Original Article

Limitation of the Augmentation Index for Evaluating Arterial Stiffness

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Although the augmentation index (AIx) is widely used to evaluate arterial stiffness in clinics and research, some conflicting data exist in regard to its validity. We therefore performed a series of studies to test the validity of AIx. The first study in 196 peritoneal dialysis patients showed that AIx in diabetics was lower than that in non-diabetic patients ($p<0.05$), which was in contradiction with the previous studies. Further analysis showed that AIx was just weakly correlated with pulse pressure (PP)—a known index of arterial stiffness. We also found that the increase of augmentation pressure (AP) was usually accompanied with increased central PP (C-PP). As AP and C-PP are used as the numerator and denominator in the AIx formula, an increase in the numerator (AP) would not necessarily result in an increase of the quotient (AIx) unless the denominator (C-PP) was stable. We then conducted a second study trying to test the validity of AIx through mathematical ratiocination. The increases in the central second peak (P_2) and AP were assumed to represent increased arterial stiffness. Different values of AIx were obtained by varying the central initial systolic peak (P_1) and diastolic pressure (DP). Mathematical ratiocination showed that AIx was dependent on multiple factors, $F=(\Delta SP-\Delta DP)\times(P_1-P_2)+(\Delta P_2-\Delta P_1)\times(SP-DP)$, which suggested that a change of AIx would not always be attributable to changes in P_2 and AP. This speculation was further proved by clinical data in our third study. In conclusion, through a series of studies and ratiocination, we showed that the augmentation index (AIx or AIx@75bpm) might not be a sensitive surrogate for a change in central pressure waveforms, which is a manifestation of change in large artery function. The limitation of AIx as an index of arterial stiffness is rooted in its formula, which has a clear mathematical flaw. (*Hypertens Res* 2007; 30: 713–722)

***Key Words*: arterial stiffness, augmentation index, diabetes, peritoneal dialysis, mathematics**

Introduction

The important role of abnormal large artery function in the pathogenesis of cardiovascular disease has been increasingly recognized in recent years. Physiologically, it is the waveform at the proximal aorta rather than the commonly measured peripheral blood pressure that determines left ventricular load and coronary blood flow (*1*). Clinical studies have also identified a strong relationship between the central waveform and left ventricular mass, an important independent predictor of all-cause mortality, in not only normotensive (*2*) but also hypertensive individuals (*3*, *4*).

In 1980, Murgo *et al*. first derived the augmentation index (AIx, defined as the ratio of augmentation to pulse pressure [PP]) from the aortic waveform and proposed three typical categories of shape in the ascending aortic pressure based on the AIx value (*5*). At first, AIx was determined invasively by intravascular catheterization. Thanks to Kelly and his colleagues, non-invasive measurement of the pulse waveform

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Table 1. Comparison of Variables between Diabetic (DM) and Non-Diabetic (Non-DM) CAPD Patients

	DM	Non-DM
No. of patients	55	141
Sex (female (%))	29 (52.7)	84 (59.6)
Age (years)	63±11	60±14
Height (cm)	161±9	160±8
Weight (kg)	64±11	61±10*
Dialysis vintage (months)	21±18	20±18
SBP (mmHg)	142±20	138±21
DBP (mmHg)	74±12	81±13‡
PP (mmHg)	68±20	57±19‡
Heart rate (bpm)	70±9	74±10†
AIx (%)	26.8±9.7	28.6±9.2
AIx@75bpm (%)	24.9±8.0	28.2±8.4*
AP (mmHg)	16±8	13±8
C-PP (mmHg)	53±16	44±14‡

CAPD, continuous ambulatory peritoneal dialysis; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; bpm, beats per minute; AIx, augmentation index; AIx@75bpm, augmentation index corrected by 75 bpm heart rate; AP, central augmentation pressure; C-PP, central pulse pressure. Between group comparisons: *$p<0.05$; †$p<0.01$; ‡$p<0.001$.

Table 2. Correlation between Peripheral Pulse Pressure and Derived Parameters in Central Waveforms

	Peripheral pulse pressure	
	Coefficient of correlation	p value
Age (years)	0.304	<0.001
Sex (male=1, female=2)	−0.05	0.484
Diabetes (yes=1, no=2)	0.281	<0.001
AIx (%)	0.185	<0.05
AIx@75bpm (%)	0.11	0.127
AP	0.723	<0.001
C-PP	0.951	<0.001
P_1	0.512	<0.001
P_2	0.686	<0.001

All were Pearson's correlation analysis except sex and diabetic status were analyzed with pulse pressure by Spearman's correlation. AIx, augmentation index; AIx@75bpm, augmentation index corrected by 75 bpm heart rate; AP, central augmentation pressure; C-PP, central pulse pressure; P_1, central initial peak; P_2, central reflective peak.

through applanation tonometry became possible in 1989 (*6*). However, this measurement was confined to the peripheral waveform at that time. In 1996, O'Rourke and Gallagher further advanced this technique by adopting a validated transfer function to generate the central arterial waveform (*7*) from recorded radial artery waveforms (*8*). Previous studies showed that the measurement of AIx by transfer function had good reproducibility (*9–11*), and numerous studies using AIx as a surrogate for arterial stiffness subsequently emerged in the literature (*12–17*). The Framingham Heart Study, for example, also employed AIx as an index of arterial stiffness (*18*).

