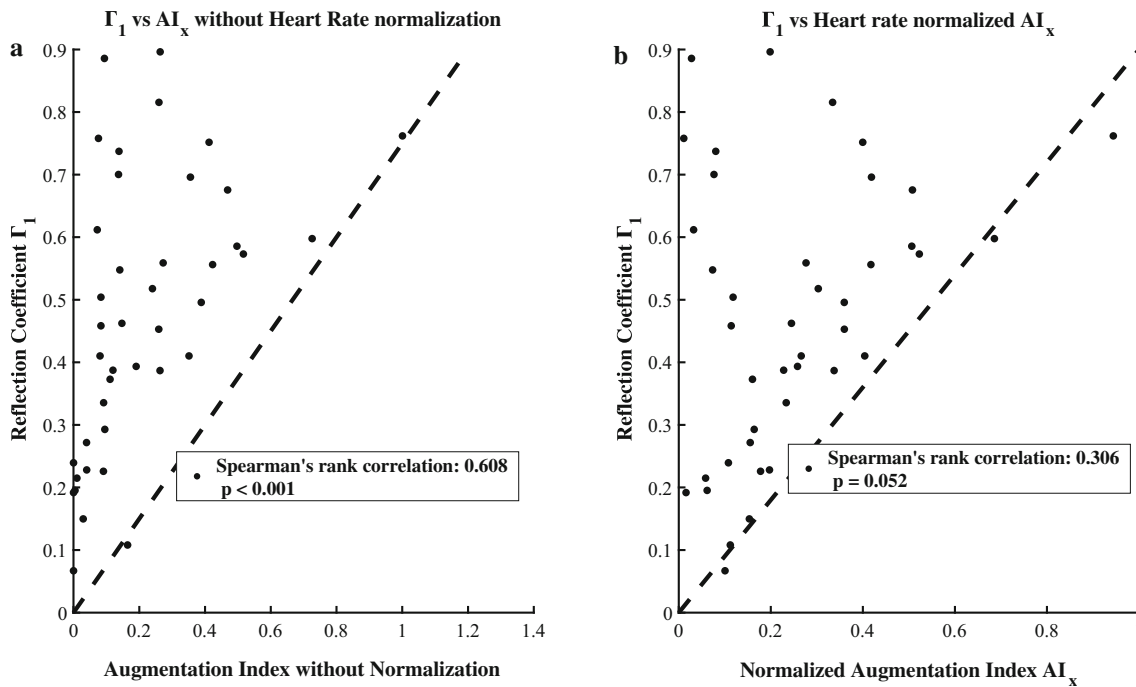


FIGURE 3. (a) Comparison of Augmentation Index (AI_x) without Heart Rate normalization with Reflection Coefficient Γ_1 . Observation shows a significant monotonic association between these two indices. The broken line represents the zero-slope line. (b) Comparison of Heart Rate normalized Augmentation Index (AI_x) with Reflection Coefficient. Observation shows an insignificant monotonic association between the two variables. The broken line represents the zero-slope line.

