# Relationship between brachial–ankle pulse wave velocity and fundus arteriolar area calculated using a deep-learning algorithm

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**Running head:** Fundus arteriolar area and baPWV

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## Abstract

**Purpose:** Retinal vessels reflect alterations related to hypertension and arteriosclerosis in the physical status. Previously, we had reported a deep-learning algorithm for automatically detecting retinal vessels and measuring the total retinal vascular area in fundus photographs (VAFP). Herein, we investigated the relationship between VAFP and brachial–ankle pulse wave velocity (baPWV), which is the gold standard for arterial stiffness assessment in clinical practice.

**Methods:** Retinal photographs (n=696) obtained from 372 individuals who visited the Keijinkai Maruyama Clinic for regular health checkups were used to analyze VAFP. Additionally, the baPWV was measured for each patient. Automatic retinal-vessel segmentation was performed using our deep-learning algorithm, and the total arteriolar area (AA) and total venular area (VA) were measured. Correlations between baPWV and several parameters, including AA and VA, were assessed.

**Results:** The baPWV was negatively correlated with AA (R = -0.40, n = 696, P < 2.2e-16) and VA (R = -0.36, n = 696, P < 2.2e-16). Independent variables (AA, sex, age, and systolic blood pressure) selected using the stepwise method showed a significant correlation with baPWV. The estimated baPWV, calculated using a regression equation with variables including AA, showed a better correlation with the measured baPWV (R=0.70, n=696, P < 2.2e-16) than the estimated value without AA (R=0.68, n = 696, P < 2.2e-16).

**Conclusions:** AA and VA were significantly correlated with baPWV. Moreover, baPWV estimated using AA correlated well with the actual baPWV. VAFP may serve as an alternative biomarker for evaluating systemic arterial stiffness.



**Keywords:** Arteriosclerosis; Imaging; Retinal arteriolar narrowing, Deep learning system, Pulse wave velocity

## Introduction

Pulse wave velocity (PWV) is considered the gold standard for arterial stiffness assessment in clinical practice.[1] Among the various non-invasive methods to measure PWV, carotid–femoral PWV and brachial–ankle PWV (baPWV) are frequently used in clinical settings. Both methods show a similar extent of association with risk factors and clinical events in patients with cardiovascular disease.[2] The baPWV is automatically measured using a separate cuff for each of the four limbs by an oscillometric method. Since baPWV is easily applied in clinical practice, it is frequently measured during medical checkups in Japan to assess cardiovascular disease risks.[3] However, baPWV requires a long measurement time more than 10 min and a wide space to place the patient in the supine position. In contrast, retinal fundus photography requires less than 1 min and a smaller space for a fundus camera.

Numerous studies have elucidated the association between the morphology of the retinal vasculature and arteriosclerosis; however, a satisfactory method to assess arterial stiffness using retinal photographs has not been established. A significant index of arterial stiffness, when automatically obtained from fundus photographs, could be used as a favorable surrogate marker for arteriosclerosis. Recently, we reported that the total retinal vascular area measured automatically on fundus photographs using our deep-learning algorithm is a novel index showing a favorable correlation with blood pressure.[4]

In the present study, we investigated the association between the total retinal vascular area in fundus photographs (VAFP) and baPWV to assess its efficiency as an index of arteriosclerosis.

# Methods

## *VAFP Measurement*

VAFP of 372 patients who visited the Keijinkai Maruyama Clinic for a regular health checkup was assessed on retinal photographs (n=696) obtained using an automatic fundus camera (AFC-330, NIDEK, Co., Ltd,, Gamagori, Japan). The mean patient age, mean systolic blood pressure (SBP), and mean diastolic blood pressure (DBP) were 54±10 years, 122±15 mmHg, and 76±10 mmHg, respectively. The deep-learning algorithm described previously[4] was used to perform retinal-vessel segmentation, arteriovenous classification, and vascular area measurement on fundus photographs. Predicted images of arterioles and venules were generated from color fundus photographs using a trained neural network. The sum of pixels in the probability map was defined as the total arteriolar area (AA) / total venular area (VA).

