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Characterizing Non-Newtonian Blood Viscosity Using Automated Scanning Capillary Viscometry: Reference Intervals and Determinants

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Abstract

Whole blood viscosity (WBV) is a key hemorheological property influenced by cellular and biochemical factors and is associated with cardiovascular, cerebrovascular, and microcirculatory disorders. Despite its clinical relevance, comprehensive reference intervals for WBV and oxygen delivery indices—the ODI (oxygen delivery index) and TODI (tissue oxygen delivery index)—in healthy male and female adults have not been established. The objectives of this study were to (1) determine sex-specific reference intervals of WBV in healthy adults, (2) establish reference intervals for the ODI and TODI, and (3) evaluate the influence of hematologic, biochemical, lipid, and non-lipid determinants—as well as the effects of age—on systolic and diastolic blood viscosity (SBV and DBV). WBV was measured across nine shear rates (1–1000 s^{-1}) in 150 healthy men and 150 healthy women using an automated scanning capillary tube viscometer (SCTV). Hematologic and biochemical profiles were obtained, and correlations with DBV and SBV were assessed. Reference intervals were calculated using CLSI-recommended nonparametric methods. WBV was consistently higher in men than women across all shear rates, with sex-based differences accentuated at low shear. Hemoglobin and hematocrit showed the strongest positive correlations with WBV ($r \approx 0.77$–0.80), while RDW and HDL cholesterol showed negative associations. Triglycerides exhibited strong viscosity-enhancing effects in men, whereas total cholesterol, LDL, and triglycerides were all significantly increased viscosity in women. Protein-related determinants (total protein, albumin, and γ-gap) displayed striking sex divergence, with strong positive associations in men but attenuated or negative associations in women. Age showed no meaningful relationship with WBV in either sex. Reference intervals for the ODI and TODI revealed modest sex differences with tighter distributions in women. WBV, ODI, and TODI demonstrate clear sex-specific physiological patterns in healthy adults. Hematocrit remains the dominant determinant of blood viscosity, while lipid and protein-related factors contribute differently in men and women. These newly established reference intervals provide essential benchmarks for clinical interpretation and for understanding viscosity-related risk in cardiovascular and microcirculatory disease.

Check for updates

Academic Editor: Weiyong Liu

Received: 11 March 2026
Revised: 16 April 2026
Accepted: 22 April 2026
Published: 6 May 2026

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Keywords: whole blood viscosity; hemorheology; oxygen delivery index (ODI); tissue oxygen delivery index (TODI); shear rate

1. Introduction

Whole blood viscosity (WBV) represents the frictional resistance between flowing blood and the vessel wall and is a key hemorheological parameter that has been reported to be directly or indirectly associated with various pathophysiological conditions, including cardiovascular and cerebrovascular diseases, metabolic disorders, and microcirculatory dysfunction [1,2]. WBV is a unique physical property of blood that varies between individuals and exhibits non-Newtonian, shear-thinning behavior. The major rheological determinants of WBV include hematocrit (HCT), plasma viscosity, and plasma proteins such as fibrinogen and immunoglobulins [1–5]. Lipid components—including LDL, VLDL, triglycerides, and HDL—also influence WBV [1,5,6]. Among these determinants, HCT accounts for approximately 75% of the magnitude of WBV, followed by red blood cell aggregability (≈10%), red blood cell rigidity (≈3%), plasma viscosity (≈3%), and other minor contributors [7].

Since the HCT carries oxygen, one may assume that the larger the HCT, the more oxygen can be delivered from the heart to tissue. Increased HCT increases WBV and the frictional resistance at the lumen wall, but it is unclear whether it is helpful in oxygen delivery.

Thus, there is a need to examine the association between HCT and WBV in the context of oxygen delivery. HCT is a fixed property in a person at a given time, while the non-Newtonian blood viscosity varies with the shear rate, which represents the ratio of mean blood velocity, V, to lumen diameter, d [1,2]. Accordingly, the WBV value constantly changes over a cardiac cycle and in position. For example, WBV has a minimum value of approximately 4 cP (centipoise) primarily due to dispersed red blood cells at large arteries (such as the aorta, femoral, carotid, and coronary arteries) at systolic flow conditions, which correspond to an asymptotic shear rate ($\geq$300 s^{-1}) [1,2].

WBV increases by three or four folds from its minimum value as blood slows down to a velocity of <0.05 cm/s in microvessels during diastolic flow conditions (excluding coronary flow) [2,8], a phenomenon which can be attributed to the aggregability and rigidity of red blood cells [1–3]. Although WBV varies over a shear rate range (1–1000 s^{-1}) in vivo, it is impractical to report WBV values at multiple shear rates in most clinical cases. Thus, the WBV measured at a shear rate of 300 s^{-1} is often used as the representative value for systolic flow conditions and is referred to as systolic blood viscosity (SBV) [9]. Similarly, the WBV measured at a shear rate of 5 s^{-1} is often used as the representative value for diastolic flow conditions (DBV) (excluding coronary flow) [9].

Kameneva et al. [10] introduced the ODI (oxygen delivery index) as a ratio of HCT to WBV at an asymptotic shear rate. The ODI can be considered an indirect characterization of oxygen transport to organs and tissues.

$$\text{ODI} = \frac{Hematocrit\ (\%)}{WBV\ at\ asymptotic\ shear\ rate} \quad (1)$$

Considering that the blood velocity at tissue level (i.e., microvessels) is extremely small [8], Yi and Youn introduced the TODI (tissue oxygen delivery index) as the ratio of hematocrit to WBV measured at a low shear rate of 5 s^{-1} [11].

$$\text{TODI} = \frac{Hematocrit\ (\%)}{WBV\ at\ 5\ s^{-1}} \quad (2)$$

To the authors' knowledge, the reference intervals of the ODI and TODI for healthy adults have not been reported. To establish these reference intervals, the reference interval of WBV in healthy male and female adults is required.