Arterial stiffness is expressed by the pressure-strain elastic modulus (E_p), which is the pressure step required for (theoretical) 100% stretch from the resting diameter at fixed vessel length, *e.g.*, $E_p=(\Delta P\times D/\Delta D$ (mmHg) (*19*). Although AIx has been used more and more widely as an index of arterial stiffness, its validity is not without controversy (*20*). In recent years, some conflicting data have emerged (*21*, *22*), indicating that AIx is not always a reliable surrogate of arterial stiffness. Therefore, we here performed a series of studies to test the validity of AIx as a surrogate for arterial stiffness.

Methods and Results

Study 1: Assessment of the Validity of the AIx in Continuous Ambulatory Peritoneal Dialysis Patients

To investigate the arterial stiffness in peritoneal dialysis patients (a population known to be at high risk for cardiovascular morbidity and mortality), we employed radial applanation tonometry to obtain AIx in our center. For this cross-sectional study, we recruited 196 continuous ambulatory peritoneal dialysis (CAPD) patients who were undergoing treatment at the Peritoneal Dialysis Center of Peking University First Hospital. This study was approved by the ethics committee of Peking University First Hospital and written informed consent was obtained from all patients. The measurement was performed with a Millar piezoresistive pressure transducer (SPC-301; Millar Instruments, Houston, USA) connected to an arterial waveform analysis device (SphygmoCor v7; AtCor Medical, Sydney, Australia). This device transforms the pressure recorded at the radial artery into aortic pressure by means of the transfer function (TF). The TF between aortic pressure and radial pressure signals was derived by a linear autoregressive exogenous model (ARX model). The linear ARX model is a parametric model that can describe the properties of a system based on its immediate past input and output data. Chen *et al*. compared the ARX model with nonparametric methods, *e.g.*, TF estimation by Fourier transform (*8*). They observed that the ARX estimation had less variance, although the results were similar between the two methods (*8*). Any pressure waveform data not achieving the

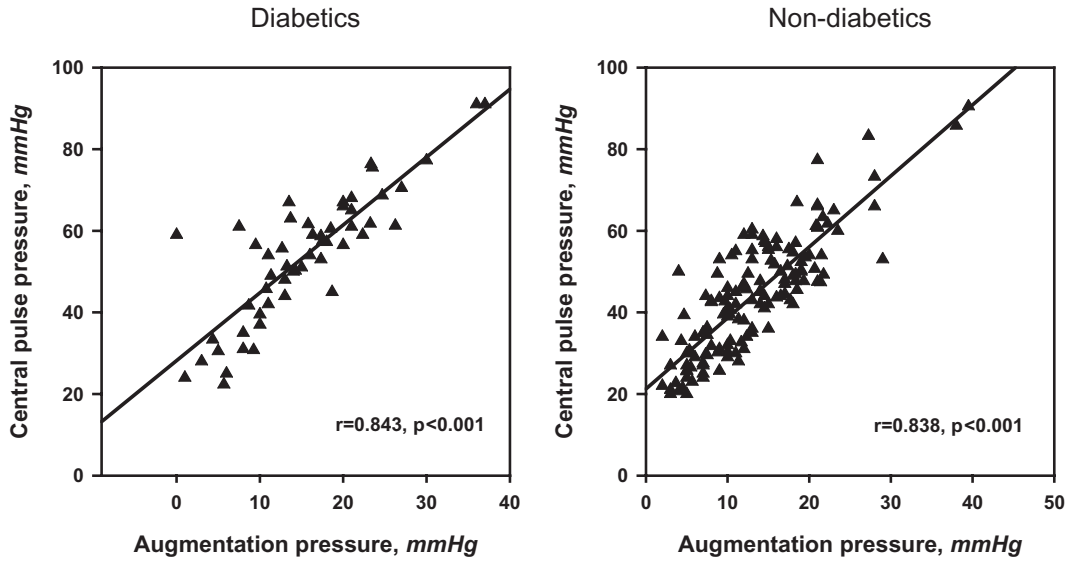

Fig. 1. *Pearson's correlation between augmentation pressure and central pulse pressure in diabetic and non-diabetic peritoneal dialysis patients.*

specified automatic quality controls of the SphygmoCor software were rejected (*22*). The aortic waveform was analyzed by the SphygmoCor software system to identify central augmentation pressure (AP) and then calculate AIx. Because AIx could be influenced significantly by heart rate (*23*), it was also corrected for a 75 bpm heart rate (AIx@75bpm) by the SphygmoCor software automatically. The mean value of three consecutive measurements was taken for each subject. All measurements were performed by the same investigator (H.Y.H.) to avoid inter-observer error. The intra-observer CV was about 5% for AIx (range, from 1.6% to 7.8%).

