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Effects of arterial blood on the venous blood vessel wall and differences in percentages of lymphocytes and neutrophils between arterial and venous blood

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Abstract

Vascular sclerosis mostly occurs in arteries and is mainly related to anatomic structure and hemodynamics of artery. This study aimed to investigate effects of arterial blood on vein wall and explore differences of composition between arterial and venous blood.

Ultrasound was used to examine the distal venous structure of arteriovenous fistula in uremia patients. Immunohistochemistry was used to study the pathology of the distal vein. Twelve patients were divided into control group and trial group. Patients received an arteriovenous fistula within 1 month in control group. Patients had undergone this surgery ≥2 years before in the trial group. Blood samples were collected from the aortic, arterial, and venous vessels of 51 patients who had taken coronary angiography and analyzed with blood routine rest, biochemical, and immunological measures to compare the differences of blood composition between artery and vein. This study was registered with the China Clinical Trial Center website under registration number ChiCTR-OOC-16008085.

In the trial group, the vascular wall of distal veins of fistula were thickened and hardened. No significant differences of blood composition were found between the aortic and radial arterial blood. However, the differences in the percentages of lymphocytes and neutrophils between arterial and venous blood were significant (Pa = .0095, Pb = .01).

Under smooth hemodynamic conditions, arterial blood caused hardening of the venous wall. Arterial and venous blood differed in the percentage of lymphocyte and neutrophils. This may contribute to the vascular sclerosis that is observed in arteries more often than veins.

Keywords: biochemistry complete set, blood components, blood routine, complete immunity, hemodynamics, lymphocyte percentage, vascular sclerosis

1. Introduction

Atherosclerosis refers to vascular wall thickening and hardening, loss of elasticity, and narrowing of lumen.[1,2] Angiosclerosis can decrease the blood supply to organs, including heart, brain, and kidney, and subsequently cause organ ischemia and dysfunction. Atherosclerosis occurs mostly in the arteries, but rarely in the veins.[3] This is attributed to differences in the anatomical structure of arteries and veins, as proposed by the most relevant studies.[4–6] However, vascular sclerosis rarely occurs in the pulmonary artery, which contains venous blood only.[7,8] This has led to a hypothesis that vascular sclerosis was associated with the particular characteristics of arterial blood. Indeed, a number of studies have suggested that the differences in physiological function and hemodynamic environment between arteries and veins contribute to the development of vascular sclerosis.[9,10]

Recently, a number of studies showed that vein grafts used in coronary artery bypass surgery also underwent hardening, similar to original coronary arteries.[11,12] The probability of lesion and occlusion arising in the postoperative venous bridge was reportedly ~15% to 30% at 1 year [13,14] and ~50% of vein grafts failed within 10 to 15 years after surgery, due to a number of issues, including intimal hyperplasia.[15] Intimal hyperplasia occurred mainly as a response to higher arterial pressures after the vein graft bypass surgery,[16] and was linked to vascular wall thickening and narrowing.[17] Hence, changes in the vascular hemodynamics in the bridge vessel can promote vascular sclerosis. In addition, it is well known that the lipid composition of the blood contributes to the pathogenesis of atherosclerosis.[18] However, whether the differences in blood composition between arterial and venous blood are factors that influence angiosclerosis is not known.

In the present study, we explored whether arterial blood components were associated with hardening of the venous wall in addition to hemodynamics, and differences in the composition of arterial and venous blood.

Editor: Yan Li.

The authors report no conflicts of interest.

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Medicine (2018) 97:26(e11201)

Received: 19 January 2018 / Accepted: 29 May 2018

http://dx.doi.org/10.1097/MD.0000000000011201

2. Methods

2.1. Study design

This study was approved by the Institutional Ethics Committee of the Third Xiangya Hospital of Central South University. All of the patients provided signed informed consent before their enrollment in the study. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was registered as Chinese Clinical Trial Registry No. ChiCTR-OOC-16008085.

2.2. Subjects

The subjects for our study are included 2 phases; in the first phase, 12 uremia patients were selected who had undergone arteriovenous fistulation to explore whether arterial blood components were associated with hardening of the venous wall in addition to hemodynamics; in the second phase, 58 patients were recruited to detect the differences in the composition of arterial and venous blood.