Therefore, the objectives of the present study are:

(1) To obtain the reference intervals of WBV in healthy male and female adults;

(2) To obtain the reference intervals of the ODI and TODI in healthy male and female adults;

(3) To investigate the effects of blood and serum test results on SBV and DBV;

(4) To investigate effects of age on SBV and DBV.

2. Methods

2.1. Viscosity Measurements

The viscosity of a non-Newtonian fluid varies with the shear rate, which is a measure of how quickly adjacent layers of a fluid move relative to each other. Mathematically, the shear rate is the velocity gradient, i.e., the first derivative of the fluid's velocity profile with respect to the spatial coordinate normal to the flow direction [1,2,12].

Figure 1 shows various viscometers used for viscosity measurements of non-Newtonian fluids (such as paint, blood, ketchup, milk, and aqueous polymer solutions) [13]. Although these viscometers do not provide shear-rate-dependent viscosity, they are currently used for quality control.

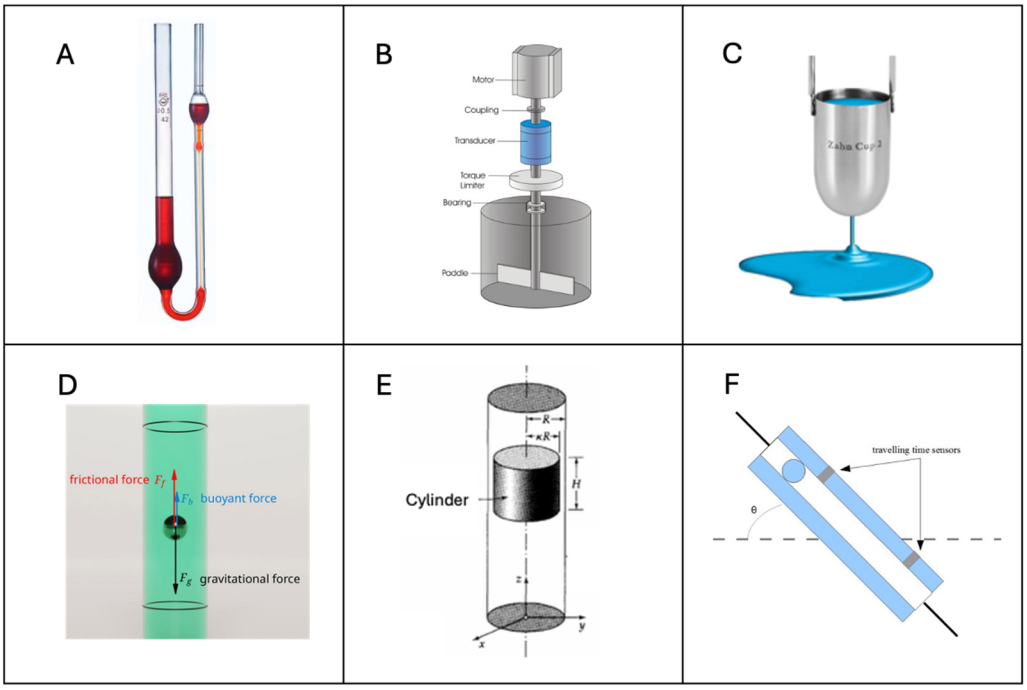


Figure 1. Various viscometers used for viscosity measurement of non-Newtonian fluids: (**A**) (cannon capillary viscometer), (**B**) (rotating paddle viscometer), (**C**) (Zahn cup viscometer), (**D**) (falling sphere viscometer), (**E**) (falling cylinder viscometer), and (**F**) (rolling sphere viscometer) [13].

2.2. Measurements of Non-Newtonian Blood Viscosity

To measure blood viscosity, viscometers with which the shear rate can experimentally be determined are required. Over the years, rotational viscometers such as Couette viscometers and cone-and-plate viscometers (see Figure 2) have been the standard in clinical studies [1,2,13]. One concern is the need to clean the test section after each measurement [14], which poses a potential risk of contact with contaminated blood. To minimize

this risk, a scanning capillary tube viscometer (SCTV) (see Figure 2) has recently been developed, which utilizes a disposable part to avoid contact with blood [15].

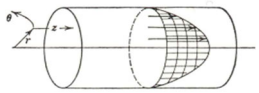
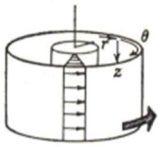
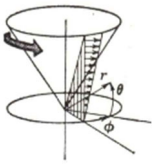
Flow geometry	Viscometer	Configuration	Coordinates (x_1 x_2 x_3)	Wall shear rate
Poiseuille flow	Scanning capillary tube viscometer (SCTV)		(z r θ)	$\dot{\gamma}_{wall} = \frac{3n+1}{4n}\frac{8V}{d}$ n is power-law model index.
Couette flow	Coaxial cylinder rotating viscometer		(θ r z)	$\dot{\gamma}_{wall} = \frac{\Omega}{\left(1-\frac{R_i}{R_o}\right)}$ Ω is angular velocity (rad/s). R is radius with small gap.
Cone-and-plate flow	Cone-and-plate rotating viscometer		(ϕ θ r)	$\dot{\gamma}_{wall} = \frac{\Omega}{\Psi_o}$ Ω is angular velocity (rad/s). Ψ_o is cone angle.

Figure 2. Simple shear flows in viscometers designed for non-Newtonian viscosity measurements and mathematical equations of the wall shear rate [1,12,13].

Viscometers designed for non-Newtonian viscosity measurements are built based on the so-called "simple shear flow", where there is a non-zero component of velocity in only a single direction (see x_1-coordinate in Figure 2) [12]. Note that the shear rate $\dot{\gamma}$ is defined as the velocity gradient of the non-zero component of velocity along the x_2-coordinate [12,13].