The study aimed to compare AIx between diabetic and non-diabetic CAPD patients. It is well known that diabetic CAPD patients have higher cardiovascular mortality than non-diabetic patients (*24*, *25*), and thus it is reasonable to hypothesize that diabetics also have harder arterial stiffness compared with their non-diabetic counterparts. Table 1 shows the comparison between the two groups. All the well-known confounding factors for AIx, such as age, gender distribution and body height, were well matched between the two groups. To our surprise, both AIx and AIx@75bpm were lower in diabetic patients than in non-diabetic patients. This obvious contradiction to our hypothesis was not easily understood at first. Nevertheless, other arterial stiffness surrogates showed the expected results; for example, AP and central pulse pressure (C-PP) were higher in diabetic patients than in non-diabetic patients (Table 1). In addition, peripheral PP, the traditional arterial stiffness surrogate in old people (*26–28*), showed the same trend (PP was significantly higher in diabetic patients than in non-diabetic patients, $p < 0.001$). To test the validity of the value of AIx for evaluating arterial stiffness, we performed correlation analysis between peripheral PP and parameters derived from central waveforms and determined that there was only a weak positive correlation between peripheral PP and AIx, as shown in Table 2. In addition, when AIx was corrected for a 75 bpm heart rate, the weak correlation between peripheral PP and AIx@75bpm disappeared. On the other hand, there were strong positive correlations between peripheral PP and each of AP, C-PP, the central initial peak (P_1) and the central reflective peak (P_2). The disassociation between AIx and other markers of arterial stiffness was not unique to our study. In another study in diabetics, Lacy *et al*. employed both AIx and pulse wave velocity (PWV) simultaneously to evaluate arterial stiffness in diabetic patients and non-diabetic patients (*22*). PWV was used as a direct measure of arterial stiffness. The authors found that diabetes was associated with increased PWV, but the difference of AIx between diabetic and non-diabetic patients was not significant, even after adjustment of the heart rate (*22*). The disassociation between PWV and AIx was also observed by Lemogoum *et al*. during β-adrenergic stimulation with isoprenaline (*29*).

Suspicion and Hypothesis

On the surface, our results and those of other authors suggested that AIx and AIx@75bpm might not be sensitive surrogates for evaluating arterial stiffness, but the reason for this finding required further consideration. According to basic physiological principles, it was easy to understand why higher peripheral PP would consistently be associated with higher AP and C-PP, as shown in Table 2. Because both AP and C-PP were used to calculate AIx, it was possible that the quotient (AIx) would not necessarily increase in patients who

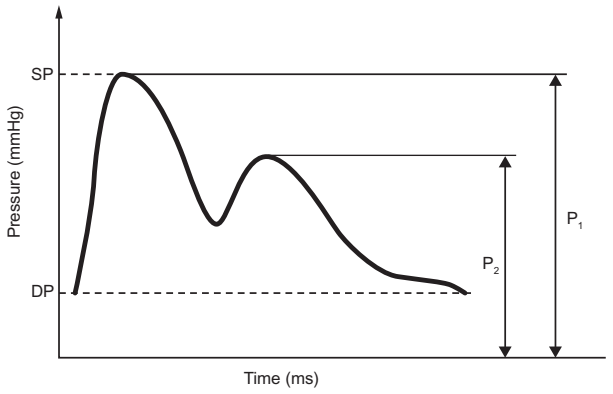

Fig. 2. *Typical waveform of central aortic pressure in young people (<40 years old). P_1, central initial peak, generated by cardiac ejection; P_2, central second peak, generated by reflective wave; SP, central systolic blood pressure; DP, central diastolic blood pressure.*

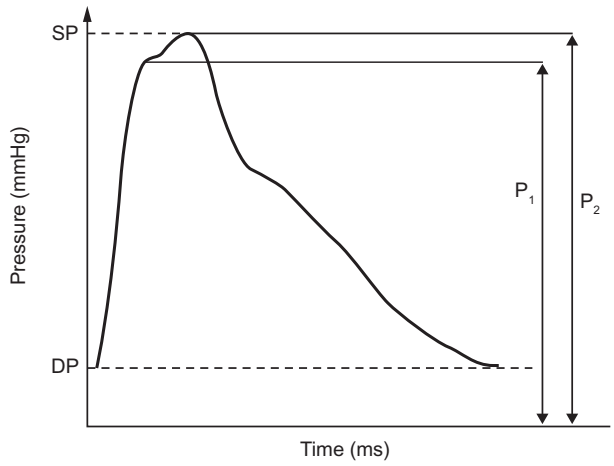

Fig. 3. *Typical waveform of central aortic pressure in old people (≥40 years old). P_1, central initial peak, generated by cardiac ejection; P_2, central second peak, generated by reflective wave; SP, central systolic blood pressure; DP, central diastolic blood pressure.*

