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RADIAL DIASTOLIC AUGMENTATION INDEX IS A USEFUL PREDICTOR OF ARTERIAL STIFFNESS

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Diastolic augmentation index (DAI), calculated from radial artery pressure waveform, has been associated with the risk of cardiovascular disease. In the present study, we aimed to evaluate whether DAI could be used as a predictor of arterial stiffness and the effect of heart rate (HR) on it. Measurements of anthropometric parameters, blood pressure (BP), Augmentation index (AI) and DAI were taken in 242 healthy subjects (130 men and 112 women; age 16−78 years). DAI and AI were measured in a subgroup of 16 subjects (10 men and 6 women; age 19−69 years) in a two-month follow-up study, which aimed to investigate the effect of HR changes. Statistically, DAI was higher in women compared to men ($44.8\% \pm 7.7\%$ compared with $43.6\% \pm 6.9\%$, $P < 0.05$). DAI was decreased with age (men: $r = -0.755$, $P < 0.05$; women: $r = -0.708$, $P < 0.05$) and negatively correlated to AI (men: $r = -0.704$, $P < 0.05$; women: $r = -0.756$, $P < 0.05$). There was no significant change in DAI when HR ranged from 60 to 80 bpm. Multiple regression analysis demonstrated fewer determinants affect DAI compared with AI. These findings indicate that the simple radial DAI might be used as an index to assess vascular aging.

Keywords: Radial diastolic augmentation index; arterial stiffness; heart rate; vascular aging.

1. Introduction

Arterial stiffness has been recognized as an important determinant of cardio-vascular risk. Augmentation index (AI) is widely used as an indicator of arterial

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stiffness.[1,2] It has been reported that AI obtained from radial artery pressure waveform is one of only a few noninvasive indices for vascular assessments.[3,4] Radial AI, a measure of wave reflection intensity, is defined as the difference of the first systolic peak and the second systolic peak.[5] However, in young adults and older subjects, the calculations of AI, forward and reflected pressure wave amplitudes, and averaged distance to wave reflection site are based on inflection point identification, and hence are suspect.[6] Therefore, we study a simple non-invasive acquired parameter Diastolic augmentation index (DAI) which is also obtained from radial arterial waveform. It originated due to elastic recoil of arterial wall during the early diastole, calculated as the ratio of the third systolic blood pressure to the first systolic peak,[7] and can be quantified by applying to second-derivative approach.[8,9] The parameter is applied to evaluate some diseases and has also been shown to correlate with the extent of coronary artery disease.[7,10]

As arteries lost their elasticity, the velocity of pulse wave and the amplitude of the reflected wave increased. This caused the changes in the pulse waveform, especially in the diastolic, dicrotic part.[11,12] The dicrotic wave, which is of central origin, followed the dicrotic notch, and takes place as the result of a reflection of a pressure wave from the aortic valves and neighboring walls of the larger vessels,[13] has long been described as a physical sign associated with low cardiac output, and has also been found in association with cardiomyopathy,[14,15] the change of the amplitude of dicrotic wave is determinated by the DAI. In previous studies, AI was influenced by heart rate (HR).[16] Our hypotheses suggest radial DAI might also be influenced by HR. Therefore, the aim of this study was to investigate the relationship between DAI and age and AI in healthy subjects and whether or not HR changes influenced DAI.

2. Methods

2.1. *Subjects*

First, a total of 266 apparently healthy subjects (age range: 16−78 years) which have neither record of cardiovascular disease nor regular prescribed medication were considered for enrollment in to this study. To be eligible for the study, people should be rigorously screened under the following constraints: first, Pulse pressure (PP, the difference between the systolic and diastolic pressure) was between 20 mmHg and 60 mmHg; second, Body mass index (BMI) was less than $25 \, kg/m^2$. Finally, the subjects (N = 242) of healthy volunteers were recruited. A subgroup of 16 subjects (10 men and 6 women) had a two-month follow-up study, in which each subject took the measurements of AI and DAI thrice every day (at AM 9:00, PM 1:00 and PM 5:00, separately). The study was approved by the local Institutional Review Board. And all subjects gave the written informed consent.