The shear rate in Couette or cone-and-plate viscometers can be mathematically determined from the rotational speed Ω (rad/s) of the cylinder or cone, as shown in Figure 2 [2,12–14]. In a capillary tube viscometer with a circular cross-section, the shear rate can be obtained from the Poiseuille flow theory, which is essentially proportional to 8 V/d [1,2,12–14].

For non-Newtonian fluids, it is common to define the apparent viscosity μ of a fluid as the ratio of the wall shear stress to the shear rate at the wall [2,12,13].

$$\mu = \frac{\tau_{wall}}{\dot{\gamma}_{wall}} \quad (3)$$

2.3. Scanning Capillary Tube Viscometer

The SCTV uses a disposable U-tube, consisting of a horizontal capillary tube that connects the lower ends of two vertical tubes [15]. The capillary tube is made of stainless steel with a circular cross-section, an inner diameter of 0.8 mm, and a length of 10 cm. The transparent vertical tubes have an inner diameter of approximately 3.0 mm and a height of about 14 cm.

The pressure drop across the capillary tube is determined from the height difference between the two vertical tubes, $h_2(t) - h_1(t)$. The wall shear rate is obtained by differentiating the h(t) curve [15]. The mathematical algorithm used to calculate shear stress, shear rate, and apparent blood viscosity is based on the Casson model [15].

For analytical performance validation, we recently reported the results of the precision tests (both within-run and between-day) in accordance with CLSI protocol using normal

and abnormal QC materials [16]. Comparison test was also conducted between the first- and second-generation SCTVs at two representative shear rates of 5 and 300 s^{-1} with 42 blood samples at 37 °C. The second-generation viscometer showed excellent CVs in both within-day and between-day precision tests. The comparison tests showed acceptable normality with the correlation coefficient (R) of 0.95 and the mean bias% of less than −3.3%. The results in the present study were obtained using the automated second-generation SCTV (Hemovister 2.0 from Ubiosis, Seongnam, Republic of Korea).

2.4. Blood Samples

In the present study, whole blood samples from 150 healthy males and 150 healthy females were analyzed to determine WBV using the SCTV. Whole blood samples were collected from the antecubital vein into EDTA-containing vacuum tubes using standardized phlebotomy procedures at accredited blood donation centers [14]. Immediately after collection, tubes were gently inverted according to routine clinical laboratory practice to ensure adequate anticoagulant mixing. Samples were handled under controlled conditions consistent with routine donor screening protocols.

Prior to viscosity measurement, all samples were equilibrated at 37 °C for a minimum of 5 min using the automated temperature-controlled chamber of the SCTV, in accordance with manufacturer recommendations and established hemorheological guidelines. Viscosity measurements were performed using disposable flow paths, minimizing pre-analytical handling variability and eliminating carryover or cleaning effects. All measurements were conducted under identical pre-analytical and analytical conditions.

2.5. Study Population and Subject Selection

Participants in this study were adult men and women who voluntarily visited the Hanmaeum Blood Center or designated blood donation cafés in Seoul, Korea. Individuals who consented to donate blood and met the standard eligibility criteria for donation were considered for inclusion. Among these, those who received a full explanation of the study and provided written informed consent were enrolled.

Eligible participants were adults aged 19 to 69 years who were assessed as being in good health based on a standardized pre-donation health questionnaire and interview. Individuals were excluded if they had a history of cardiovascular or cerebrovascular disease, malignancy, or chronic inflammatory conditions (e.g., rheumatoid or other autoimmune rheumatic disorders). Those diagnosed with diabetes mellitus, hypertension, or dyslipidemia and currently receiving pharmacologic treatment for these conditions were also excluded. The use of non-pharmaceutical health supplements, such as vitamins or red ginseng products, was not considered an exclusion criterion.

The study protocol was approved by the Ethics Committee of the Hanmaeum Blood Center (Korea), and informed consent was obtained in accordance with institutional guidelines.

2.6. Statistical Analysis

Statistical analyses were performed using SAS software (PROC TTEST). Continuous variables are presented as the mean ± standard deviation (SD). Differences between males and females were assessed using the Welch two-sample *t*-test, which does not assume equal variances between groups. Degrees of freedom were estimated using the Satterthwaite approximation, and all statistical tests were two-sided. A p-value < 0.05 was considered statistically significant.

3. Results

Table 1 summarizes the baseline characteristics of the healthy male and female subgroups for the reference interval study. In the whole blood analysis, there was no sig-

nificant difference in age between males and females (35.5 ± 11.3 vs. 35.5 ± 11.3 years, $p = 0.165$). Compared with females, males exhibited significantly higher levels of WBC, RBC, hemoglobin (Hb), and hematocrit (HCT) (all $p < 0.001$). Conversely, RDW and ESR were significantly higher in females than in males ($p < 0.001$).

Table 1. Baseline characteristics of healthy male and female subgroups in the present study.

		Mean ± SD (cP)	**Mean ± SD (cP)**	***p* Value**
		Male (n = 150)	**Female (n = 150)**	
Blood test	Age	35.5 ± 11.3	35.5 ± 11.3	0.165
	WBC	6.2 ± 1.4	6.7 ± 1.7	<0.004
	RBC	5.0 ± 0.4	4.4 ± 0.3	<0.0001
	Hb	14.7 ± 1.1	12.7 ± 1.0	<0.0001
	HCT	44.5 ± 3.0	39.3 ± 2.7	<0.0001
	RDW	12.5 ± 1.3	13.2 ± 1.4	<0.0001
	Platelet	262.7 ± 57.9	266.0 ± 65.0	0.644
	ESR	2.9 ± 2.2	6.5 ± 6.8	<0.0001
Serum test		Male (n = 150)	Female (n = 134)	
	Protein, total	7.1 ± 0.9	6.8 ± 1.1	<0.024
	Albumin	4.3 ± 0.5	4.0 ± 0.6	<0.0001
	BUN	13.7 ± 3.8	11.8 ± 3.7	<0.0001
	Creatinine	1.0 ± 0.2	0.7 ± 0.1	<0.0001
	AST	26.6 ± 9.9	21.4 ± 8.2	<0.0001
	ALT	26.4 ± 18.6	15.6 ± 10.3	<0.0001
	T. Chol	196.8 ± 18.6	196.2 ± 43.8	0.916
	TG	176.3 ± 169.0	108.6 ± 67.1	<0.0001
	HDL-C	53.4 ± 13.7	63.6 ± 16.9	<0.0001
	LDL-C	112.3 ± 30.3	106.8 ± 32.8	0.142
	Ferritin	91.0 ± 94.1	43.2 ± 46	<0.0001

