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Decreased peripheral arterial volume distensibility in patients with branch retinal vein occlusion in comparison with normal subjects

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This study aimed to quantify arterial volume distensibility in patients with branch retinal vein occlusion (BRVO) in comparison with normal subjects and to investigate factors associated with their differences. 40 normal subjects and 30 BRVO patients were studied. Brachial-ankle pulse wave velocity (baPWV) was measured to determine arterial volume distensibility. In comparison with the normal subjects, after adjusting for pulse pressure, baPWV in the BRVO patients was significantly higher by 2.3 m/s ($P < 0.01$) and arterial distensibility was significantly lower by 0.015% per mmHg ($P < 0.01$). No subject in the normal group had an arterial distensibility lower than 0.04% per mmHg, in comparison with 67% (20/30) in the BRVO group. Arterial distensibility was significantly related to systolic and diastolic blood pressures (SBP and DBP) and ageing for both groups (all $P < 0.05$), but in the BRVO group, blood pressures and ageing had more prominent effect on arterial volume distensibility. Peripheral arterial distensibility has been shown to be significantly lower in BRVO patients in comparison with normal subjects. The more prominent effect of SBP, DBP and ageing on arterial distensibility indicates the potential underlying mechanisms of the interaction between higher blood pressures, ageing and BRVO disease.

Arteries, arterioles and capillaries play important roles in cardiovascular physiology and pathophysiology. The peripheral arteries and arterioles in the microcirculation are the primary sites of vascular resistance, and therefore the primary site for regulation of blood pressure and blood flow. However, the pathogenesis of decreased arterial elasticity is still clinically uncertain¹. A loss of arterial elastic properties has been considered intrinsic to the ageing process of the arterial wall², and also been associated with other different clinical and physiological factors, such as hypertension, heart failure, diabetes, smoking and alcohol^{3–7}. Microvascular processes may also contribute to the loss of arterial elasticity⁸. More recently, it has been accepted that the elastic properties of arteries can provide an early marker of risk for cardiovascular disease⁹ and is an independent predictor of cardiovascular mortality¹⁰.

Patients with advanced retinal vascular disease have higher risks of cardiac and peripheral vascular diseases^{11,12}. Branch retinal vein occlusion (BRVO) is a very common retinal vascular disease and a major cause of vision loss, affecting approximately 16 million people worldwide¹³. Therefore, a better understanding of the changing elastic properties of arteries in patients with BRVO is of pathophysiological importance. Although aortic stiffening has been observed in patients with retinal microvascular disease¹⁴, to the best of our knowledge, there is no information available on how the peripheral arterial properties change in patients with BRVO.

Various assessment techniques have been developed to non-invasively quantify the peripheral arterial properties¹⁵. Pulse wave velocity (PWV) is one of the most commonly used indirect techniques¹⁶. In practice, PWV is often calculated from the pulse transmission time over two superficial artery sites with known distance. The stiffer or less elastic the artery is, the higher the velocity of arterial pulse transmission. Arterial volume distensibility, giving the relative change in blood volume with a known change in arterial pressure, is a direct quantification of the elastic and hence structural properties of the arterial wall¹⁷. Typically, it is calculated from the measurement of the percentage change in arterial diameter within each cardiac cycle using ultrasound technique¹⁵. However, ultrasound technique is highly operator-dependent with large errors in the measurement of artery size, especially



Table 1 | Physiological characteristics from the normal subjects and BRVO patients