2.2. *Measurements*

2.2.1. *Blood pressure measurements*

After taking the measurements of height and body mass and 10 min of rest, with the subject lying in the supine position in a quiet room, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured on the left wrist using a validated, automatic, oscillometric wrist Sphygmomanometer (HEM-6000; Omron Healthcare Co., Ltd., Kyoto, Japan). The PP was calculated as the difference between SBP and DBP.

2.2.2. *Radial-derived parameters*

Radial pulse wave was recorded from the left radial artery of the wrist with the applanation tonometry-based automated vascular testing device (IIM-2010A; Institute of Intelligent of Machines, Hefei, China).

The IIM-2010A device was programmed to determine automatically the pressure against the radial artery to obtain the optimal radial arterial waveform. 10 seconds of consistent radial arterial waveforms were recorded, the first, second and third systolic peaks of which were automatically detected by using algorithms of the device based on a band-pass filtering ($0.02-80\,\mathrm{Hz}$) and peak detection algorithm. The amplitude of the first and third systolic peaks was calculated and averaged value was reported as DAI.

Radial DAI and AI were calculated as follows[5,7]:

$$DAI = (P3 - DBP)/(SBP - DBP) \tag{1}$$
$$AI = (P2 - DBP)/(SBP - DBP) \tag{2}$$

DBP was diastolic blood pressure. SBP was systolic blood pressure. P3 was the third systolic blood pressure and P2 was the second systolic pressure showed in Fig. 1.

2.3. *Data analysis*

All values were expressed as the form of mean $\pm$ SD if not specified. The difference between men and women was evaluated based on the variance (ANOVA). Multiple linear regression analysis for DAI and AI were performed with the following parameters: age, gender, SBP, DBP, heart rate, body height, body weight, and BMI. An analysis of covariance (ANCOVA) was performed with radial DAI as the dependent variable and HR as covariate. The effect of HR on AI and DAI was tested by one-way, within-subjects ANOVA with repeated measurements. A least significant difference (LSD) post hoc analysis with a LSD test was performed to determine which levels of HR led to significant changes in AI and DAI. The test reliability of radial DAI and AI were evaluated using the intra-class correlation (ICC) coefficient.[17] An ICC equal to or greater than 0.70 was considered acceptable for test−retest reliability.[18] A probability value of $P < 0.05$ was considered to be statistically significant.
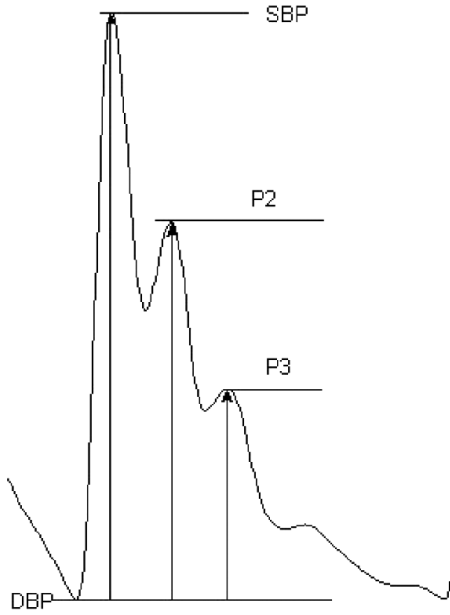
Fig. 1. Radial artery pulse waveform. DBP was diastolic blood pressure. SBP was the first systolic blood pressure. P3 was the third systolic blood pressure and P2 was the second systolic pressure.

3. Results

Characteristics of the study population are listed in Table 1. The mean age was 37.2 ± 15.8 years (range from 16 to 78 years). The radial DAI was higher in women than men ($44.8\% \pm 7.7\%$ compared with $43.6\% \pm 6.9\%$, $P < 0.05$).

Table 1.   Selected characteristics of the study population.

Parameter	Male ($n=130$)	Female ($n=112$)	P values
Age (years)	38.9 ± 16.6	35.2 ± 14.6	0.065
Height (cm)	171.0 ± 5.4	160.5 ± 4.3	0.000
Weight (kg)	63.5 ± 7.5	53.3 ± 5.9	0.000
BMI (kg/m^2)	21.7 ± 2.1	20.7 ± 2.1	0.000
SBP (mmHg)	114.4 ± 11.3	108.6 ± 10.6	0.000
DBP (mmHg)	72.0 ± 9.2	68.9 ± 7.4	0.005
PP (mmHg)	42.4 ± 6.1	39.7 ± 6.8	0.001
HR (bpm)	71.1 ± 10.1	76.3 ± 10.2	0.000
AI (%)	67.1 ± 9.1	68.6 ± 7.2	0.042
DAI (%)	43.6 ± 6.9	44.8 ± 7.7	0.001

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; HR = heart rate; AI = augmentation index; DAI = diastolic augmentation index; Values are mean $\pm$ SD.