In the serum analysis, males demonstrated significantly higher concentrations of total protein, albumin, blood urea nitrogen (BUN), creatinine, AST, ALT, triglycerides, LDL cholesterol, and ferritin compared with females (all $p < 0.05$). In contrast, HDL cholesterol concentrations were significantly higher in females ($p < 0.001$).

Table 2 shows the Pearson correlation coefficients (r) and corresponding *p*-values for associations between WBV and selected hematologic parameters, serum biochemical markers, lipid indices, and oxygen delivery indices (ODI and TODI). Significant associations were observed between WBV and multiple hematologic and biochemical markers. Hemoglobin and hematocrit demonstrated the strongest positive correlations with blood viscosity (DBV: r = 0.784 and r = 0.770; SBV: r = 0.797 and r = 0.786; all $p < 0.001$). RBC distribution width showed a modest negative association (DBV: r = –0.214; SBV: r = –0.211; both $p < 0.001$), while platelet count was not significantly correlated with viscosity at either shear rate.

Among inflammatory and metabolic markers, ESR was weakly but significantly inversely associated with blood viscosity (DBV: r = –0.147, $p = 0.011$; SBV: r = –0.157, $p = 0.006$). Total protein and albumin showed small but significant positive correlations (DBV r = 0.237 and r = 0.257; SBV r = 0.223 and r = 0.245; all $p < 0.001$), whereas BUN was not significantly associated with blood viscosity. Liver enzymes demonstrated moderate positive relationships with blood viscosity, particularly ALT (DBV: r = 0.466; SBV: r = 0.477; both $p < 0.001$) and AST (DBV: r = 0.418; SBV: r = 0.409; both $p < 0.001$). Lipid parameters showed divergent patterns: triglycerides and LDL-C correlated positively with blood viscosity, while HDL-C correlated negatively (all $p < 0.05$). Ferritin was moderately associated with blood viscosity (DBV: r = 0.318; SBV: r = 0.319; both $p < 0.001$). Oxygen delivery indices, the ODI and TODI, exhibited strong inverse correlations with both DBV and SBV, particularly the TODI (DBV:

r = –0.846; SBV: r = –0.762; both $p < 0.001$). Collectively, these findings demonstrate that both hematologic concentration parameters and metabolic factors contribute significantly to variations in WBV across physiologically relevant shear conditions.

Table 2. Pearson correlation coefficients (r) and corresponding *p*-values for associations between WBV and selected hematologic parameters, serum biochemical markers, lipid indices, and oxygen delivery indices (ODI and TODI).

		vs. DBV (cP)		vs. SBV (cP)	
Marker	**n**	**r**	***p* Value**	**r**	***p* Value**
WBC	300	0.021	0.072	0.006	0.915
Hb	300	0.784	<0.0001	0.797	<0.0001
HCT	300	0.770	<0.0001	0.786	<0.0001
RDW	300	−0.214	<0.0001	−0.211	<0.0001
Platelet	300	0.009	0.872	0.010	0.868
ESR	300	−0.147	0.011	−0.157	0.006
T. Protein	284	0.237	<0.0001	0.223	<0.0001
Albumin	284	0.257	<0.0001	0.245	<0.0001
BUN	284	0.083	0.162	0.082	0.169
Creatine	284	0.399	<0.0001	0.375	<0.0001
AST	284	0.418	<0.0001	0.409	<0.0001
ALT	284	0.466	<0.0001	0.477	<0.0001
T. Chol.	284	0.153	0.010	0.145	0.014
TG	284	0.377	<0.0001	0.388	<0.0001
HDL-c	284	−0.196	<0.0001	−0.210	<0.0001
LDL-c	284	0.141	0.017	0.134	0.023
Ferritin	284	0.318	<0.0001	0.319	<0.0001
ODI	300	−0.687	<0.0001	−0.743	<0.0001
TODI	300	−0.846	<0.0001	−0.762	<0.0001

Table 3 presents the reference intervals for WBV at nine shear rates, determined using the central 90th percentile distribution from measurements in 150 healthy males and 150 healthy females. WBV is consistently higher in males in the entire shear rate range. The sex-related difference is small at high shear rates but becomes more pronounced at lower shear rates. For example, at a shear rate of 300 s^{-1}, male WBV is approximately 4% higher than female WBV, whereas at a shear rate of 5 s^{-1}, male WBV is approximately 18% higher

Table 3. Results of reference intervals for whole blood viscosity based on central 90 percentiles in healthy men and women for specific shear rates. Note that the 90% reference interval was evaluated with the nonparametric method, which is recommended by the CLSI guidelines for sample sizes of 120 or more.