Variables	Normal subjects	BRVO patients	P-value
No.	40	30	-
Men	26	14	0.4
Smoker	12	8	0.2
Age (year)	51 ± 5	54 ± 8	0.1
Height (cm)	167 ± 8	163 ± 7	<0.05
Weight (kg)	66 ± 10	68 ± 15	0.5
BMI (kg/m ²)	24 ± 2	26 ± 4	<0.05
Heart rate (beats/min)	71 ± 10	79 ± 14	<0.01
Systolic blood pressure (SBP, mmHg)	111 ± 9	143 ± 16	<0.01
Diastolic blood pressure (DBP, mmHg)	65 ± 8	84 ± 10	<0.01
Pulse pressure (PP, mmHg)	46 ± 5	59 ± 9	<0.01
Blood glucose (mmol/L)	5.0 ± 0.5	5.4 ± 0.7	<0.05
Total cholesterol (mmol/L)	5.0 ± 1.0	4.7 ± 1.0	0.2
Triglyceride (mmol/L)	1.7 ± 1.0	1.7 ± 0.5	0.8
Low density lipoprotein (LDL) (mmol/L)	3.0 ± 0.7	2.6 ± 0.6	<0.05

Data are expressed as number or mean ± standard deviation (SD).

with small and medium sized peripheral arteries. Recently, Zheng and Murray reported a simple measurement technique to obtain the peripheral arterial volume distensibility from PWV¹⁷. Because of its simplicity, its application to BRVO patients is worth further investigation.

The aim of this study was to quantify arterial volume distensibility of peripheral arteries in patients with BRVO by measuring peripheral PWV, and to compare with measurements from normal subjects. The factors influencing peripheral arterial volume distensibility in BRVO patients were also investigated.

Methods

Subjects. Sample size required for clinical trials of the PWV measurement has been reported by Liang et al¹⁸. With a reference coefficient of variation of 10%, 30 subjects were enough to achieve a confidence level of 95% and a statistical power of 80%. In this study, 40 normal subjects and 30 BRVO patients were studied. They were matched by age between 36 and 70 years. The study obtained full approval of the Local Clinical Ethics Committee of the Second Affiliated Hospital of Zhejiang University. The investigation conformed to the principles in the Declaration of Helsinki. All subjects gave their written informed consent to participate in the study, and confirmed that they had not have participated in any other clinical trials within the previous three months.

Diagnosis of branch retinal vein occlusion (BRVO). All BRVO patients had eye disease history between 3 to 6 months before they presented for their first eye examination at the Eye Center of Second Affiliated Hospital of Zhejiang University. Patients with previous history of diabetes mellitus and coronary heart disease were excluded. Each patient was initially examined by a consultant ophthalmologist using a funduscopy, following by a further examination performed on the same day by a retinal specialist using fundus fluorescein angiography (FFA, Heidelberg Engineering Inc., Germany). The diagnosis of BRVO was made by fundus examination by finding retinal hemorrhages in the distribution of an obstructed retinal vein. FFA was used to confirm the diagnosis and determine the degree of retinal ischemia and diagnose macular edema according to the diagnostic criteria summarized by Jaulim et al¹⁹. The final diagnosis of BRVO was agreed between the two ophthalmologists. In addition, four biochemical indices, including blood glucose, total cholesterol, triglyceride and low density lipoprotein (LDL), were also tested for each patient.

Brachial-ankle pulse wave velocity (baPWV) measurement. Brachial-ankle PWV measurements were performed immediately after the eye examinations in a quiet, temperature controlled examination measurement room (25°C) at the Second Affiliated Hospital of Zhejiang University. All the PWV measurements were done by one experienced technician. Before formal recording, each subject lay supine on a measurement bed for 10 min to allow cardiovascular stabilization. At the beginning and end of the baPWV measurements, manual auscultatory systolic and diastolic blood pressures and pulse pressure (SBP, DBP and PP) were recorded. During the whole measurement, subjects were asked to breathe regularly and gently.

A VP 1000 automated PWV/ABI analyzer VP1000 (PWV/ABI, Colin Co. Ltd., Komaki, Japan) was used to simultaneously record pulse waveforms of the brachial and posterior tibial arteries based on an automated oscillometric method. The bilateral values of ankle-brachial index (ABI) and baPWV were obtained. The validation of the VP1000 device and its reproducibility has been previously published¹⁶.