3.1. *Radial DAI and age*

Figure 2 illustrates the relationship between radial DAI and age. There was a significant negative correlation between age and DAI in men and women ($r = -0.755$ and $r = -0.708$, respectively, $P < 0.05$ for both). Age-related changes in DAI, expressed as mean value in each decade of life, were also shown in Fig. 2(b). There were significant age-dependent decreases in radial DAI from 20 to 30 years in men and women. In addition, an age dependent significant decrease in DAI was observed from the age groups of 40−50 and 60−70 in females, and 30's−40's and 50's−60's in males.
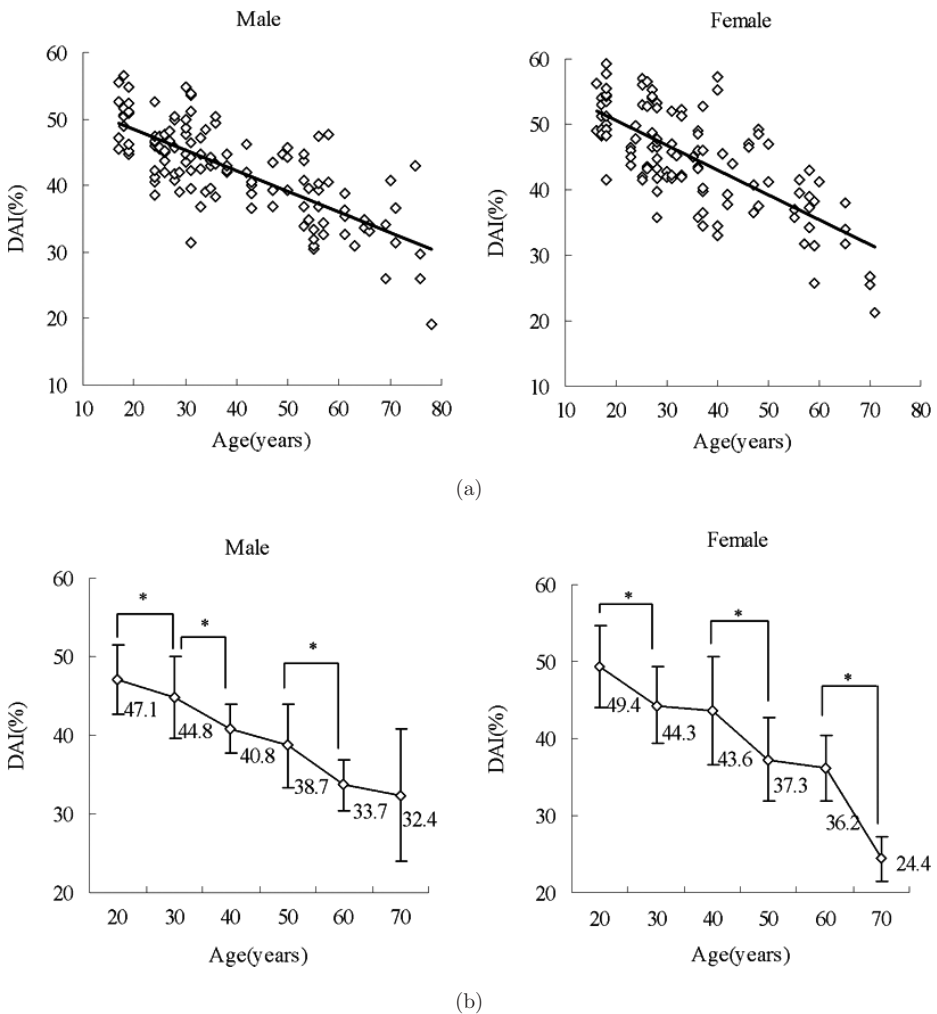

(a)

(b)