	WBV for Males (n = 150)				WBV for Females (n = 150)			
Shear Rate (s^{-1})	**Mean (cP)**	**SD (cP)**	**Median (cP)**	**90% Ref. Interval (cP)**	**Mean (cP)**	**SD (cP)**	**Median (cP)**	**90% Ref. Interval (cP)**
1	36.19	6.18	35.15	25.3–54.3	29.57	3.2	29.6	22.7–36.3
2	23.34	3.98	22.55	16.6–35.1	19.12	1.92	19.2	15–23.1
5	14.28	2.47	13.65	10.4–21.6	11.76	1.07	11.8	9.4–13.9
10	10.52	1.8	10	7.8–15.8	8.72	0.73	8.7	7.1–10.3
50	6.34	1.03	6	4.9–8.8	5.38	0.38	5.4	4.5–6.3
100	5.57	0.89	5.3	4.3–7.9	4.7	0.32	4.7	3.9–5.5
150	5.2	0.79	4.9	4.1–7.1	4.41	0.28	4.4	3.7–5.1
300	4.72	0.69	4.5	3.7–6.6	4.02	0.27	4	3.4–4.6
1000	4.16	0.67	4	3.1–6.1	3.51	0.32	3.5	2.8–4.4

Figure 3 shows WBV plotted against age for healthy male and female adults. WBV exhibited no meaningful dependence on age in either sex, as reflected by the regression co-

efficients (β) that were effectively zero at both shear rates (DBV: male β = −0.0176 cP/year, female β = +0.0089 cP/year; SBV: male β = −0.0036 cP/year, female β = +0.0009 cP/year). These near-zero β values confirm that WBV does not increase with age in this population. Across age groups, WBV levels in women differed only modestly from those of men, and the age-stratified patterns remained broadly similar. Notably, WBV values displayed substantially greater dispersion in males, whereas females showed tighter clustering around their fitted regression lines at both shear rates, consistent with smaller standard deviations. Overall, these findings indicate that WBV remains stable with age in healthy adults and that sex-related differences reflect differences in variability—with greater inter-individual variability in men and narrower dispersion in women—rather than differences in age-related trajectories.

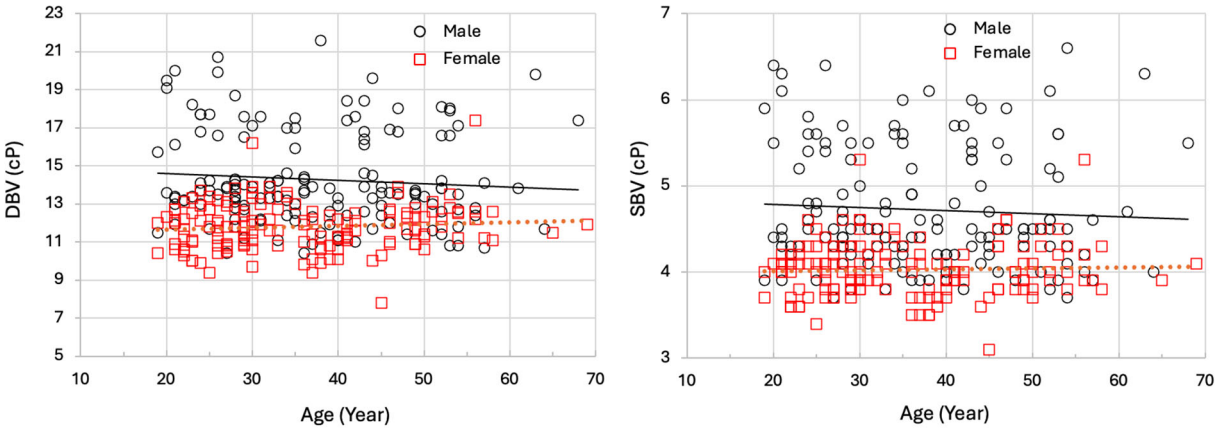


Figure 3. DBV and SBV vs. age for healthy male and female adults.

Figure 4 shows blood viscosity vs. HCT and ferritin for healthy male and female adults. Hematocrit demonstrated a consistently positive association with blood viscosity across measurement conditions, with males showing a steeper relationship than females. At a low shear rate, DBV increased more sharply with rising hematocrit in males (β = +0.5806 cP per % HCT) compared with females (β = +0.2907), indicating a stronger rheological sensitivity to red cell volume fraction in males. In contrast, ferritin displayed sex-divergent associations with viscosity. Among females, increases in ferritin were accompanied by modest elevations in viscosity at both low and high shear rates (DBV β = +0.0132; SBV β = +0.0034), whereas males exhibited negative slopes (DBV β= −0.0064; SBV β= −0.002), suggesting that viscosity tended to decrease as ferritin rose. These patterns indicate that while hematocrit exerts a predictable and uniform effect on blood viscosity in both sexes, ferritin relates to viscosity in a sex-specific manner, potentially reflecting underlying differences in iron metabolism, inflammatory signaling, or erythrocyte/plasma compositional factors between males and females.

Figure 5 shows the ODI vs. SBV and the TODI vs. DBV for healthy male and female adults. Both the ODI and TODI exhibited clear inverse linear relationships with blood viscosity, and in both indices, the fitted values for males were consistently higher than those for females across the observed viscosity range, a pattern attributable to generally higher hematocrit levels in men, which enhance oxygen delivery capacity. The ODI declined with increasing SBV for both sexes, with similarly negative slopes (male β = −1.2023; female β = −0.9646), yet the male regression line remained uniformly above the female line, indicating greater overall oxygen delivery efficiency in men despite comparable viscosity-dependent trends. Likewise, the TODI decreased with rising DBV, with nearly identical slopes in males and females (male β = −0.1443; female β = −0.1568). Again, male fitted values exceeded female counterparts throughout the viscosity range, reflecting a modest

but consistent advantage in microvascular oxygen delivery capacity. The tight clustering of data around the fitted lines for both the ODI and TODI further underscore their stability in healthy adults.