The first phase of the retrospective study included 12 uremia patients who had undergone arteriovenous fistulation sometime between November 27, 2015, and January 20, 2017. These patients were divided into those who had had surgery within 1 month (control group) and those who had undergone surgery ≥2 years before (trial group). Arteriovenous vascular ultrasonography was conducted on their arteriovenous fistulas. If the patients had undergone fistulation or refistulation because of vascular occlusions, vein vessels on the surgical areas were taken for pathological examination.

The second phase of the study included patients aged 18 to 75 years in whom both arterial and venous blood were readily collectible. The participants consisted of patients with cardiovascular diseases who required coronary angiography. Patients with any of the following were excluded from the present analysis: taking statins within the recent 3 months; acute infection; malignant tumor; intractable hypertension or arrhythmia; thyroid disease; or use of systemic steroids or cyclosporine therapy. This study began on November 27, 2015, and ended September 30, 2016. Among the initial 58 patients enrolled, 4 failed to complete the blood collection process and were excluded from the study, and 3 were excluded due to the hemolysis test results. Thus, 51 patients participated in the second phase of the study. Blood samples were collected from the following locations: the radial artery's outer periphery during coronary angiography with implantation of radial artery sheath; the aortic sinus when the angiography catheter was inserted into the aortic sinus; and a left arm vein.

Data were regularly reviewed by the independent China Clinical Trials Registry. Raw data were audited and published by the ResMan Clinical Trial Public Management Platform for Research. As the study collected blood and pathological specimens from the sampled patients, all patients involved in the study have signed the informed consent.

2.3. Research method

The PHILPS epiq7c color Doppler ultrasound system was used for vascular ultrasound examinations, and hematoxylin and eosin (H&E) staining was used for immunohistochemical examination.

During the coronary angiography, 6 mL of blood were collected from each of the following: the radial artery, aortic sinus, and peripheral veins. The blood specimens were sent for laboratory tests, including routine blood, liver and kidney function, blood lipid, blood glucose, electrolyte, and complete immunity tests.

2.4. Statistical analysis

The second phase of the study analyzed the data from the blood specimens. The data from these 3 groups of specimens (aortic sinus, radial artery, and peripheral vein) were compared using analysis of variance and the Bonferroni post-hoc test for 2-group comparison. All descriptions of the test results are presented as mean ± standard deviation, and a P value $< .05$ was considered statistically significant.

3. Results

3.1. Hardening and thickening intima of veins in patients of trial group

We selected uremia patients who had undergone arteriovenous fistula surgery within 1 month (control group) or ≥2 years previously (trial group) for vascular ultrasonographic examination. In the normal arteries of patients, blood flow was fast, and the blood flow spectrum was a serrated or wavy waveform. In veins, the blood flow was smooth and slow, and the blood flow spectrum waveform was continuous.

In the patients in the trial group, the blood flow around the fistula opening was fast, and its blood flow spectrum was also a serrated waveform. On a site far away from the fistula opening, the blood flow spectrum was similar to the continuous waveform of the venous blood flow. This suggests that hemodynamically, the blood flow had restored the venous blood flow.

Currently, in artificial fistulation, a narrow vascular lumen is considered if the peak systolic velocity at the fistula opening is ≥2.5 times that of the arterial blood inflow 2 cm from the fistula, or if the diameter stenosis rate of the fistula ≥50%.[19] In the present study, the intimal thickness of the veins 5 cm away from the fistula in the control group for a short time after surgery was normal (Fig. 1 A, B). However, in the trial group, the vascular ultrasound showed that the blood flow spectrum for veins ≥5 cm away from the fistula opening registered as a continuous waveform, and the vascular intima was hardening as well as thickening (Fig. 1C, D).

3.2. Long-term fistulation promotes venous wall hardening and thickening

Next, we selected veins behind the fistula for immunohistochemical examination. In the control group, the venous wall contained a few layers of endothelial cells (Fig. 2 A). However, in patients of the trial group, the endothelial cells of the venous wall were thick, and mucoid degeneration of the venous wall, fiber hyperplasia, and fibroblast proliferation in the venous wall were obvious. In addition, proliferation of small vessels occurred outside the vascular wall, and the vascular intima was thickened and hardened (Fig. 2 B). This suggests that long-term fistulation promotes venous wall hardening and thickening.