Fig. 2. (a) The correlation between the radial DAI and the age in male ($r = -0.755$, $P < 0.05$) and female ($r = -0.708$, $P < 0.05$). (b) Age-related changes in men and women were shown for each decade. Values are means $\pm$ SD. *$P < 0.05$ between age groups.
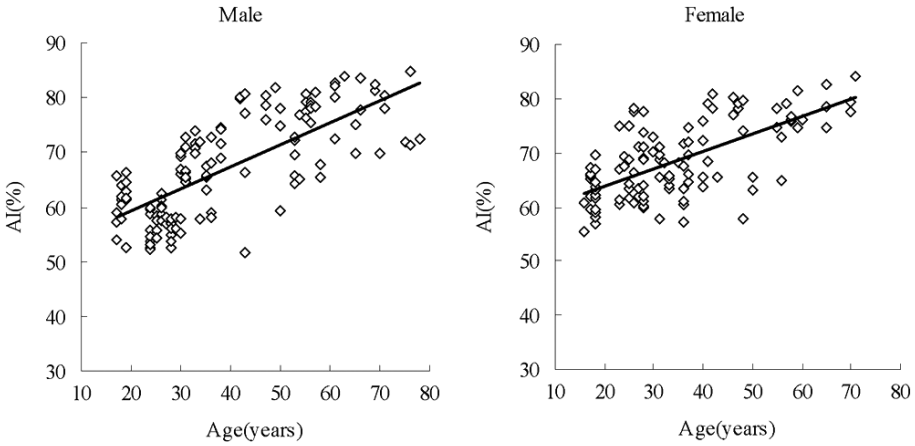
Fig. 3. Correlation between radial AI and age in men ($r = 0.734$, $P < 0.05$) and women ($r = 0.665$, $P < 0.05$).

3.2. *Radial AI and age*

Figure 3 depicts the relationship between radial AI and age. There was a significant positive correlation between age and radial AI in men and women ($r = 0.734$ and $r = 0.665$, respectively, $P < 0.05$ for both).

3.3. *Radial DAI and AI*

Figure 4 illustrates the correlation between DAI and radial AI determined by the device. The DAI showed a highly significant correlation with the radial AI ($r = 0.704$ and $r = 0.756$, respectively, $P < 0.05$).
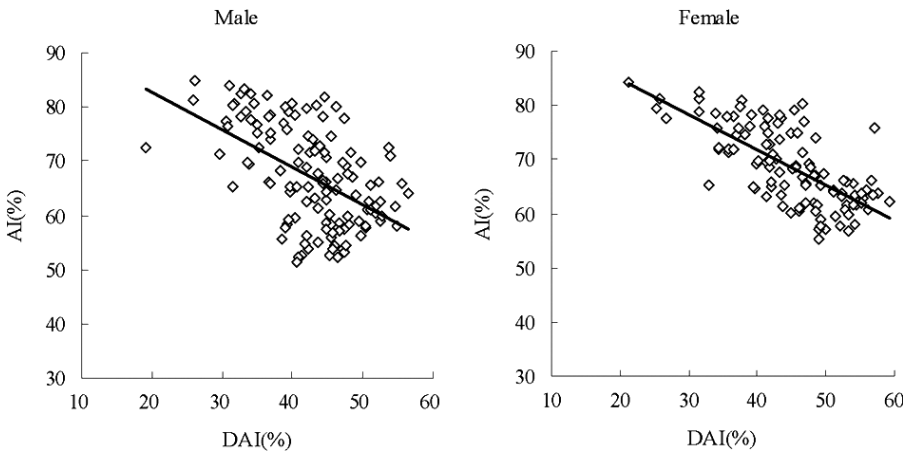

Fig. 4. The correlation between radial DAI and AI in men ($r = 0.704$, $P < 0.05$) and women ($r = 0.756$, $P < 0.05$).

Table 2.   Multiple regression analysis for DAI.

Variables	β	t	P value
Age (years)	−0.699	−15.616	0.000
Sex	−0.132	−2.951	0.003
Height (cm)	0.004	0.059	0.953
Weight (kg)	0.010	−0.179	0.858
HR (bpm)	0.014	0.302	0.763
DBP (mmHg)	0.026	0.569	0.570
PP (mmHg)	−0.037	−0.773	0.036
SBP (mmHg)	0.000	0.004	0.997
BMI (kg/m^2)	−0.017	−0.316	0.752

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; HR = heart rate; AI = augmentation index; DAI = diastolic augmentation index; Values are mean ± SD.