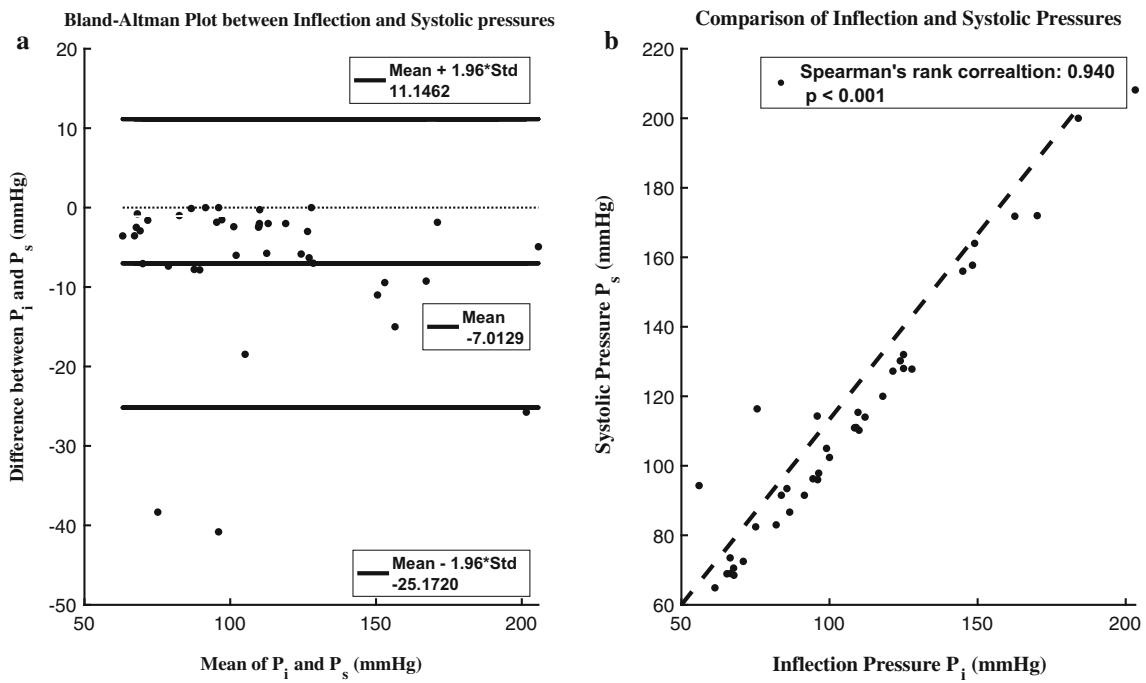


FIGURE 4. (a) Bland Altman plot between Inflection Pressure (P_i) and Systolic Pressure (P_s). (b) Comparison of Inflection Pressure (P_i) with Systolic Pressure (P_s). A monotonic association between systolic pressure and inflection pressure is observed. The broken line represents the zero-slope line.