had increased arterial stiffness if both the numerator and denominator increase simultaneously. To test this possibility, we also investigated the correlation between AP and C-PP in these patients. The results showed that AP was highly and positively correlated with C-PP ($r=0.836$, $p<0.001$), and this close association between AP and C-PP could be observed in both diabetic and non-diabetic dialysis patients when separate analyses were performed (Fig. 1). The results of the correlation analysis strongly suggested that AIx could potentially minimize the degree of arterial stiffness, because two highly correlated variables were used as the numerator and denominator in its formula. Thus, an inherent limitation in the formula used to calculate AIx was highly suspected. If present, such a limitation would properly explain the contradictory results in the present and previous studies. This suspicion prompted us to test the validity of the AIx formula through a mathematical approach.

Study 2: Mathematical Investigation of the AIx Formula

The central arterial pressure wave is composed of a forward traveling wave (P_1, generated by left ventricular ejection) and a later arriving reflected wave (P_2, generated by the reflection from the periphery). The amplitude of central arterial pressure waveforms varies significantly among different age groups (*5*, *30*, *31*). The typical waveforms of young people (<40 years) and old people (≥40 years) are illustrated in Figs. 2 and 3, respectively. In young healthy people, because the large arteries are compliant, the initial systolic pressure wave (P_1) traveling from the heart to the periphery is responsible for the central peak systolic blood pressure (SP). The reflected pressure wave (P_2) arrives at the central aorta in diastole, augmenting the central diastolic blood pressure (DP) and coronary artery filling. Thus in young healthy people, P_2 is lower than P_1 (negative AP). In old people, as the large arteries stiffen, wave reflection occurs earlier and falls into systole, leading to increased P_2. P_2 thus becomes higher than P_1 (positive AP). As an index to evaluate arterial stiffness, AIx should in theory reflect the changes in central aortic pressure waveforms. Increased arterial stiffness would lead to increased AP and thereby to increased P_2. However, which of AP and P_2 is the better representative of arterial stiffness remains a matter of controversy. For the present consideration of the AIx formula, therefore, we assumed that an increase in either AP or P_2 was equally effective at representing arterial stiffness.

In this case, the principle of mathematical ratiocination is apagogic: if the increase or decrease in AP or P_2 is reflected by a corresponding increase or decrease in the quotient (AIx), then the formula for calculating AIx is logically sound; but if AIx does not reflect the change in AP or P_2, then the AIx formula should be considered as having an inherent flaw.

Mathematic Ratiocination

The mathematical ratiocinations of the AIx formula in younger and older people are shown in the Appendix. These mathematical ratiocinations clearly showed that the change in AIx was not determined by either the change of any single variable (P_2, P_1, SP and DP) or any component (AP and C-PP) in the AIx formula, but by the final values of a series of variables in the Eq. (2).

Table 3 shows the changes in AIx under different arterial pressure waveforms based on Eqs. (3) and (5). Similarly, Table 4 shows the changes in AIx under different values of AP based on Eqs. (4) and (6).

Table 3. Various Combinations of Changes in Central Pressure Waveforms and Corresponding Changes in AIx According to Eqs. (3) and (5) in Appendix

Age and condition	ΔP_1	ΔP_2	ΔSP	ΔDP	ΔAIx	SP and AIx have the same changing direction
Less than 40 years old						
I	—	≥0	≥0	≥0	Dependent on F	If $F\geq 0$, then True
						If $F<0$, then False
II	—	≥0	≥0	≤0	Dependent on F	If $F\geq 0$, then True
						If $F<0$, then False
III	—	≥0	≤0	≥0	Dependent on F	If $F\leq 0$, then True
						If $F>0$, then False
IV	—	≥0	≤0	≤0	≥0	False
V	—	≤0	≥0	≥0	≤0	False
VI	—	≤0	≥0	≤0	Dependent on F	If $F\geq 0$, then True
						If $F<0$, then False
VII	—	≤0	≤0	≥0	Dependent on F	If $F\leq 0$, then True
						If $F>0$, then False
VIII	—	≤0	≤0	≤0	Dependent on F	If $F\leq 0$, then True
						If $F>0$, then False
More than 40 years old						
IX	≥0	—	≥0	≥0	Dependent on F	If $F\geq 0$, then True
						If $F<0$, then False
X	≥0	—	≥0	≤0	Dependent on F	If $F\geq 0$, then True
						If $F<0$, then False
XI	≥0	—	≤0	≥0	Dependent on F	If $F\leq 0$, then True
						If $F>0$, then False
XII	≥0	—	≤0	≤0	≤0	True
XIII	≤0	—	≥0	≥0	≥0	True
XIV	≤0	—	≥0	≤0	Dependent on F	If $F\geq 0$, then True
						If $F<0$, then False
XV	≤0	—	≤0	≥0	Dependent on F	If $F\leq 0$, then True
						If $F>0$, then False
XVI	≤0	—	≤0	≤0	Dependent on F	If $F\leq 0$, then True
						If $F>0$, then False

AIx, augmentation index; Δ, changes; P_1, central initial peak; P_2, central second peak; SP, systolic blood pressure; DP, diastolic blood pressure.