## *baPWV Measurement*

The baPWV was measured in all patients (n=372) using BP-203RPEII (Colin Co., Ltd., Japan) during a regular health check-up. Briefly, cuffs were applied to the four extremities and electrocardiographic electrodes were attached to the upper arm. A microphone was placed on the left second intercostal space for phonocardiography, and the patients rested in a supine position for 15 min.

## *Estimation of baPWV using Multiple Regression Analysis*

Independent variables associated with baPWV (AA, sex, SBP, and age) were selected from parameters related to arteriosclerosis (age, body mass index, sex, SBP, DBP, smoking, AA, and VA) using the stepwise method. The correlation coefficient between baPWV and each variable was calculated. Next, the estimated baPWV was calculated by multiple regression analysis using AA, sex, SBP, and age. The correlation coefficient between the actual and estimated baPWVs was calculated. Then, we excluded parameters individually from the multiple regression to show the contribution of each parameter to the baPWV.

## *Statistical Analysis*

Pearson's product-moment correlation was used for the statistical analysis to calculate the correlation efficiency between baPWV and other parameters using the statistical software RStudio 1.1.456(Available via http://www.R-project.org.).

## Results

### *Correlation between the VAFP and baPWV*

The baPWV was negatively correlated with AA (R = -0.40, n = 696, $P < 2.2e-16$, Figure 1A) and VA (R = -0.36, n = 696, $P < 2.2e-16$, Figure 1B).

### *Correlation between baPWV and independent variables*

AA showed a negative correlation with baPWV (R = -0.40, n = 696, $P < 2.2e-16$), male showed a mild positive correlation with baPWV (R = 0.20, n = 696, $P = 1.4e-07$), and SBP (R=0.48, n=696, $P < 2.2e-16$) and age (R=0.57, n=696, $P < 2.2e-16$) both showed a positive correlation with baPWV (Table 1).

### *Correlation between the actual baPWV and estimated baPWV*

As presented in Table 2, baPWV estimated using all the parameters (AA, sex, SBP, and age) showed a higher positive correlation with the actual baPWV (R=0.70, n = 696, $P < 2.2e-16$) than baPWV estimated excluding each parameter individually.

## Discussion

In this study, we demonstrated that: 1) both AA and VA showed a negative correlation with baPWV; 2) all independent variables, including AA, sex, SBP, and age showed significant correlations with baPWV; and 3) the estimated baPWV based on AA and other variables showed a slightly better correlation with the actual baPWV than with the estimated value calculated without AA. To the best of our knowledge, this is the first to provide evidence that the newly established index, *i.e.*, VAFP, could be a potential biomarker for the evaluation of arteriosclerosis.

We previously reported that VAFP including AA and VA is a novel index of hypertension-related vascular changes.[4] Using fundus photographs as an input, our deep-learning algorithm is capable of performing retinal-vessel segmentation with high accuracy and measuring the total area of arterioles and venules, both of which show a significant correlation with blood pressure. Furthermore, compared to the arteriovenous ratio manually measured by trained ophthalmologists, AA showed a better correlation with blood pressure.[4] Herein, we demonstrate the association between VAFP and baPWV, by using a deep-learning algorithm.

Several studies have reported the relationship between retinal vascular caliber and PWV,[5,6] including the correlation between PWV and the machine-measured arterio-venous ratio.[6] Furthermore, both central arteriolar equivalent and central venular equivalent are correlated with PWV.[5] Previous studies have clearly demonstrated that retinal vasculature is sensitively affected by systemic atherosclerotic changes[7-9]. Interestingly, both AA and VA showed a favorable correlation with baPWV in the present study. Since higher baPWV indicates advanced arteriosclerosis, it may lead to the decreased areas of the retinal vessels. Particularly, AA showed a stronger correlation with baPWV than VA. In line with the present data, previous studies have also elucidated that the retinal arteriolar morphology is significantly associated with systemic arterial parameters, including baPWV, compared with the retinal venous morphology.[10-12] Since aortic stiffness increases pulse pressure, which in turn causes narrowing of the retinal arterioles,[11] it is plausible that the morphology of retinal arterioles shows a stronger association with systemic circulatory conditions than that of retinal venules. The present data indicate the potential of AA as a novel marker for evaluating systemic arteriosclerosis.