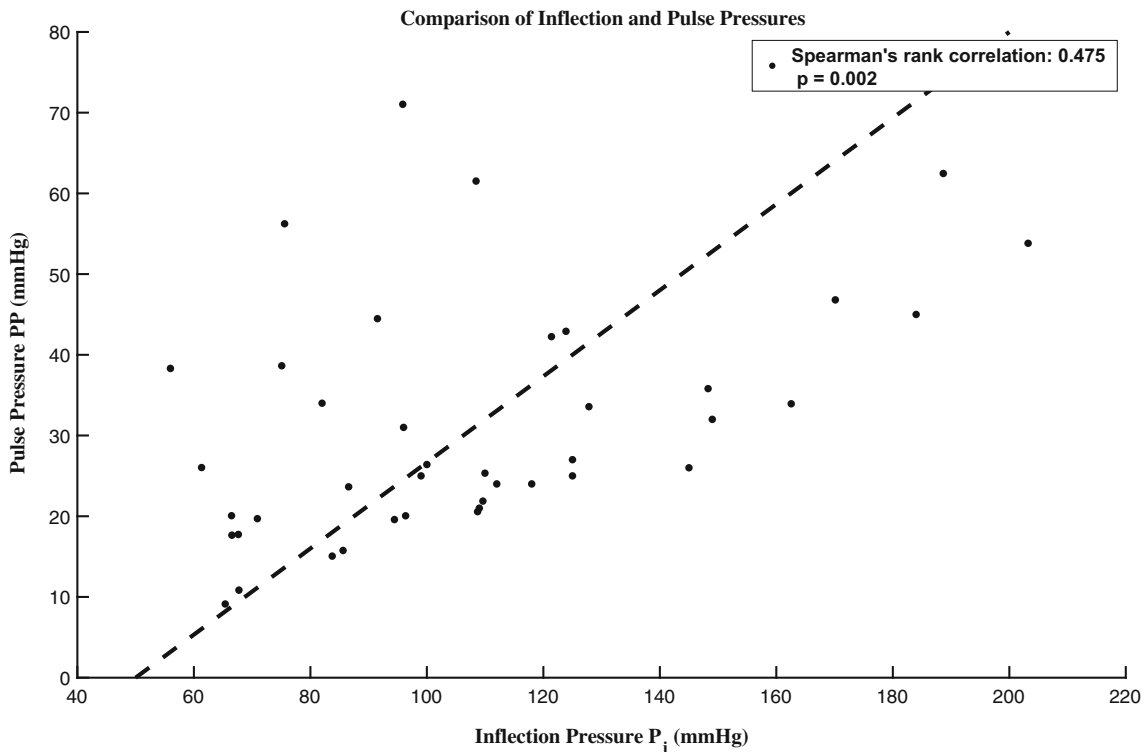


FIGURE 5. Comparison of Inflection Pressure (P_i) with Pulse Pressure (PP). Broken lines represent the zero-slope line.

TABLE 4. Covariates of AI_x considered for analysis.

| Covariate | r^* | p -value |
|---------------------------------------|---------|------------|
| Heart rate (HR) | − 0.382 | 0.014 |
| Ejection period (EP) | 0.259 | 0.102 |
| Reservoir pressure (P_{res}) | 0.070 | 0.664 |
| Stroke work (SW) | − 0.117 | 0.465 |
| Reflection coefficient (Γ_1) | 0.608 | <0.001 |
| Characteristic impedance (Z_0) | 0.111 | 0.486 |

* r represents the strength of the monotonic relationship that is quantified by Spearman's rank correlation.

DISCUSSION

Vascular stiffness is an important clinical marker for various cardiovascular diseases. In our experimental study, we chose to use methoxamine and nitroprusside as they principally altered the vascular state rather than cardiac contractility. Furthermore, the datasets we extracted from the literature helped us develop a population where changes in vasoactive states was achieved by different mechanisms. The increase in the number of datasets helped us achieve the necessary statistical power to obtain meaningful comparison results to evaluate the relationship between AI_x and vascular stiffness. We chose animal models for our analysis since it was rare to find open-source, simultaneous aortic pressure-aortic flow datasets to the best of our knowledge. A preliminary analysis on animal datasets would also allow us to replicate our hypothesis on simulated datasets in the future and the results of the study would act as references for comparison. Besides, vascular stiffness was taken as the inverse of compliance ($C = dV/dP$) computed from the linear Windkessel model (C_l), stroke volume to pulse pressure ratio (C_v), and compliance derived from the non-linear pressure-dependent arterial system model ($C(P_i)$). This allowed us to compare the different methods of vascular stiffness estimation methods with AI_x . The augmentation index was found to be poorly associated with vascular stiffness that was calculated from either Windkessel model (C_l) or pressure-dependent compliance model (C_{Pi}) (Figs. 1, 2 and 6). Removal of stiffnesses that were outside the interquartile range decreased the strength of relationship to an even weaker coefficient for both the comparisons (Figs. 1b and 6b) and the outliers did not pertain to one specific group for both the comparisons. This might mean that some of the data points outside the interquartile range had a non-linear relationship with augmentation indices. However, none of these relationships were statistically significant.

Additionally, analysis of the components that define AI_x shows that inflection pressure (P_i) does not necessarily change linearly with pulse pressure (PP) (see Fig. 5). Increased pulse pressure is an important clinical marker of increased vascular stiffness.^{4,39,40} Moreover, inflection pressure is closely correlated to systolic pressure under all conditions (see Fig. 3), and this results in an underestimation of the augmented pressure. Even though the AI_x without heart rate normalization has a trend similar to the reflection coefficient, heart rate normalization defeats the purpose. This combination of underestimating augmented pressure and reduced strength of relationship with reflection coefficient after heart rate normalization should be carefully considered in cases where AI_x is used to quantify reflections. More detailed analysis of multiple groups can be found in our previous publication.¹⁸ Augmented pressure during systole has been shown to be an important clinical marker of the amount of wave reflections, with the latter dependent on arterial stiffness.^{2,8,13,32,48} However, augmented pressure has significant limitations regarding quantifying wave reflections in addition to being less than the augmented pressure quantified by the reflection coefficient.¹⁸ Hughes *et al.*¹⁶ showed that type C pulse pressure waveforms where the peak systolic pressure precedes the inflection point resulted in negative augmented pressure (and thus negative AI_x) that is not associated with reflection magnitude. Segers *et al.*⁴² showed that inflection time calculated from the pressure waveform analysis is different from the timing of the return of the reflected wave, which led to reduced estimations of augmented pressure.