Peripheral arterial volume distensibility calculation. With the recorded baPWV, the arterial volume distensibility from both the left and right sides were calculated using the method proposed by Zheng and Murray¹⁷. The detailed process is summarized as follows:

From the definition of arterial volume distensibility (Distensibility = $(\Delta V/V)/\Delta P$, where ΔV is the change in blood volume in each cardiac cycle, and ΔP is pulse

pressure) and the Bramwell and Hill equation ($PWV = \sqrt{\frac{V \cdot \Delta P}{\rho \cdot \Delta V}}$, where ρ is blood

density = 1025 kg · m⁻³), peripheral arterial volume distensibility was then derived as follows²⁰:

$$PWV^2 = \frac{V \cdot \Delta P}{\rho \cdot \Delta V} = \frac{V}{\rho} \cdot \frac{\Delta P}{\Delta V} = \frac{1}{\rho} \cdot \frac{\text{Distensibility}}{\rho},$$

and then Distensibility = $\frac{1}{\rho \cdot PWV^2}$.

Data and statistical analysis. The overall means and SDs of ABI, bilateral baPWVs and arterial volume distensibilities were obtained, separately for the normal subjects and BRVO patients. Next, their differences between the left and right sides were compared, as well as their differences between the two groups after the adjustment for PP. Finally, multiple regression analysis was performed to determine the effect of SBP, DBP, age, sex, height, weight, smoking, body mass index (BMI), heart rate and the four biochemical indices on baPWV and arterial volume distensibility, with the correlation coefficient *R*-value and *P*-value obtained. SPSS 19.0 software package (SPSS Inc.) was used for the statistical analysis, and a value of *P* < 0.05 was considered statistically significant.

Results

Physiological characteristic information. The subject demographic information is summarized in Table 1. For all the manual blood pressures (SBP, DBP and PP), there was no significant differences between the measurements taken at the beginning and end of the baPWV measurement (all *P* > 0.05). The average SBP, DBP and PP from the two measurements were used as the reference blood pressures for that subject. As expected, there was a significant difference in blood pressures (SBP, DBP and PP, all *P* < 0.01) between the normal and BRVO groups. The measured blood glucose and total cholesterol from over 90% of the subjects were within the normal range of 3.89–6.11 mmol/L and 3.10–6.0 mmol/L, respectively. Blood glucose and LDL had significant differences between the two groups (both *P* < 0.05), but not for age, gender, weight, smoking, total cholesterol and triglyceride (all *P* > 0.05).

Differences of ABI, baPWV and arterial volume distensibility between the two groups. Table 2 gives the overall means and SDs of ABI, baPWV and arterial volume distensibility from the two groups. All parameters had no significant differences between the left and right sides (*P* > 0.05). Their average values from the left and



Table 2 | Ankle-brachial index (ABI), brachial-ankle pulse wave velocity (baPWV) and arterial volume distensibility from the normal subjects and BRVO patients

Variables	Normal subjects	BRVO patients	P-value after adjusting for pulse pressure
Left side ABI	1.11 ± 0.09	1.12 ± 0.12	NS
Right side ABI	1.13 ± 0.09	1.12 ± 0.12	NS
Average ABI	1.12 ± 0.09	1.12 ± 0.12	NS
Left side baPWV (m/s)	12.7 ± 0.9	15.7 ± 2.6	<0.01
Right side baPWV (m/s)	12.8 ± 1.0	16.0 ± 3.0	<0.01
Average baPWV (m/s)	12.7 ± 0.9	15.8 ± 2.6	<0.01
Left side distensibility (% per mmHg)	0.06 ± 0.01	0.04 ± 0.02	<0.01
Right side distensibility (% per mmHg)	0.06 ± 0.01	0.04 ± 0.02	<0.01
Average distensibility (% per mmHg)	0.06 ± 0.01	0.04 ± 0.02	<0.01

Data are expressed as mean ± SD. NS: no significant difference, ABI: ankle brachial index, PWV: pulse wave velocity.

right sides of each subject were then used as reference values for that subject.