Study 3: Counterexample of AIx Formula in Clinical Data

The mathematical ratiocination above clearly demonstrated that an increase in AP or P_2 will not necessarily lead to an increase in the AIx quotient, and *vice versa*. In fact, the change of AIx was dependent on F—which was otherwise determined by the final value of five variables: $\Delta P_2\times(\mathrm{SP}-\mathrm{DP})+(-\Delta\mathrm{SP})\times(P_2-\mathrm{DP})+(-\Delta\mathrm{DP})\times(\mathrm{SP}-P_2)$ in young people and $(-\Delta P_1)\times(\mathrm{SP}-\mathrm{DP})+\Delta\mathrm{SP}\times(P_1-\mathrm{DP})+\Delta\mathrm{DP}\times(\mathrm{SP}-P_1)$ in old people. In other words, the AIx formula could not always reflect the change in central arterial waveforms, which suggested that the AIx formula had an inherent mathematical flaw. However, this mathematical ratiocination was based on a series of assumptions: *e.g.*, that DP and P_1 changed along with P_2 and AP. Whether or not these assumptions are correct should be investigated using clinical data. We therefore checked the longitudinal data in our patients and found a number of counterexamples to refute the rationality of the AIx formula. Figure 4 provides an example that supports the results in Tables 3 and 4. In this case, both P_2 (SP) and AP longitudinally increased in the same patient, while P_1 increased and DP decreased slightly, leading to noticeable decreases in both AIx and AIx@75bpm, which supported the idea that condition X in Table 3 was operative.

Discussion

This study demonstrated that the augmentation index (AIx or AIx@75bpm) was not a sensitive surrogate for a change in central pressure waveforms, which is a manifestation of change in large artery function. The limitation of AIx as an

Table 4. Various Combinations in Changes of Augmentation Pressure and Corresponding Changes in AIx According to Eqs. (4) and (6) in Appendix

Age and condition	$\Delta SP-\Delta DP$	$\Delta DP-\Delta P_1$	$\Delta DP-\Delta P_2$	ΔAIx	(SP−DP) and AIx have the same changing direction
Less than 40 years old					
I	≥0	—	≥0	≤0	False
II	≥0	—	≤0	Dependent on F	If $F\geq 0$, then True If $F<0$, then False
III	≤0	—	≥0	Dependent on F	If $F\leq 0$, then True If $F>0$, then False
IV	≤0	—	≤0	≥0	False
More than 40 years old					
V	≥0	≥0	—	≥0	True
VI	≥0	≤0	—	Dependent on F	If $F\geq 0$, then True If $F<0$, then False
VII	≤0	≥0	—	Dependent on F	If $F\leq 0$, then True If $F>0$, then False
VIII	≤0	≤0	—	≤0	True

Abbreviations are the same as in Table 3.

index of arterial stiffness is rooted in its formula, which was found to have a clear mathematical flaw.

The formula for calculating AIx was first proposed by Murgo *et al*. in 1980 (*5*). In his original study, Murgo *et al*. grouped their patients according to the magnitude of ΔP/PP and stated "this was an obvious differentiating factor based on the pressure wave forms," which might be the earliest ratiocination of the AIx formula. Thereafter, AIx was increasingly accepted as a standard formula to evaluate arterial stiffness, despite the fact that the formula was never validated mathematically. In 1989 Kelly *et al*. employed an invasive evaluation of arterial pressure waves (*32*), but still did not provide any ratiocination. Subsequently investigators using this formula to study arterial stiffness might have to a large extent taken the formula for granted.

Why Was the AIx Formula Not Mathematically Ratiocinated for So Long?