Similar to previous studies, [13] [14] in the present study we estimated baPWV by multiple linear regression using parameters related to arterial stiffness such as sex, SBP, age, and AA. The estimated baPWV showed a slightly higher association with the actual baPWV when calculated using independent variables including AA, compared to that when calculated without AA. This indicates that AA is a significant parameter associated with baPWV, holding an element independent of other variables. In particular, since age has the strongest correlation with arterial stiffness among a number of parameters, discovering a new index that holds an age-independent element related to arteriosclerosis has an impact on the development of novel arteriosclerosis markers.

In previous studies, artificial intelligence has been used to assess the relationship between the retina and systemic vascular diseases. A deep-learning model has been shown to estimate cardiovascular risk[13] and baPWV[15] from retinal fundus photographs. However, these estimations were ambiguous during the picture analysis process. While the parameters of fundus photographs suitable for assessing cardiovascular risk or baPWV remain unknown, the present data indisputably demonstrate that AA is significantly associated with arteriosclerosis. The method used in the current study could be advantageous for automatically analyzing the association between retinal vascular morphology and arteriosclerosis with the support of artificial intelligence.

The present study has some limitations such as the relatively small number of subjects, and the absence of other arteriosclerotic indices for comparison, *e.g.,* ankle–brachial index or cardio–ankle vascular index. Further studies with larger populations and other indices are necessary to establish the significance of AA as a novel index of arterial stiffness. Furthermore, VAFP may be affected by the alignment or magnification of the photographs, ametropia, and media opacities. Those points are to be carefully analyzed in the future study to assess the necessity of VAFP correction by refractive value, axial length, or the alignment of image.

In summary, the study shows that AA is correlated with baPWV, and is a potential novel yet easy-to-use technique for assessing arterial stiffness. Establishing a method to assess arterial stiffness using AA can be useful at health checkups having less time and space, thus reducing the burden of both the patients and clinical staff, and creating a positive economic effect. If the similar relation could be found in patients with cardiovascular diseases, the credibility of AA as a novel-arteriosclerosis index would be even higher. Future investigations with a large number of participants with variety of backgrounds (e.g. cardiovascular diseases) are warranted to improve the present method for detecting the risk of arteriosclerosis using AI.

**Data availability statement**

The data that support the findings of this study are available on request from the corresponding author, KF, and MS. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

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**Conflict of Interest**:

Kanae Fukutsu, Michiyuki Saito, Kousuke Noda, and Susumu Ishida have a patent with NIDEK Co., Ltd. Gamagori, Japan. Department of Ophthalmology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University received a grant from NIDEK Co., Ltd. to establish the endowed course named as "Department of Ocular Circulation and Metabolism." Ryosuke Shiba and Naoki Isogai are employees of NIDEK Co., Ltd.

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# Figure Legends

**Figure 1**

**Correlation betweenVAFP and brachial–ankle pulse wave velocity (baPWV)**

**(A)** Correlation between the total arteriolar area (AA) and baPWV. R = -0.40, n = 696, $P <$ 2.2e-16. **(B)** Correlation between the total venular area (VA) and baPWV. R = -0.36, n = 696, $P <$ 2.2e-16.

**Table 1**

**Correlation between baPWV and independent variables**

**Table 2**

**Comparison of the correlation coefficients between the actual baPWV and the estimated baPWV using different parameters**