3.4. *Determinants of AI and DAI*

Multiple stepwise regression analysis further revealed that DAI was significantly associated with age in addition to gender (Table 2). And radial AI was significantly associated with age in addition to gender, height, and DBP. However, Height, HR and DBP were not associated with DAI which associated with AI (Table 3).

3.5. *Effect of HR changes on DAI and radial AI*

In the second experiment, the selected subjects ranged from 19 to 69 years. For each subject, the changes of HR contained the range 58 to 82 bpm. The following five different levels (60, 65, 70, 75 and 80 bpm) were selected and the values of DAI at the HR most close to the selected level entered the study.

Table 3.   Multiple regression analysis for AI.

Variables	β	t	P value
Age (years)	0.591	11.759	0.000
Sex	−0.044	−0.593	0.035
Height (cm)	−0.169	−3.375	0.001
Weight (kg)	−0.430	−0.533	0.059
HR (bpm)	−0.356	0.689	0.049
DBP (mmHg)	0.111	2.191	0.029
PP (mmHg)	−0.042	−0.799	0.425
SBP (mmHg)	−0.072	−0.799	0.412
BMI (kg/m^2)	0.023	−0.390	0.697

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; HR = heart rate; AI = augmentation index; DAI = diastolic augmentation index; Values are mean ± SD.
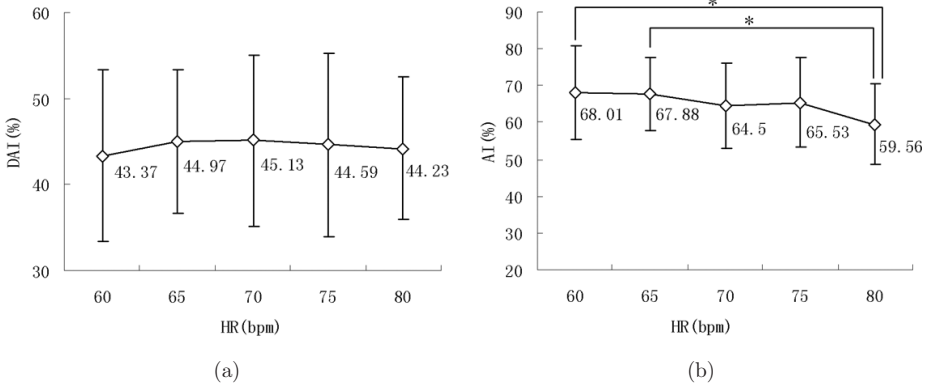
Fig. 5.   (a) DAI for each heart rate (HR) level, (b) AI for each HR. Values are means $\pm$ SD. *$P < 0.05$ between HR levels.

The effect of HR on DAI was illustrated in Fig. 5(a). Radial DAI remained stable on average (not significant for HR effect). The values of radial DAI at each HR level (60, 65, 70, 75 and 80 bpm) were 43.37 ± 9.95, 44.97 ± 8.37, 45.13 ± 10.00, 44.59 ± 10.6, $44.23 \pm 8.23\%$ respectively. The values of radial AI at each HR level (60, 65, 70, 75 and 80 bpm) were 68.01 ± 12.66, 67.88 ± 9.94, 64.5 ± 11.68, 65.53 ± 12.21, $59.56 \pm 10.93\%$, respectively. A post hoc test showed that significant differences in radial AI were just observed between 80 bpm and each other HR levels except 75 bpm (60: $P = 0.042$, 65: $P = 0.045$, respectively). AI obtained for consecutive HR values were not statistical.

3.6. *Reliability of DAI and AI*

The correlation coefficients for two measurements performed on the same day were: DAI ($r = 0.92$) and AI ($r = 0.89$) ($P < 0.05$). We studied the intra-observer variability based on re-measurement of 40 subjects by the same operator. The intra-observer agreement by the same operator for the DAI (ICC $= 0.872$) and AI (ICC $= 0.831$).