We believe there are several possible reasons for the failure to ratiocinate the AIx formula. 1) The AIx formula seemed to be self-evident. This view is well expressed by the following comment from a review (*33*) on the assessment of large artery function: "Assessment of AIx has appeal however because, as a ratio, it is dimensionless and obviates the need for scaling of non-invasively obtained pressure waveforms, a potential cause of error." 2) The inherent flaw in the AIx formula was latent. Most of the studies using AIx to evaluate arterial stiffness showed that AIx could be considered a reliable index. Previous studies showed that AIx increased with advancing age (*18*) and was closely associated with known risk factors for cardiovascular disease, such as diabetes (*14*), hypercholesterolemia (*34*), smoking (*35*) and left ventricular hypertrophy (*36*). These results seemed quite logical in terms of physiological principles, and thus may have tended to minimize or dampen any suspicions of the AIx formula. 3) Conflicting data were always ascribed to a limitation of the generalized transfer function. The transfer function was crucial for the non-invasive measurement of central pressure waveform; however, since its first introduction as a means of generating central pressure waveforms, it has been subject to much doubt and criticism (*37*). Some studies did find that AIx was not consistent with their well-expected hypotheses, but these results were usually attributed to a limitation of the transfer function (*38*, *39*). 4) Publication bias might also have play a role. It is commonplace that positive studies are more readily published, while those with negative implications have far fewer opportunities to appear in the literature (*40*, *41*), and this may have affected the objective evaluation of AIx and the formula used to calculate it.

Rationale of the Mathematical Disproof

In the above mathematical ratiocination, we assumed that the change in P_2 was the major manifestation of the change in large artery function, though we also provided additional data for the case in which AP was considered a typical manifestation. To understand these assumptions, we need to discuss how these central pressure parameters would change when arterial stiffness worsened.

Changes in P_1 with Increasing Arterial Stiffness

In theory, P_1 would increase with advancing age. This is because when the aorta becomes increasingly stiffened, its buffer function would be expected to decrease, and thus the ejection pressure would be reflected more adequately, pro-

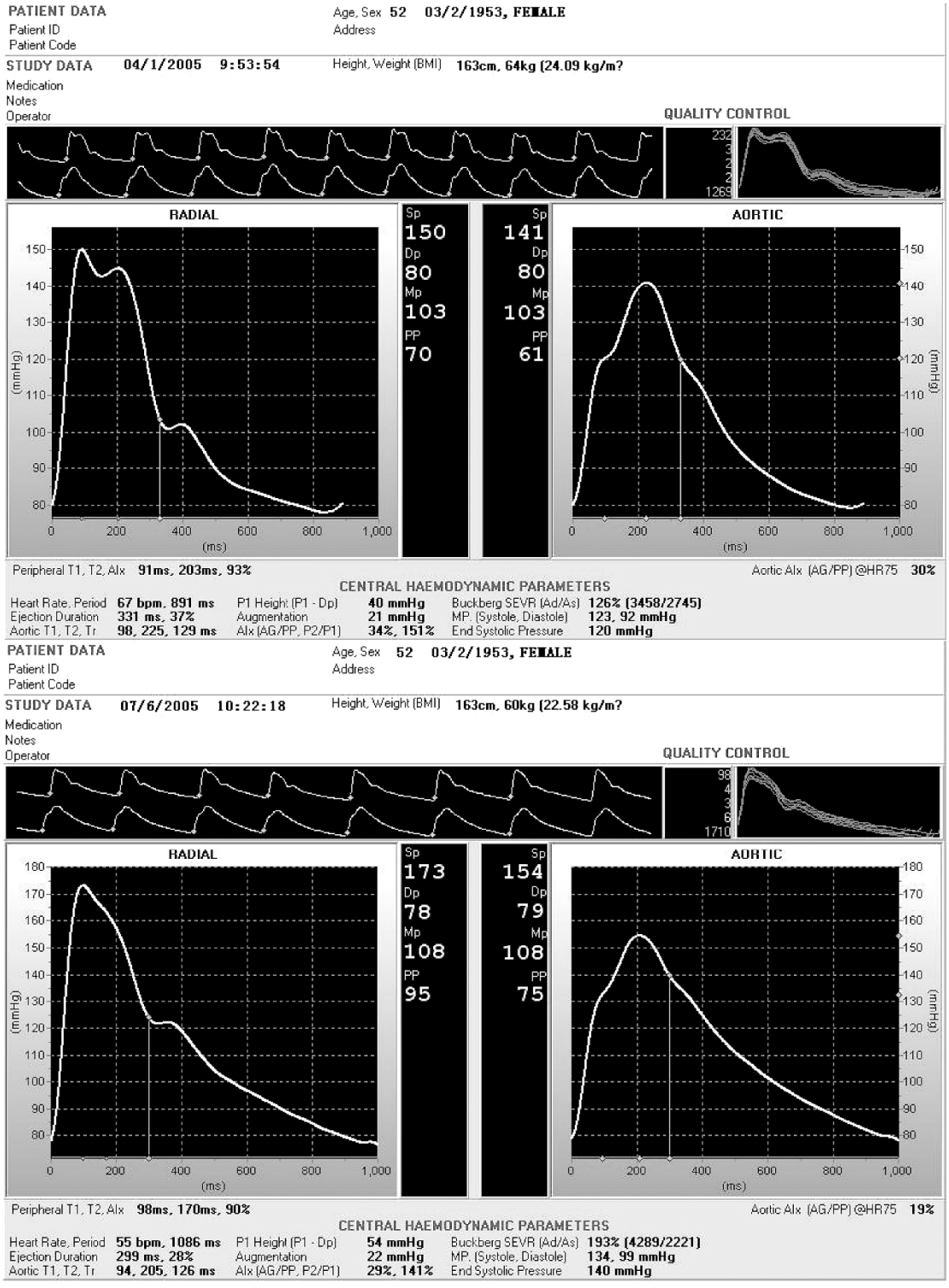

Fig. 4. *Clinical counterexample to refute the validity of the formula used to calculate AIx in the case of condition X in Table 3.*