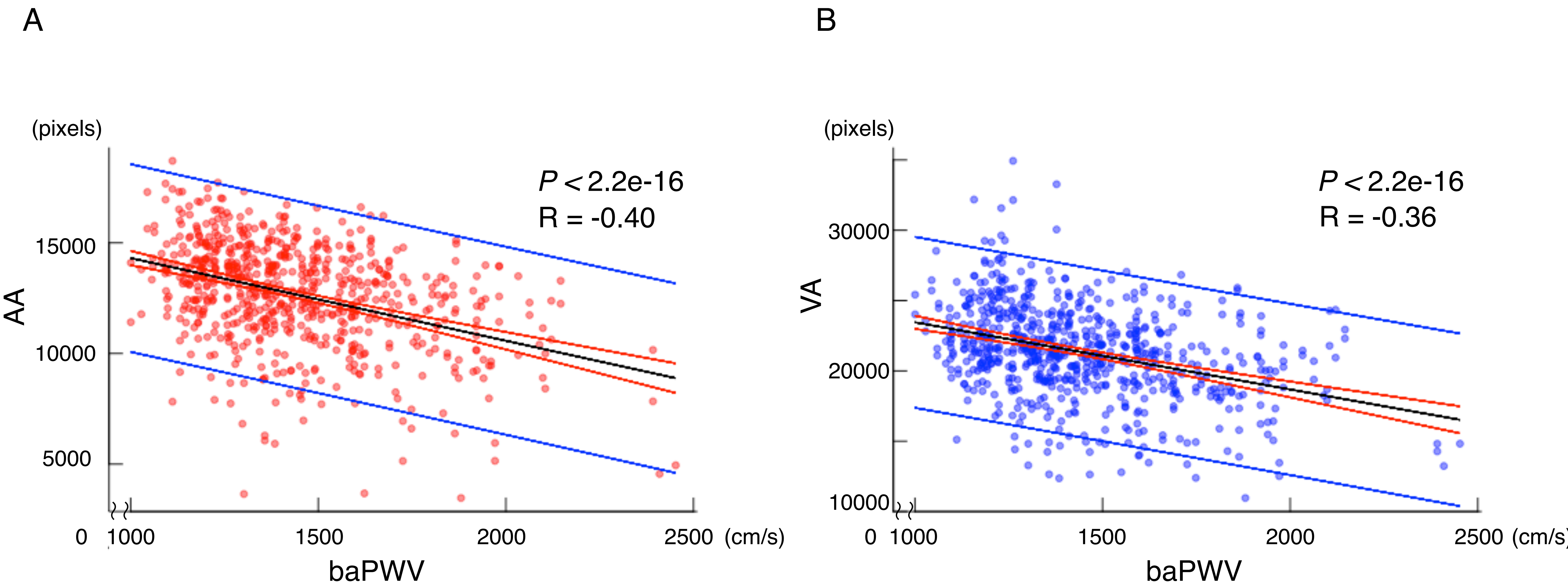
A
(pixels)
15000
10000
5000
AA
0
1000
1500
2000
2500
(cm/s)
baPWV
P < 2.2e-16
R = -0.40
B
(pixels)
30000
20000
10000
VA
0
1000
1500
2000
2500
(cm/s)
baPWV
P < 2.2e-16
R = -0.36

Figure 1 A B

| independent variable | R | 95% confidence interval | | *p* value | standardized regression coefficients | *t* value |
|---|---|---|---|---|---|---|
| AA | -0.40 | -0.46 | -0.33 | 2.2e-16 | -0.158 | -5.265 |
| sex | 0.20 | 0.13 | 0.27 | 1.4e-07 | 0.426 | 14.08 |
| SBP | 0.48 | 0.42 | 0.53 | 2.2e-16 | 0.134 | 4.837 |
| age | 0.57 | 0.52 | 0.62 | 2.2e-16 | 0.318 | 11.05 |

Table 1

| factors | R | 95% confidence interval | | *p* value |
|---|---|---|---|---|
| AA, sex, SBP | 0.58 | 0.53 | 0.63 | 2.2e-16 |
| AA, sex, age | 0.63 | 0.58 | 0.67 | 2.2e-16 |
| AA, SBP, age | 0.68 | 0.64 | 0.72 | 2.2e-16 |
| sex, SBP, age | 0.68 | 0.64 | 0.72 | 2.2e-16 |
| AA, sex, SBP, age | 0.70 | 0.66 | 0.73 | 2.2e-16 |

Table 2