Our multivariable correlation showed that AI_x is dependent on parameters that are dependent on both cardiac and arterial functions, as shown by Heu-sinkveld *et al.*¹⁴ There was a strong monotonic association with the reflection coefficient, while the relationships heart rate and ejection period were moderate. Aortic characteristic impedance, and stroke work have a weak association with AI_x . Reservoir pressure had no association with AI_x . This shows that multiple parameters affect AI_x with varying strengths and normalization of AI_x with heart rate alone is not enough to completely nullify the effects of other parameters that AI_x depends on, and a recent review highlighted the need for a cautious approach when AI_x is normalized with heart rates that were elevated progressively over a long period.⁴⁵ It should also be noted that normalization with heart rate does not add additional information on whether AI_x can be used as a vascular stiffness index.¹⁸ Besides, the characteristic aortic impedance is a measure of aortic stiffness,³⁴ and we found only a weak association of the aortic impedance with AI_x .

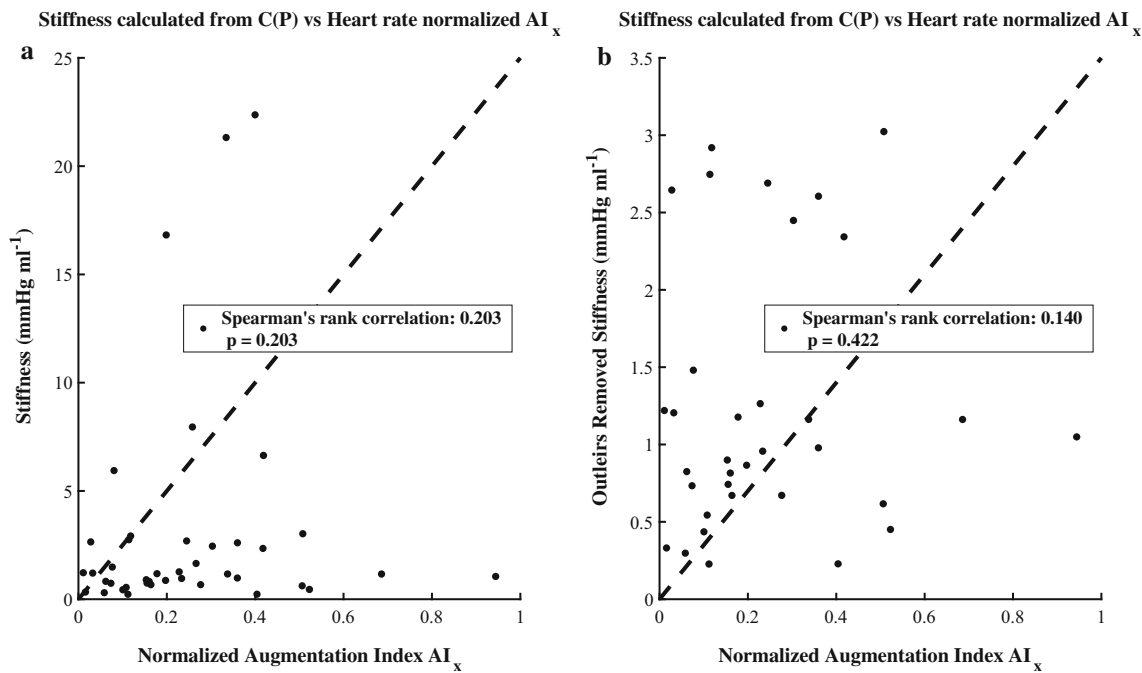


FIGURE 6. (a) Comparison of Heart Rate normalized Augmentation Index (AI_x) with Arterial Stiffness calculated from compliance corresponding to the inflection pressure ($1/C(P_i)$). Observation shows a lack of significant monotonic association between these two indices. The broken line represents the zero-slope line. (b) Comparison of Heart Rate normalized Augmentation Index (AI_x) with Arterial Stiffness calculated from compliance corresponding to the inflection pressure ($1/C(P_i)$) after removing the outliers in $1/C(P_i)$. Observation shows an insignificant monotonic association between the two variables. The broken line represents the zero-slope line.

Pulse pressure amplification,² in large artery such as the aorta, is a vital clinical consideration in the systolic loading of the heart. It should be noted here that we have shown here that the increase in pulse pressure is not linearly correlated to observed changes in AI_x . Also, the strong correlation of systolic pressure P_s to inflation pressure P_i indicates the redundancy in the use of P_i . We have also recently shown that an increase in AI_x does not indicate a proportional amount of increase in pulse wave reflections or an associated increase in pulse pressure. However, AI_x describes the general trend.¹⁸

Limitations of the Study

We have verified our hypothesis that the augmentation index does not linearly relate to vascular stiffness calculated from the inverse of either Windkessel compliance (C_l) or pressure-dependent arterial compliance C_v , nor does AI_x correlate to wave reflections. The limitation of the present investigation is the lack of pulse wave velocity (PWV) data. Central aortic pulse wave velocity or specifically, carotid to femoral pulse wave velocity (PWVc-f) has been shown by several studies to provide a reasonable index of aortic vascular stiffness,^{22,31,37,50} more so than the carotid to radial PWV (PWVc-r).^{46,47,55} Some investigators have shown