3.3. Compositions of blood from the aortic sinus, radial artery, and peripheral vein

We performed a complete analysis of the composition of the blood specimens collected from the aortic sinus, radial artery, and peripheral vein (Table 1). The complete immunity tests showed no statistically significant differences among the 3 sites of

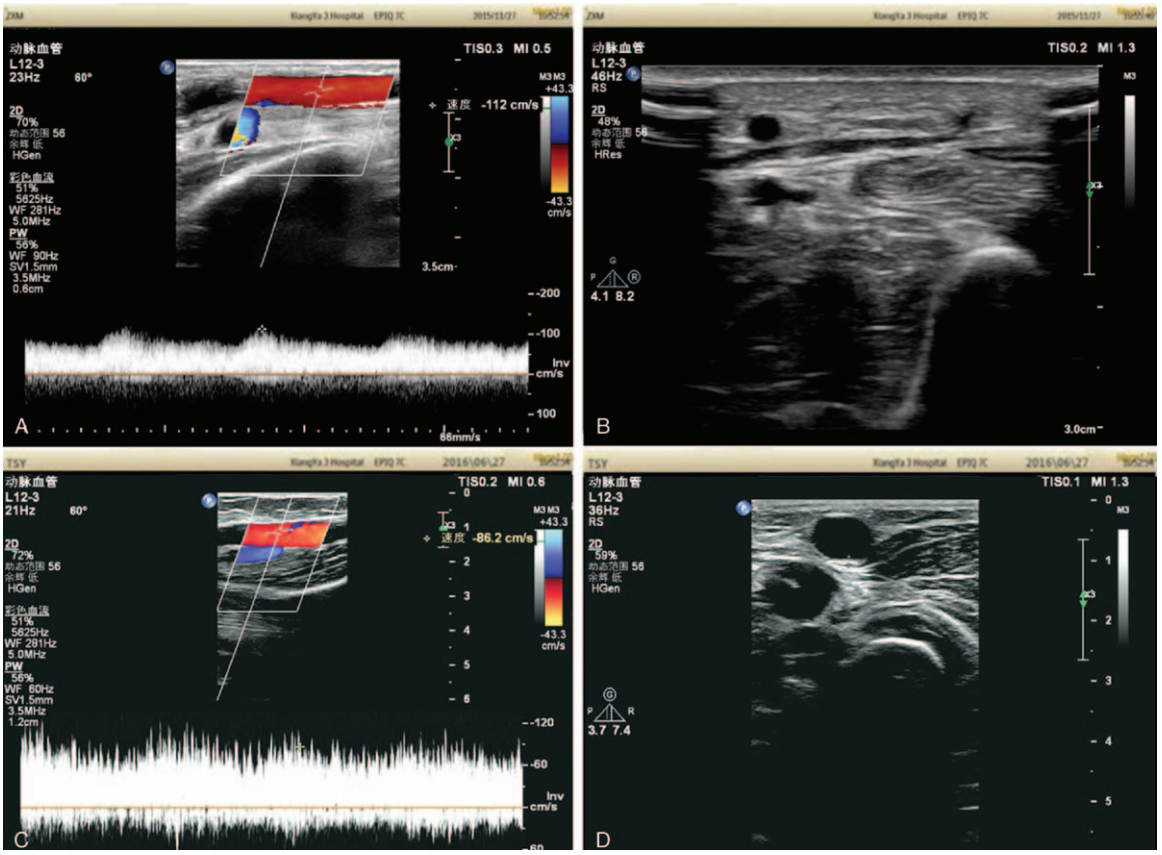

Figure 1. Typical color Doppler ultrasound images of the distal end of the arteriovenous fistula. (A and B) Control group; (C and D) Trial group. (C cf. A) The longitudinal section of the blood vessel shows the upper vein wall becoming thicker two years ago when the blood flows in the continuous spectrum. (D cf. B) The transverse section of the blood vessel shows the upper vein wall becoming thicker 2 years ago and shows the vein vessel diameter enlarging in the trial group.