As shown in Figure 1 and Table 2, before the adjustment for PP, there was no significant difference in ABI between the two groups ($P > 0.05$). baPWV in the BRVO group was significantly higher by 3.0 m/s (15.7 ± 2.6 vs 12.7 ± 0.9 m/s, $P < 0.01$) and arterial volume distensibility was significantly lower by 0.02% per mmHg (0.04 ± 0.02 vs 0.06 ± 0.01 per mmHg, $P < 0.01$). After the adjustment for PP, baPWV in the BRVO group was still significantly higher by 2.3 m/s and arterial volume distensibility significantly lower by 0.015% per mmHg (both $P < 0.01$). No subject in the normal group had an arterial distensibility lower than 0.04% per mmHg, in comparison with 67% (20/30) in the BRVO group.

Effect of blood pressures and ageing on baPWV and arterial volume distensibility. Multiple regression analysis showed that both baPWV and arterial volume distensibility were significantly related to SBP, DBP and age for both the normal and BRVO groups, but they had no relationship with other physiological characteristics (including sex, height, weight, smoking, BMI, heart rate, blood glucose, total cholesterol, triglyceride and LDL) for both groups.

As given in Figure 2–3 and Table 3–4, both baPWV and arterial volume distensibility had significant relationships with SBP and DBP in both normal and BRVO groups (all $P < 0.05$). It has also been shown that their absolute regression slopes increased in BRVO group. As demonstrated in Table 3 and 4, in the normal group, baPWV increased by 17% for a SBP increase from 90 to 150 mmHg and 21% for a DBP increase from 45 to 105 mmHg. These increases were more than double in the BRVO group (37% against 17% for SBP, and 48% against 21% for DBP). For the same

blood pressure increase, more obvious decrease in arterial volume distensibility was obtained in the BRVO group in comparison with the normal group (38% against 30% for SBP, and 56% against 36% for DBP).

Regarding the effect of ageing on both baPWV and arterial volume distensibility, there were significant relationships in the two groups (both $P < 0.05$). As demonstrated in Table 3 and 4, in the normal group, baPWV increased by 11% and arterial volume distensibility decreased by 18% for an age increase from 45 to 65 year old, but their decrease was nearly double in the BRVO group (22% against 11% for baPWV, and 35% against 18% for arterial distensibility).

Discussion

This study has demonstrated that, after adjusting for PP, peripheral arterial volume distensibility was significantly lower in BRVO patients by simply measuring peripheral baPWV. It is clinically useful to have a simple measurement technique to assess arterial elastic properties. Several non-invasive techniques have been reported, but most of them are indirect measurements by assessing factors influenced by arterial properties¹⁵. The ultrasound technique has been used to directly measure arterial distensibility of medium-sized arteries^{21,22}. However, the ultrasound technique for arterial distensibility measurement has not been accepted in real clinical use due to the disadvantage of large variability in measuring the diameter of medium or small-sized arteries. The non-invasive method (baPWV) employed in this study to obtain peripheral arterial volume distensibility from baPWV is much simpler, and its application to measure the differences in elastic properties of peripheral arteries between normal subjects and heart failure patients has been investigated³. In this study, its potential to measure arterial volume distensibility differences between normal subjects and BRVO patients has been