4. Discussion

The present study demonstrated an age-related decrease in radial DAI (Fig. 2) and age-related increase in radial AI (Fig. 3) in healthy men and women with no cardiovascular disease between 16 and 78 years of age, and the value of DAI were higher in women than men. At the same time, we evaluated the association between DAI and AI. There was a highly significant and close association between them. The difference of determinants between DAI and AI showed that height, HR and DBP were not associated with DAI which associated with AI. The experiment on effect of HR changes on DAI and radial AI demonstrated DAI remained stable when HR contained the range 58 to 82 bpm. The intra-observer agreement was excellent.

The radial DAI were higher in women than men. This was probably explained by the PP being lower in women than in men (39.7 ± 6.8 mmHg in women versus 42.4 ± 6.1 mmHg in men ($P < 0.05$)). As we know that cardiovascular risk and the incidence of cardiovascular diseases is higher in men compared with women,[19,20] this is in accordance with the result.

The Fig. 2(a) indicated DAI decreased with age, that was possible by the presence of a well-defined dicrotic wave in healthy young people, whereas most arteriosclerosis had a diminution or disappearance of the dicrotic wave.[21] There were significant age-dependent decreases in radial DAI from the 20's−30's in subjects. It is possibly mean the age at onset of cardiovascular disease is advanced.[22] In addition, an age dependent significant decrease in DAI was observed from the 40's−50's and the 60's−70's for women. During the age group of 40−50, we found the mean value and SD value in woman was fast declined than in man. As we know, atherosclerosis and cardiovascular disease rates will increase in woman after Menopause for lack of estrogen.[23] Therefore, that was the possible reason causing fast decreased in woman. At the age of 60's−70's in women, it is the most mortality for female.[24] At the age group 30−40 in men, it showed a significant age dependent decrease in DAI that may be caused by randomization status in the dietary and stress in the work,[25] for the onset of Erectile dysfunction (ED) is at the age 50's−60's in male, some of those studies indicate that the onset of ED can be an important risk factor of cardiovascular disease.[26]

Figure 3 depicted age-related increase in radial AI, which is consistent with previous studies.[5] We evaluated the association between DAI and radial AI shown in Fig. 4. There was a highly significant and close association between DAI and radial AI. These findings indicate the validity of DAI that detects the radial artery and determines the appropriate pressure of tonometry to obtain the most proper pressure waveform.

As shown in Fig. 5(a), the result of the ANCOVA with dependent variable of radial DAI and covariate of HR showed no significant difference with a wide age range even if the effect of HR was considered. Radial AI changed only little when HR ranged from 60 to 75 bpm while it decreased significantly when HR was up to 80 bpm.

From multivariable regression analysis, several parameters have been shown to influence AI whereas parameters that do not affect DAI include body height and heart rate. AI is resulted by the reflected pressure wave from peripheral vessel and DAI takes place as the result of a reflection of a pressure wave from the aortic valves and neighboring walls of the larger vessels. The distance of the two reflected pressure wave is not the same. The time of the reflected wave from peripheral vessel is longer. Some evidence suggests that the timing of the reflected wave is related to the dimensions of the body namely body height.[27] That is the possible reason. Each heart beat or cardiac cycle includes two major phases the ejection time and the relaxation time. AI is affected by ejection time and DAI is affected by relaxation time. The impact of HR on the ejection time is more than the relaxation time.[28] DAI

could not be easily affected because it was only determined by age and pulse pressure. As pulse pressure was a powerful independent predictor of cardiovascular disease over age, it was not necessary to take those confounding factors into account when assessing DAI as an index for atherosclerosis. These findings furthermore indicate that factors defining DAI are subject to age-dependent alterations.

In this paper, we have shown that it is feasible to make reliable measurements of DAI and AI. We obtained good intra-observer agreement and then demonstrated it with a hypothesis test for equivalence. The most common approach has been the use of the ICC. To the best of our knowledge, no prior study has measured DAI and then used to assess the observer variability. The excellent ICC values observed in this study means that the measurements of DAI and AI are reliable.

The main limitation of this study is that there is no comparison between clinical indicators and DAI. Unfortunately, this is due to the difficulties of recruiting healthy subjects with that condition for research work. However we have recruited patients for further study. Last but not least, we believe that further studies that will shed light on the clinical implications of our findings are warranted.

5. Conclusion

In summary, the present study showed that DAI might be an index of vascular aging. It provides the important information of the vascular as AI. These findings further support our hypothesis that as a simple and reliable parameter, DAI could be a potential clinical indicator to assess vascular aging.

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