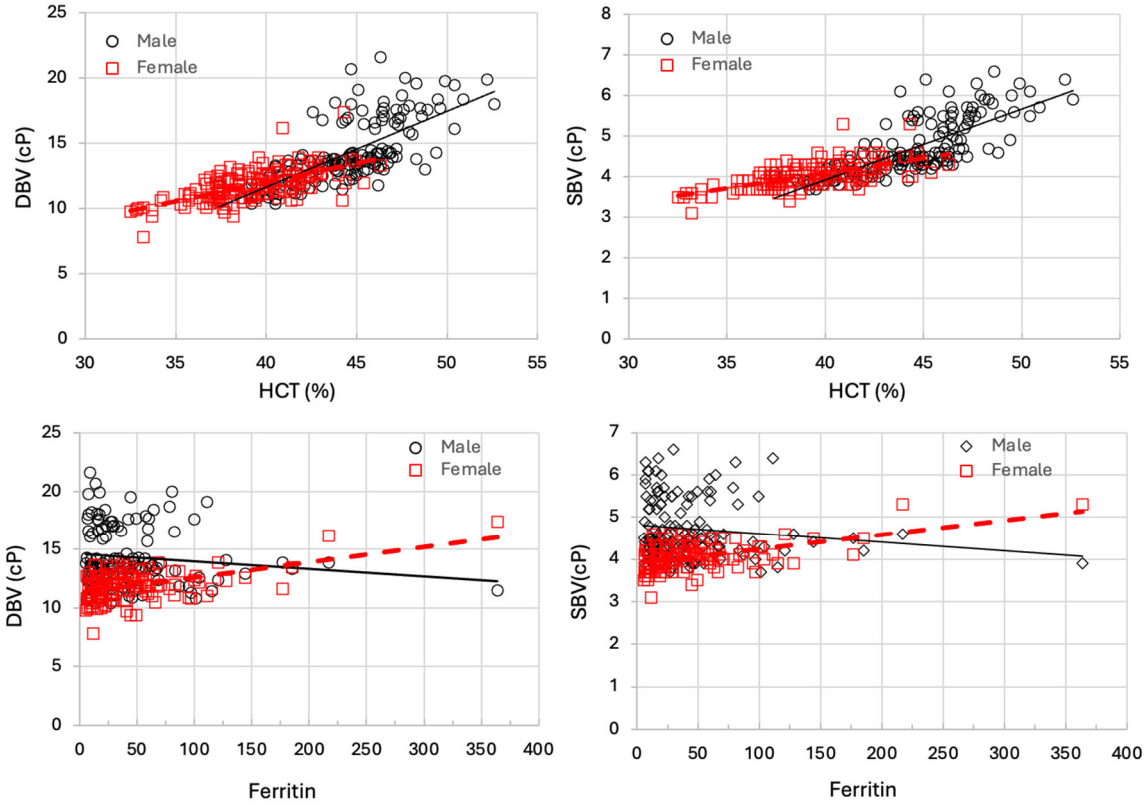


Figure 4. WBV data at shear rates of 5 and 300 s^{-1} vs. HCT and ferritin for male and female adults.

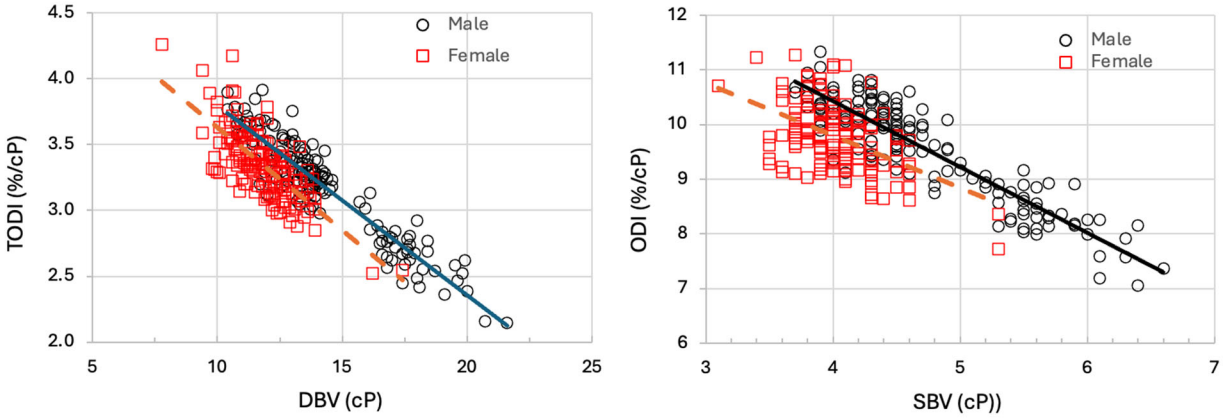


Figure 5. TODI vs. DBV and ODI vs. SBV for healthy male and female adults.

Table 4 shows sex-specific and overall distributions and nonparametric reference intervals for the TODI and ODI, which show clear but modest sex-related differences in this healthy cohort. The mean ODI was slightly higher in females than males (9.776 vs. 9.558), and females also exhibited a narrower distribution, as reflected by a smaller standard deviation (0.603 vs. 0.922) and tighter 2.5th–97.5th percentile range (8.647–11.056 vs. 7.585–10.811). The mean TODI values were also higher in females (mean 3.349 vs. 3.179) and displayed less variability (SD 0.267 vs. 0.382), with higher median values and narrower reference limits (2.899–3.900 vs. 2.410–3.778). These results indicate that females demonstrated slightly greater and more tightly regulated oxygen delivery efficiency at both the large artery and tissue levels, whereas males exhibited wider physiologic variability

across both indices. These reference intervals provide clinically meaningful benchmarks. For example, when a patient's TODI value falls below the mean value, it indicates reduced oxygen delivery capability at tissue level.

Table 4. Sex-specific and overall distributions and nonparametric reference ranges for TODI and ODI (2.5th–97.5th percentiles). Unit of ODI and TODI: HCT%/cP.