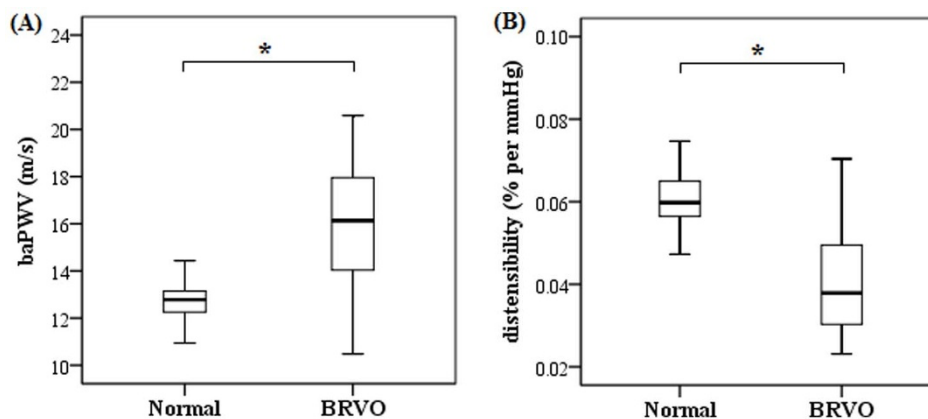


Figure 1 | Box-plots of brachial-ankle pulse wave velocity (baPWV) (A) and arterial volume distensibility (B) for the normal and BRVO groups. ‘*’ means statistically significant between the normal and BRVO groups after adjusting for pulse pressure.

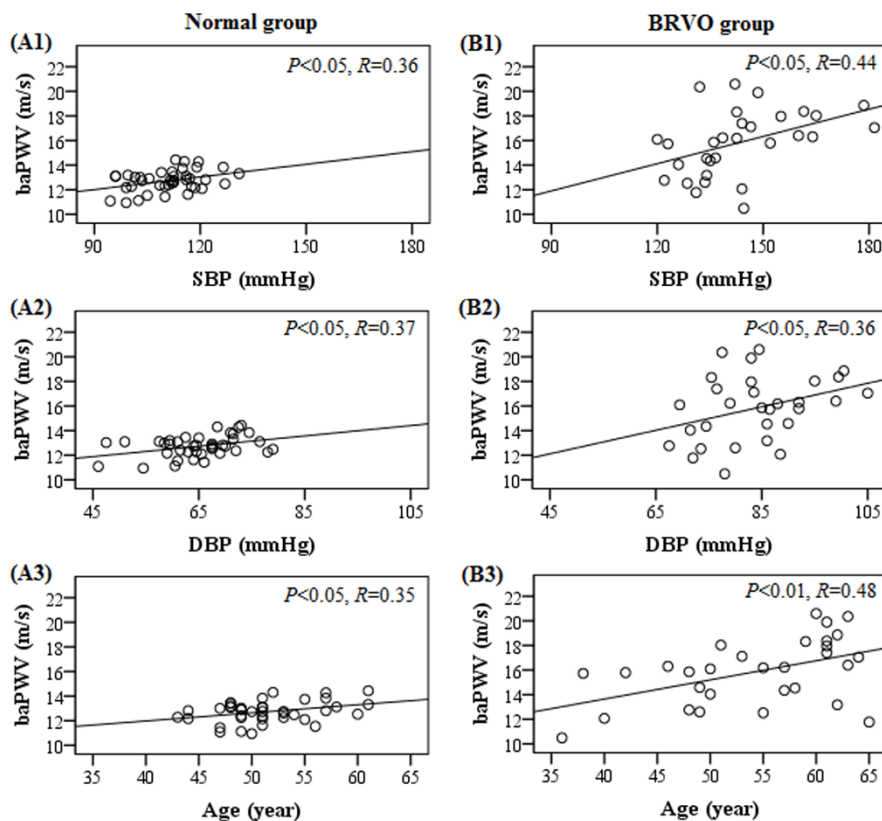


Figure 2 | Brachial-ankle pulse wave velocity (baPWV) as a function of systolic blood pressure (SBP), diastolic blood pressure (DBP) and age for the normal (A1–A3) and BRVO groups (B1–B3). The regression lines with P values and R values are also shown.