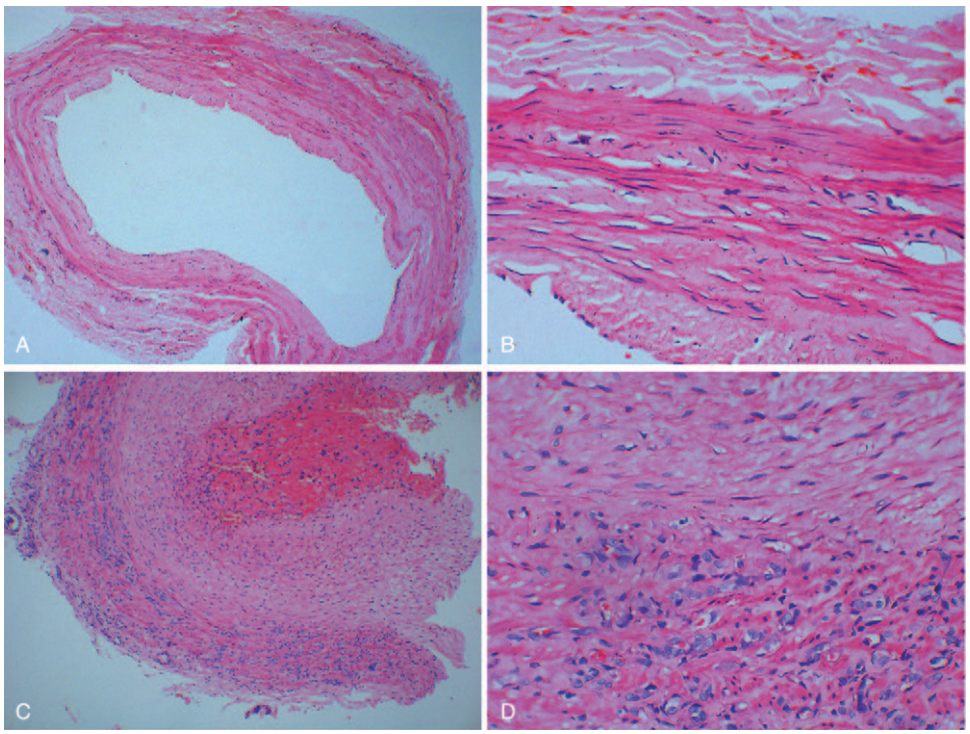

Figure 2. Immunohistochemical images (H&E staining) of the venous vessels at the fistula opening. (A) The fistula opening vein vessel, control group (10 × 10). (B) Fistula opening vein vessel (10 × 40), control group. (C) Fistula opening vein vessel (10 × 10), trial group. (D) Fistula opening vein vessel, trial group (10 × 40).

Table 1

Comparisons of blood compositions from the aortic sinus, radial artery, and peripheral vein by various indexes (n = 51).