Metric	Sex	n	Mean (%/cP)	SD (%/cP)	Median (%/cP)	2.5–97.5 Percentiles	Min (%/cP)	Max (%/cP)
ODI	All	300	9.667	0.786	9.800	7.983–10.922	7.047	11.333
	Male	150	9.558	0.922	9.821	7.585–10.811	7.047	11.333
	Female	150	9.776	0.603	9.788	8.647–11.056	7.717	11.270
TODI	All	300	3.264	0.340	3.293	2.501–3.866	2.144	4.256
	Male	150	3.179	0.382	3.245	2.410–3.778	2.144	3.915
	Female	150	3.349	0.267	3.345	2.899–3.900	2.525	4.256

Figure 6 shows age-stratified distributions for the ODI and TODI for healthy male and female adults. Across age decades, the ODI remained relatively stable, with males generally exhibiting higher ODI values than females in most age groups, consistent with the expected influence of higher hematocrit on oxygen delivery capacity. In contrast, the TODI displayed a more mixed pattern: while TODI values were similar between sexes overall, females in their 20 s, 30 s, and 40 s showed higher median TODI values, indicating slightly greater tissue-level oxygen delivery efficiency during these age decades. Both indices demonstrated substantial overlap between male and female distributions, and neither the ODI nor TODI showed a clear age-related decline across the adult lifespan.

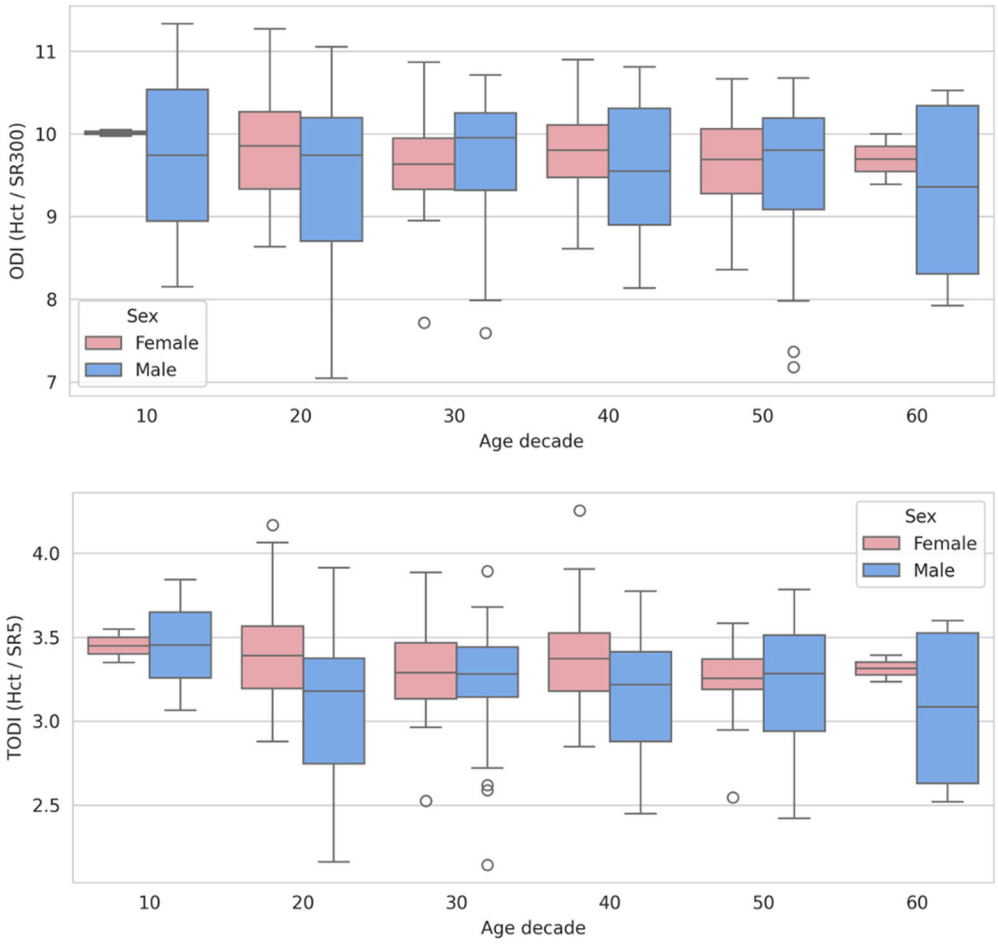


Figure 6. Age-stratified distributions of ODI and TODI in healthy male and female adults.

Additional decade-based age stratification (19–29, 30–39, 40–49, 50–59, ≥60 years) revealed no emergent nonlinear or threshold effects for WBV, ODI, or TODI in either sex. Across age bands, observed differences were driven primarily by interindividual variability rather than systematic shifts in central tendency, supporting age-independent reference behavior in this healthy cohort.

Figure 7 presents sex-stratified slopes (cP per mg/dL) relating lipid markers to DBV and SBV. Distinct patterns emerged between sexes. In males, TG showed the strongest positive association with SBV, whereas HDL consistently demonstrated negative slopes, indicating an inverse relationship with both DBV and SBV. LDL exhibited modest negative slopes in males across both viscosity measures, and total cholesterol (T-Chol) showed slopes near zero or slightly negative. In females, total cholesterol, TG, and LDL showed large positive slopes for DBV, indicating a stronger viscosity-enhancing effect relative to males. HDL displayed negative associations with both DBV and SBV in both sexes [6]. Overall, TG was the only lipid parameter strongly associated with increasing viscosity in males, while in females, a broader set of lipids—total cholesterol, TG, and LDL—exhibited stronger positive associations with both DBV and SBV.