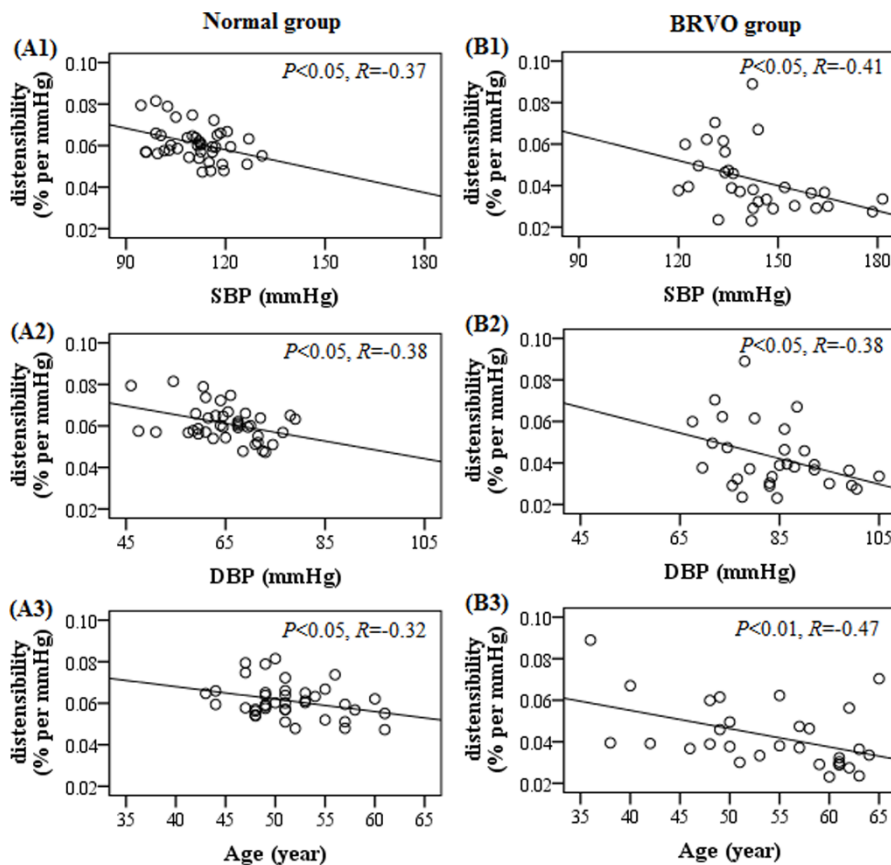


Figure 3 | Arterial volume distensibility as a function of systolic blood pressure (SBP), diastolic blood pressure (DBP) and age for the normal (A1–A3) and BRVO groups (B1–B3). The regression lines with P values and R values are also shown.


Table 3 | A summary of brachial-ankle pulse wave velocity (baPWV) as a function of systolic blood pressure (SBP), diastolic blood pressure (DBP) and age

Variables	Regression function: baPWV (m/s) =	P-value	R-value	% change of baPWV
SBP				
Normal	$0.034 \times \text{SBP} + 8.9$	0.023*	0.36	17 (from 90 to 150 mmHg)
BRVO	$0.074 \times \text{SBP} + 5.3$	0.016*	0.44	37 (from 90 to 150 mmHg)
DBP				
Normal	$0.042 \times \text{DBP} + 10.0$	0.018*	0.37	21 (from 45 to 105 mmHg)
BRVO	$0.096 \times \text{DBP} + 7.8$	0.047*	0.36	48 (from 45 to 105 mmHg)
Age				
Normal	$0.066 \times \text{Age} + 9.3$	0.028*	0.35	11 (from 45 to 65 year)
BRVO	$0.156 \times \text{Age} + 7.4$	0.007**	0.48	22 (from 45 to 65 year)

*: $P < 0.05$;
 **: $P < 0.01$.

Table 4 | A summary of arterial volume distensibility as a function of systolic blood pressure (SBP), diastolic blood pressure (DBP) and age

Variables	Regression function: distensibility (% per mmHg) =	P-value	R-value	% change of distensibility
SBP				
Normal	$-0.00034 \times \text{SBP} + 0.099$	0.021*	0.37	-30 (from 90 to 150 mmHg)
BRVO	$-0.00040 \times \text{SBP} + 0.10$	0.027*	0.41	-38 (from 90 to 150 mmHg)
DBP				
Normal	$-0.00042 \times \text{DBP} + 0.089$	0.016*	0.38	-36 (from 45 to 105 mmHg)
BRVO	$-0.00062 \times \text{DBP} + 0.094$	0.037*	0.38	-56 (from 45 to 105 mmHg)
Age				
Normal	$-0.00060 \times \text{Age} + 0.092$	0.045*	0.32	-18 (from 45 to 65 year)
BRVO	$-0.00088 \times \text{Age} + 0.090$	0.008**	0.47	-35 (from 45 to 65 year)

*: $P < 0.05$;
 **: $P < 0.01$.

demonstrated, suggesting that baPWV could be a useful technique in assessing BRVO patients.