	Aortic sinus	Radial artery	Peripheral vein	Test	*P*	*P*1	*P*2	P3
IgA, g/L	2.16 ± 0.96	2.11 ± 0.88	2.19 ± 0.92	0.10	.9049	1.0000	1.0000	1.0000
IgE, IU/mL	109.96 ± 186.81	111.62 ± 179.24	104.71 ± 165.29	0.02	.9823	1.0000	1.0000	1.0000
IgG, g/L	10.59 ± 2.94	10.61 ± 2.05	10.77 ± 2.47	0.07	.9321	1.0000	1.0000	1.0000
IgM, g/L	0.75 ± 0.49	0.76 ± 0.42	0.81 ± 0.45	0.17	.8464	1.0000	1.0000	1.0000
C3, g/L	0.95 ± 0.23	19.14 ± 122.09	0.97 ± 0.18	0.96	.3841	.6851	1.0000	0.7118
C4, g/L	0.27 ± 0.09	0.26 ± 0.08	0.27 ± 0.09	0.30	.7393	1.0000	1.0000	1.0000
ALT, U/L	34.26 ± 27.34	32.60 ± 25.59	33.04 ± 22.06	0.05	.9490	1.0000	1.0000	1.0000
TP, g/L	66.26 ± 6.51	64.52 ± 4.63	65.11 ± 4.43	1.16	.3173	.4091	.9581	1.0000
ALB, g/L	39.90 ± 3.77	39.00 ± 3.42	40.04 ± 2.87	1.13	.3263	.6936	1.0000	0.5058
GLB, g/L	26.36 ± 4.62	25.52 ± 3.87	25.31 ± 4.15	0.71	.4920	1.0000	.7816	1.0000
A/G	1.56 ± 0.28	1.57 ± 0.30	1.63 ± 0.26	0.68	.5087	1.0000	.8805	1.0000
TBIL, μmol/L	12.90 ± 7.02	13.20 ± 6.93	16.95 ± 16.86	1.68	.1915	1.0000	.3075	0.3853
AST, U/L	30 ± 24.54	29.21 ± 23.22	33.96 ± 25.84	0.50	.6092	1.0000	1.0000	1.0000
BUN, mmol/L	4.49 ± 1.72	4.52 ± 1.91	5.17 ± 1.62	2.04	.1346	1.0000	.2327	0.2555
Cr, μmol/L	80.02 ± 28.81	82.09 ± 26.04	79.04 ± 23.03	0.15	.8623	1.0000	1.0000	1.0000
UA, μmol/L	299.92 ± 94.47	310.58 ± 87.87	315.59 ± 87.50	0.33	.7193	1.0000	1.0000	1.0000
GLU, mmol/L	7.42 ± 2.51	7.33 ± 2.49	6.14 ± 1.84	4.33	.0152	1.0000	.0277	0.0540
TG, mmol/L	1.69 ± 1.34	1.95 ± 1.42	1.95 ± 1.84	0.36	.6950	1.0000	1.0000	1.0000
CHOL, mmol/L	4.19 ± 1.05	4.13 ± 0.95	4.47 ± 1.02	1.42	.2463	1.0000	.6159	0.3264
K, mmol/L	3.85 ± 1.04	3.81 ± 0.72	4.67 ± 4.69	1.22	.2994	1.0000	.5730	0.5168
Na, mmol/L	137.35 ± 21.17	142.73 ± 4.06	141.90 ± 2.73	2.23	.1119	.1529	.2956	1.0000
Ca, mmol/L	2.21 ± 0.27	2.27 ± 0.21	2.31 ± 0.15	2.14	.1216	.5661	.1327	1.0000
WBC, $\times 10^9$/L	6.63 ± 2.04	6.46 ± 1.65	7.22 ± 2.27	2.01	.1380	1.0000	.4114	0.1655
L, %	30.60 ± 9.30	30.09 ± 9.51	25.21 ± 9.84	4.82	.0095 *	1.0000	.0167	0.0336
N, %	60.38 ± 9.25	61.00 ± 9.37	65.95 ± 10.63	4.77	.0100 †	1.0000	.0165	0.0382
RBC, $\times 10^{12}$/L	4.18 ± 0.56	4.29 ± 0.64	4.42 ± 0.42	2.08	.1285	1.0000	.1303	0.8507
Hb, g/L	128.84 ± 18.06	131.60 ± 19.16	136.39 ± 13.60	2.29	.1049	1.0000	.1085	0.5680
Pt, $\times 10^9$/L	206.84 ± 69.29	203.16 ± 55.60	205.80 ± 56.46	0.04	.9569	1.0000	1.0000	1.0000
EO, %	1.76 ± 1.03	1.74 ± 0.86	1.67 ± 1.28	0.11	.8997	1.0000	1.0000	1.0000
BASO, %	0.39 ± 0.28	0.37 ± 0.25	0.38 ± 0.22	0.15	.8628	1.0000	1.0000	1.0000
MONO, %	6.63 ± 1.48	6.68 ± 1.47	6.13 ± 1.58	1.91	.1525	1.0000	.3263	0.2386

The blood composition data represented in the form of Xs following the tests and *P* values among the 3 different parts.

P values are the results of the variance analysis among the 3 groups: P1 is derived from the comparison between aortic sinus and radial artery; P2 is from the comparison between aortic sinus and peripheral vein; and P3 from the comparison between radial artery and peripheral vein.

A/G = albumin/globulin, ALB = albumin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BASO = basophils, BUN = urea nitrogen, C3 = complement C3, C4 = complement C4, Ca = calcium, CHOL = total cholesterol, Cr = creatinine, EO = eosinophils, GLB = globulin, GLU = glucose, Hb = hemoglobin, IgA = immunoglobulin A, IgE = immunoglobulin E, IgG = immune immunoglobulin G, IgM = immunoglobulin M, K = serum potassium, L = lymphocytes, MONO = monocytes, N = neutrophils, Na = blood sodium, Pt = platelet, RBC = red blood cells, TBIL = total bilirubin, TG = triglyceride, TP = total protein, UA = uric acid, WBC = white blood cells.