that an increase in AI_x is uncorrelated to an increase in pulse wave velocity^{20,27} during vasoactive drug therapies, which may imply that the changes in stiffness may be regional depending on the mechanism of action of the vasoactive drug. Climie *et al.*⁸ have found that patients with Type 2 diabetes have increased arterial stiffness, but not AI_x , and reported aortic PWVc-f (7.6 vs. 6.7 m/s) and brachial PWVc-r (8.1 vs. 8.5 m/s). The disparity in AI_x and PWV changes may imply that the stiffness of the entire vascular tree is increased in type 2 diabetes. Without the PWV velocity data, we could not surmise the effectiveness of AI_x in differentiating the global and the regional stiffness variations in these instances.

Clinical Implications and Translational Importance

In this study we have shown that AI_x is dependent on many hemodynamic factors and cannot solely reflect vascular stiffness. A recent recommendation by the American Heart Association Council on Hypertension states that pressure-flow analysis and the use of arterial compliance are more precise in characterizing vascular stiffness.⁴⁹ The translational importance of the results of current analysis based on experimental studies thus has direct relevance to the quantification of risk factors to many forms of cardiovascular dis-

eases. For instance, hypertension affects some 75 million Americans, and the increased vascular stiffness contributes to overall reduced arterial compliance and compromised cardiac function. The progression of hypertension into other cardiac complications can be tracked with changes in compliance.

To sum up, AI_x cannot be used as an exclusive marker of vascular stiffness as it depends on confounding factors involving other cardiac and arterial parameters. This is the first study that makes a direct evaluation of AI_x against several measures of arterial compliance, which is a well-recognized clinical parameter for assessing vascular stiffness. Arterial compliance should be used instead of the augmentation index as a compass in the therapeutic management of cardiovascular diseases through tracking vascular stiffness changes.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. All authors contributed to writing the manuscript and all authors read and approved the final manuscript.

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DATA AVAILABILITY

Data will be made available on request.

CODE AVAILABILITY

Code will be made available on request.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

ETHICAL APPROVAL

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. This article does not contain any studies with human participants performed by any of the authors.

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