Our results also showed that arterial volume distensibility is significantly and inversely related to SBP and DBP for both normal subjects and BRVO patients, but not to the biochemical parameters (blood glucose, total cholesterol, triglyceride and LDL). The inverse relationship between arterial distensibility and blood pressures was more pronounced in BRVO patients. This indicates that high blood pressure could be an important factor associated with low arterial volume distensibility in BRVO patients, and confirms that hypertension is one of the main factors contributing to the pathophysiology of BRVO.

The effect of ageing on arterial volume distensibility is clinically controversial, especially for peripheral medium-sized arteries^{23,24}. Since baPWV includes peripheral components of the arterial tree, its potential use in clinical research study and for screening vascular disease has been demonstrated¹⁶. Our results in normal subjects indicate that the systemic volume distensibility of the peripheral artery calculated from baPWV had statistical relationship with age, which agreed with the published validation study²⁵. However, the ageing effect on baPWV and arterial volume distensibility in BRVO patients has not been well investigated. To the best of our knowledge this is the first study to demonstrate the ageing effect in BRVO patients. We have shown that ageing had prominent effect on baPWV and arterial volume distensibility in BRVO patients in comparison with normal subjects, suggesting the potential underlying mechanisms of the interaction between ageing and BRVO disease. In patients with BRVO, ageing could enhance structural and functional abnormalities of arterial wall and degeneration or disorganization of the medial layer, leading to measurably increased baPWV and decreased distensibility. Nevertheless, further investigation is still required to better understand the underlying mechanism for the changes of arterial elastic properties in BRVO patients.

One of the limitations of this study is that the BRVO patients were uncontrolled hypertensive patients with anti-hypertensive medication. However, all the arterial pulse measurements were performed immediately after the eye examinations. Blood pressures at the beginning and end of the PWV measurement were measured by the gold standard manual auscultatory method, and there were no significant differences at the two timing points. This indicates that the cardiovascular hemodynamics was stable during the study, and also confirms that using the average blood pressures from the two measurements as a reference blood pressure to investigate its relationship with PWV is acceptable. Secondly, only BRVO patients were studied in this preliminary investigation partly because the risk factors associated with the development of BRVO are much simpler than these for the central retinal vein occlusion (CRVO). In addition, the site of occlusion in BRVO is usually at arteriovenous crossings. Therefore the effect of pathophysiologic changes of arteries on retinal veins could be more obvious and direct at the junctions. The investigation with CRVO patients, as well as the comparison with BRVO patients, could be our future work. Furthermore, the comparison of micro- and macro-vascular function/structure markers and the relationship between microvascular abnormalities and cardiovascular parameters in patients with other retinal vascular diseases are also worth investigation.

Conclusion

The current study demonstrated that BRVO patients had higher baPWV and lower peripheral arterial volume distensibility in comparison with normal subjects. It has also been demonstrated that, in patients with BRVO, blood pressures and ageing had more prominent effect on baPWV and arterial volume distensibility. These findings are clinically and pathophysiologically important, and have made an important contribution in understanding the underlying mechanism for the changes of arterial elastic properties in BRVO patients.



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Author contributions

D.Z. and Z.C. designed the study. Z.C. and L.M. collected the data. Z.C., L.M., C.L., J.R.B. and D.Z. performed the data and statistical analyses, interpreted the results, and drafted and reviewed the manuscript. Z.C. and C.L. obtained the funding for this study.

Additional information

Competing financial interests: The authors declare no competing financial interests.

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