vided there is no significant change in cardiac function during this process. Previous studies have confirmed that P_1 does indeed increase with advancing age. Using applanation tonometry, Kelly *et al*. observed that carotid P_1 was higher in the eighth than in the first decade of life. However, it seemed there was no linear change of P_1 with age (*6*). This was possibly due to the relatively loose inclusion criteria in this study: only subjects with valvular heart disease or chronically

treated cardiovascular disease were excluded. On the other hand, in the recent Framingham study, which was conducted in a healthy sample with no evidence of cardiovascular disease and a low burden of risk factors, Mitchell *et al*. observed an increase of carotid P_1 in almost all subjects, irrespective of sex (*18*).

Changes in P_2 with Increasing Arterial Stiffness

It is generally accepted that P_2 increases as the aorta becomes increasingly stiffened. When arterial stiffness decreases with advancing age, the buffer function of the aorta also decreases, leading to accelerated travel of the initial wave (P_1) in the arterial tree. Thus, the pressure wave arrives at the peripheral reflection site more quickly and subsequently travels back to the central aorta earlier. The earlier arriving reflective wave falls in systole and is superposed on the already increased P_1, resulting in a more remarkable increase in P_2 (*30*, *31*). Indeed, an age-related increase in P_2 has been repeatedly observed in separate studies, such as those by Kelly *et al*. in 1989 (*6*) and Mitchell *et al*. in 2004 (*18*). Therefore, in the present study, the increase in P_2 was assumed to be a major manifestation of increased arterial stiffness in the mathematical ratiocination.

Changes in AP with Increasing Arterial Stiffness

Whether AP changes with advancing age remains somewhat controversial. The study by Kelly *et al*. observed a steady increase of carotid AP from the first to the eighth decade of life (*6*). However, the Framingham study observed this phenomenon only in men, while in women, an initial increase and a later fall of AP was observed (*18*). We believed that whether AP increases with age is most likely dependent on the relative change of P_1 and P_2. As described above, both P_1 and P_2 would increase with increasing arterial stiffness. Because AP is calculated as $P_2 - P_1$, the actual change in AP is determined by its divisor and dividend. From this line of reasoning, it follows that AP would not be as effective as P_2 in representing the change of arterial stiffness. However, further studies are warranted to examine this important issue.

Change in DP with Increasing Arterial Stiffness

It remains unclear how increasing arterial stiffness affects DP. Previous studies have tended to neglect this important parameter. The increase in C-PP along with the increase of arterial stiffness could not be simply interpreted as the result of decreased DP, because P_2 also increased during this process. The data in our longitudinal study showed that DP tended to increase when P_2 was increasing. However, there were also examples showing unchanged or even decreased DP when P_2 was increasing in our longitudinal data (data not shown). Further studies will be needed to address this important issue.

Based on the above assumptions and the employed mathematic apagogic method, we were able to prove that irrespective of whether AP or P_2 increased or decreased, AIx would not necessarily show corresponding changes. In fact, the change of AIx is actually dependent on F—which is determined by the final value of five variables: $\Delta P_2 \times (\mathrm{SP}-\mathrm{DP}) + (-\Delta \mathrm{SP}) \times (P_2 - \mathrm{DP}) + (-\Delta \mathrm{DP}) \times (\mathrm{SP} - P_2)$ in young people and $(-\Delta P_1) \times (\mathrm{SP}-\mathrm{DP}) + \Delta \mathrm{SP} \times (P_1 - \mathrm{DP}) + \Delta \mathrm{DP} \times (\mathrm{SP} - P_1)$ in old people. These results clearly demonstrated that there is inherent flaw in the formula for calculating AIx, which might help to explain the conflicting results among previous studies using AIx as a surrogate of arterial stiffness.

In conclusion, through a series of studies and ratiocination, we showed that the augmentation index (AIx or AIx@75bpm) might not be a sensitive surrogate for a change in central pressure waveforms, which is a manifestation of change in large artery function. The limitation of AIx as an index of arterial stiffness is rooted in its formula, which has a clear mathematical flaw.