* *P* value is derived from the aortic sinus and peripheral vein, radial artery and peripheral vein, of lymphocyte percentage.

† *P* value is derived from the aortic sinus and peripheral vein, radial artery and peripheral vein, of neutrophil percentage.

collection, while the complete biochemical examinations indicated a significant difference in the glycemic index among the 3 groups ($F = 4.33$, $P = .0152$).

Further pairwise comparisons using the Bonferroni post-hoc test revealed that the glycemic value of blood from the peripheral vein group was significantly lower than that of the aortic sinus group ($P = .0277$). The glycemic value in the peripheral vein group was also lower than that of the radial artery group, although the difference was statistically insignificant ($P = .054$). In addition, the percentage of lymphocytes from these 3 groups showed statistically significant differences ($F = 4.82$, $P = .0095$). Further comparisons using the Bonferroni post-hoc test revealed that the percentage of lymphocytes in the blood of the peripheral vein group was significantly lower than that of the aortic sinus group ($P = .0167$) or radial artery group ($P = .0336$).

In addition, there was a significant difference in the percentages of neutral granulocytes among these 3 groups ($F = 4.77$, $P = .01$). Similar to the results for the percentage of lymphocytes, Bonferroni post-hoc analysis revealed that the percentage of neutral granulocytes of the peripheral vein group was significantly higher than that of the aortic sinus group ($P = .0165$) or the radial artery group ($P = .0382$). Thus, we conclude that the major difference in the compositions of arterial and venous blood is the percentages of lymphocytes and neutral granulocytes.

4. Discussion

There were 3 major findings obtained from the present study. In the trial group of patients who had undergone arteriovenous fistula surgery ≥2 years previously, vascular sclerosis occurred in the wall of the vein ≥5 cm away from the fistula opening. Second, in this group, also the vein under the fistula had obviously thickened and hardened. Finally, arterial blood contained a higher percentage of lymphocytes, and a lower percentage of neutral granulocytes, than venous blood. This may potentially contribute to the development of angiosclerosis, in addition to hemodynamics.

In the present study, we first conducted ultrasonography to examine the vessel walls in uremia patients who had undergone a venous fistula operation, either ≤1 month before (control group), or ≥2 years previously (trial group). We observed that in patients of the trial group, vascular sclerosis occurred in the walls of veins

>5 cm away downstream from the fistula opening. That is, obvious hardening and thickening had occurred after the veins had delivered a flow of arterial blood for a prolonged time, while hemodynamically the blood flow had turned into a stable and smooth venous blood flow. These findings were further supported by the immunohistochemical examination, which revealed significant intimal thickening of the venous wall under the fistula. Although previously a number of studies indicated an important role for hemodynamic changes after fistulation in the development of vascular sclerosis,[20] our findings support another notion that arterial blood may also contribute to the pathogenesis of angiosclerosis.

Previous studies relevant to ours mainly focused on the differences in oxygen saturation between arterial and venous blood.[21,22] To the best of our knowledge, our study is the first to comprehensively explore the differences between human arterial and venous blood, based on routine blood test, biochemical, and immunological indexes. We did not see any significant differences in composition in the blood between the aortic sinus and radial artery. Although a significant difference was detected in the blood glucose level between arterial and venous blood, the blood glucose level remained within the normal range. Thus, it is unlikely that the differences in blood glucose levels between arterial and venous blood contributed to the development of angiosclerosis.

Intriguingly, we found that the blood from the peripheral vein had a significantly lower percentage of lymphocytes, but a higher percentage of neutrophils, than that of the aortic sinus or radial artery. Previous studies suggested a link between blood components such as lipids, uric acid, and arterial sclerosis.[23,24] However, our study did not show any significant difference in these components between arterial and venous blood. The mechanisms accounting for this discrepancy between our findings and others are not clear; it is likely due to the participants selected and the sample size.

In the present study, we found that the percentage of lymphocytes in the arterial blood was significantly higher, but the percentage of neutrophils was lower, than that in venous blood. Previous studies proposed a link between the ratio of neutrophils and lymphocytes (N:L) in circulating blood and a number of cardiac diseases, including critical limb ischemia, coronary ectasia, and inflammatory vascular diseases.[25,26] However, those studies mainly used peripheral blood to investigate a link between the N:L and the severity of vascular diseases, and failed to show any difference between arterial and venous blood. In addition, an increase in the percentage of neutrophils generally reflects the presence of acute lesions,[27,28] while atherosclerosis is regarded as a chronic disease.[29,30]

On the basis of our findings, we speculate that high lymphocyte levels may promote filtration into venous walls and subsequently contribute to hardening and thickening of the venous wall.[31] However, the exact mechanisms by which an elevated percentage of lymphocytes in arterial blood (compared with that in venous blood) promote the pathogenesis of angiosclerosis remain to be elucidated.

The recycling of lymphocytes may potentially account for differences in the percentages of lymphocytes and neutrophils between the peripheral vein and artery.[32,33] In this recycling process, lymphocytes and other immune cells penetrate the postcapillary micro veins and enter the lymphatic tissues and organs, and from there they enter the lymphatic circulation. Thus, the lymphatic circulation and blood circulation are closely connected. On the basis of the recycling path of lymphocytes, we hypothesize a mechanism for the differences in percentages of lymphocytes between arterial and venous blood: at the postcapillary micro veins, some lymphocytes from the arterial blood may be transmitted to the lymphatic circulation, causing a change in the percentage of lymphocytes in the veins.

There are some limitations present in this study. While the sample size was small, the difference in the percentages of lymphocytes between arterial and venous blood was significant and consistent. In addition, the study only empirically indicated that lymphocytes might have an essential role in causing atherosclerosis. Further studies with a large cohort will be needed to provide further evidence that may directly link elevated lymphocyte levels in arterial blood to atherosclerosis.

In conclusion, we have demonstrated that arterial blood has a substantially higher percentage of lymphocytes, but a lower percentage of neutrophils, compared with venous blood. This is potentially responsible for the more frequent occurrence of vascular sclerosis in arteries than veins. This hypothesis needs to be further examined in more mechanistic studies, both in vitro and in vivo.

Author contributions

Conceptualization: Li-ping Peng, Juan Wen.
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Formal analysis: Li-ping Peng, Juan Wen.
Investigation: Li-ping Peng, Juan Wen.
Methodology: Li-ping Peng, Juan Wen, Kan Yang, Shao-li Zhao, Jia Dai, Zhong-shu Liang, Yu Cao.
Project administration: Li-ping Peng.
Writing – original draft: Li-ping Peng.
Writing – review & editing: Juan Wen.

References

[1] Newby AC. Metalloproteinases promote plaque rupture and myocardial infarction: a persuasive concept waiting for clinical translation. Matrix Biol 2015;44–46:157–66.
[2] Williams KJ, Tabas I. The response-to-retention hypothesis of early atherogenesis. Arterioscler Thromb Vasc Biol 1995;15:551–61.
[3] Wysokinski W, Karnicki K, McBane RD2nd. Individual propensity for thrombosis: comparison of venous and arterial circulations. Thromb Res 2008;122:390–6.
[4] Coccheri S. Biological and clinical effects of sulodexide in arterial disorders and diseases. Int Angiol 2014;33:263–74.
[5] dela Paz NG, D'Amore PA. Arterial versus venous endothelial cells. Cell Tissue Res 2009;335:5–16.
[6] Lippi G, Franchini M, Targher G. Arterial thrombus formation in cardiovascular disease. Nat Rev Cardiol 2011;8:502–12.
[7] Hagger D, Condliffe R, Woodhouse N, et al. Ventricular mass index correlates with pulmonary artery pressure and predicts survival in suspected systemic sclerosis-associated pulmonary arterial hypertension. Rheumatology (Oxford) 2009;48:1137–42.
[8] Morales-Cardenas A, Perez-Madrid C, Arias L, et al. Pulmonary involvement in systemic sclerosis. Autoimmun Rev 2016;15:1094–108.
[9] Davi G, Patrono C. Platelet activation and atherothrombosis. N Engl J Med 2007;357:2482–94.
[10] Ucar FM, Acar B, Gul M, et al. The association between platelet/lymphocyte ratio and coronary artery disease severity in asymptomatic low ejection fraction patients. Korean Circ J 2016;46:821–6.
[11] Desai M, Mirzay-Razzaz J, von Delft D, et al. Inhibition of neointimal formation and hyperplasia in vein grafts by external stent/sheath. Vasc Med 2010;15:287–97.
[12] Jeremy JY, Mehta D, Bryan AJ, et al. Platelets and saphenous vein graft failure following coronary artery bypass surgery. Platelets 1997;8:295–309.
[13] Fitzgibbon GM, Kafka HP, Leach AJ, et al. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. J Am Coll Cardiol 1996;28:616–26.