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Appendix

The AIx was defined as the ratio of augmentation to PP and was expressed as a percentage according to the following formulae:

$$\mathrm{AIx} = (P_2 - P_1)/\mathrm{PP}; \quad (1)$$

$$\mathrm{PP} = \mathrm{SP} - \mathrm{DP}.$$

Where PP means C-PP, SP means central systolic pressure, and DP means central diastolic pressure. These acronyms are also applied in the following discussion.

We can assume two groups of data. The first group is SP, DP, P_1, P_2 and AIx (1), where AIx (1)$=(P_2 - \mathrm{SP})/(\mathrm{SP} - \mathrm{DP})$; the second group is $\mathrm{SP} + \Delta \mathrm{SP}$, $\mathrm{DP} + \Delta \mathrm{DP}$, $P_1 + \Delta P_1$, $P_2 + \Delta P_2$ and AIx (2), where AIx (2)$= [(P_2 + \Delta P_2) - (P_1 + \Delta P_1)]/[(\mathrm{SP} + \Delta \mathrm{SP}) - (\mathrm{DP} + \Delta \mathrm{DP})]$.

Thus, when

$$[(P_2 + \Delta P_2) - (P_1 + \Delta P_1)]/[(\mathrm{SP} + \Delta \mathrm{SP}) - (\mathrm{DP} + \Delta \mathrm{DP})] > (P_2 - P_1)/(\mathrm{SP} - \mathrm{DP}),$$

$$\mathrm{AIx}(2) > \mathrm{AIx}(1);$$

and when

$$[(P_2 + \Delta P_2) - (P_1 + \Delta P_1)] \times (\mathrm{SP} - \mathrm{DP}) > [(\mathrm{SP} + \Delta \mathrm{SP}) - (\mathrm{DP} + \Delta \mathrm{DP})] \times (P_2 - P_1),$$

$$\mathrm{AIx}\ (2) > \mathrm{AIx}\ (1),$$

if and only if

$$(\Delta \mathrm{SP} - \Delta \mathrm{DP}) \times (P_1 - P_2) + (\Delta P_2 - \Delta P_1) \times (\mathrm{SP} - \mathrm{DP}) > 0,$$

$$\mathrm{AIx}\ (2) > \mathrm{AIx}\ (1).$$

According to the above, we can assume a polynomial F defined as

$$F = (\Delta \mathrm{SP} - \Delta \mathrm{DP}) \times (P_1 - P_2) + (\Delta P_2 - \Delta P_1) \times (\mathrm{SP} - \mathrm{DP}). \quad (2)$$

Based on Eq. (2), the mathematical ratiocination of the AIx formula in younger and older people could be performed as follows.

In younger people (<40 years old):

$$P_1 = \mathrm{SP}, \qquad \Delta P_1 = \mathrm{SP}.$$

According to Eq. (2),

$$F_y = F|_{\text{when people are younger}} = \Delta P_2 \times (\mathrm{SP} - \mathrm{DP}) + (-\Delta \mathrm{SP}) \times (P_2 - \mathrm{DP}) + (-\Delta \mathrm{DP}) \times (\mathrm{SP} - P_2), \quad (3)$$

$$F_y = [-(\Delta \mathrm{SP} - \Delta \mathrm{DP})] \times (P_2 - \mathrm{DP}) + [-(\Delta \mathrm{DP} - \Delta P_2)] \times (\mathrm{SP} - \mathrm{DP}), \quad (4)$$

$$\mathrm{SP} - \mathrm{DP} > 0, \qquad P_2 - \mathrm{DP} > 0, \qquad \mathrm{SP} - P_2 > 0.$$

In older people (≥40 years old):

$$P_2 = \mathrm{SP}, \qquad \Delta P_2 = \Delta \mathrm{SP}.$$

According to Eq. (2),

$$F_o = F|_{\text{when people are older}} = (-\Delta P_1) \times (\mathrm{SP} - \mathrm{DP}) + \Delta \mathrm{SP} \times (P_1 - \mathrm{DP}) + \Delta \mathrm{DP} \times (\mathrm{SP} - P_1), \quad (5)$$

$$F_o = (\Delta \mathrm{SP} - \Delta \mathrm{DP}) \times (P_1 - \mathrm{DP}) + (\Delta \mathrm{DP} - \Delta P_1) \times (\mathrm{SP} - \mathrm{DP}), \quad (6)$$

$$\mathrm{SP} - \mathrm{DP} > 0, \qquad P_1 - \mathrm{DP} > 0, \qquad \mathrm{SP} - P_1 > 0.$$

The mathematical ratiocinations showed that irrespective of age, the changes in AIx could not be predicted by changes either in single variable or in multiple variables in the AIx formula. Instead, the changes in AIx in younger people were determined by Eq. (3) or (4), while in older people, they were determined by Eq. (5) or (6). These results indicated that the increase in P_2 or AP would not necessarily lead to a corresponding increase in AIx, and *vice versa*.

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