[14] Grondin CM, Campeau L, Thornton JC, et al. Coronary artery bypass grafting with saphenous vein. Circulation 1989;79:I24–9.
[15] Parang P, Arora R. Coronary vein graft disease: pathogenesis and prevention. Can J Cardiol 2009;25:e57–62.
[16] de Vries MR, Simons KH, Jukema JW, et al. Vein graft failure: from pathophysiology to clinical outcomes. Nat Rev Cardiol 2016;13:451–70.
[17] Subbotin VM. Analysis of arterial intimal hyperplasia: review and hypothesis. Theor Biol Med Model 2007;4:41.
[18] Singh RB, Mengi SA, Xu YJ, et al. Pathogenesis of atherosclerosis: a multifactorial process. Exp Clin Cardiol 2002;7:40–53.
[19] Zwiebel WJ. Peripheral vascular system. Ultrasound Med Biol 2000;26 (suppl 1):S92–6.
[20] Beggs CB. Venous hemodynamics in neurological disorders: an analytical review with hydrodynamic analysis. BMC Med 2013;11:142.
[21] Englund EK, Langham MC, Ratcliffe SJ, et al. Multiparametric assessment of vascular function in peripheral artery disease: dynamic measurement of skeletal muscle perfusion, blood-oxygen-level dependent signal, and venous oxygen saturation. Circ Cardiovasc Imaging 2015;8(4.):
[22] Langham MC, Floyd TF, Mohler ER3rd, et al. Evaluation of cuff-induced ischemia in the lower extremity by magnetic resonance oximetry. J Am Coll Cardiol 2010;55:598–606.
[23] Dorn GW2nd. Shared genetic risk for sclerosis of valves and vessels. N Engl J Med 2013;368:569–70.
[24] Hurtubise J, McLellan K, Durr K, et al. The different facets of dyslipidemia and hypertension in atherosclerosis. Curr Atheroscler Rep 2016;18:82.
[25] Belaj K, Pichler M, Hackl G, et al. Association of the derived neutrophil-lymphocyte ratio with critical limb ischemia. Angiology 2016;67: 350–4.
[26] Hyun S, Kwon S, Cho S, et al. Can the neutrophil-to-lymphocyte ratio appropriately predict carotid artery stenosis in patients with ischemic stroke? A retrospective study. J Stroke Cerebrovasc Dis 2015;24:2646–51.
[27] Yu C, Chen M, Chen Z, et al. Predictive and prognostic value of admission neutrophil-to-lymphocyte ratio in patients with CHD. Herz 2016;41:605–13.
[28] Zhao N, Mi L, Zhang Y, et al. Altered human neutrophil FcgammaRI and FcgammaRIII but not FcgammaRII expression is associated with the acute coronary event in patients with coronary artery disease. Coron Artery Dis 2017;28:63–9.
[29] Boteanu RM, Suica VI, Uyy E, et al. Alarmins in chronic non-communicable diseases: atherosclerosis, diabetes and cancer. J Proteomics 2017;153:21–9.
[30] Fatkhullina AR, Peshkova IO, Koltsova EK. The role of cytokines in the development of atherosclerosis. Biochemistry (Mosc) 2016;81:1358–70.
[31] Pattanaik D, Brown M, Postlethwaite AE. Vascular involvement in systemic sclerosis (scleroderma). J Inflamm Res 2011;4:105–25.
[32] Suzuki K, Hayano Y, Nakai A, et al. Adrenergic control of the adaptive immune response by diurnal lymphocyte recirculation through lymph nodes. J Exp Med 2016;213:2567–74.
[33] Wiedle G, Dunon D, Imhof BA. Current concepts in lymphocyte homing and recirculation. Crit Rev Clin Lab Sci 2001;38:1–31.