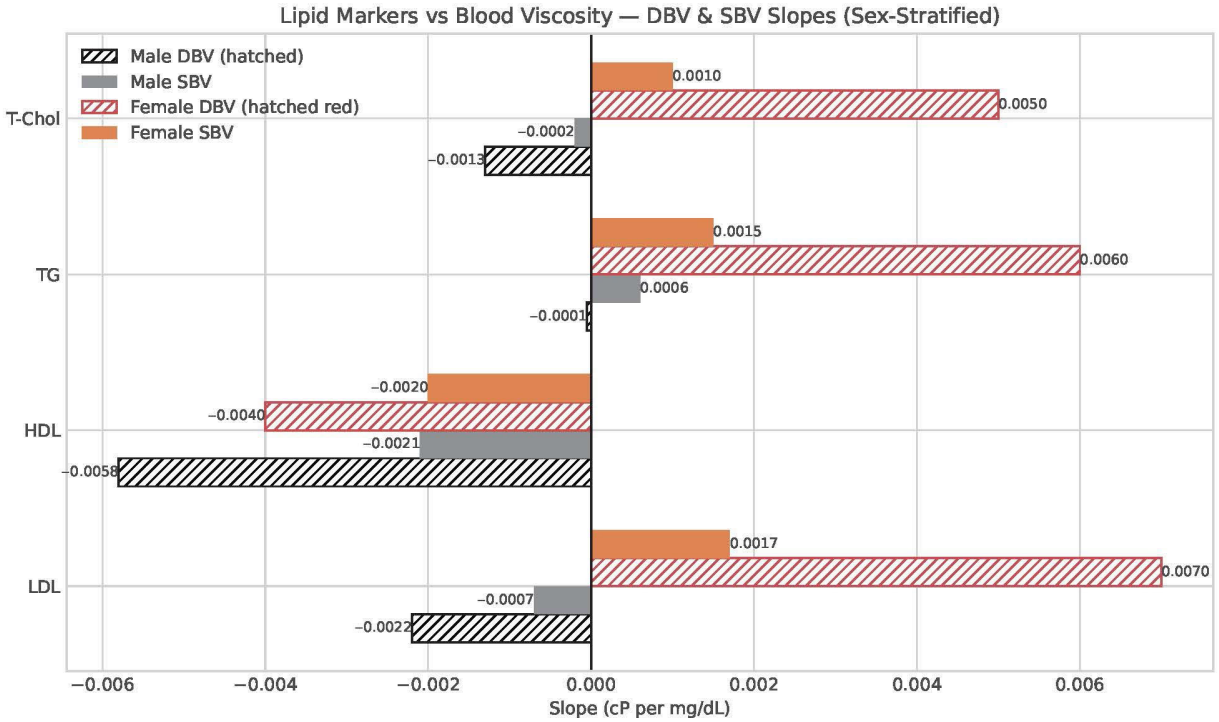


Figure 7. Sex-stratified slopes relating lipid markers to DBV and SBV in healthy male and female adults.

Figure 8 shows sex-stratified slopes of non-lipid determinants associated with blood viscosity for key biochemical and hematologic markers in healthy males and females. Across all evaluated non-lipid determinants, clear sex-specific differences in their associations with blood viscosity were observed. For DBV, HCT showed one of the strongest positive relationships in both sexes, with a steeper slope in men (0.581) compared with women (0.291). Total protein and albumin demonstrated a pronounced sex divergence: in men, both were strongly positively associated with DBV (0.685 for total protein; 0.685 for albumin), but the slopes were negative in women (–0.207 for both), indicating an opposite directional effect. The γ-gap (total protein minus albumin) was the strongest determinant overall, with a markedly higher slope in men (1.667) relative to women (0.321). Smaller positive slopes were observed for WBC, ESR, AST, and ALT, with women consistently

showing equal or slightly higher slopes for inflammatory markers such as WBC (0.086 vs. 0.074) and ESR (0.006 vs. 0.003).

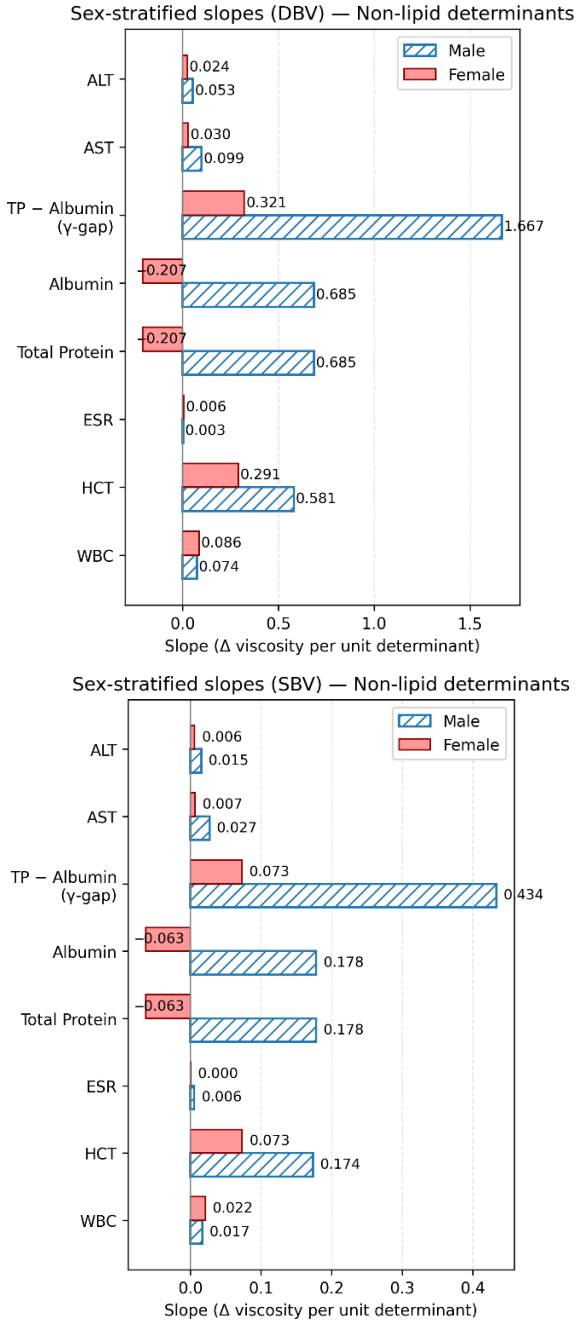


Figure 8. Sex-stratified associations between non-lipid determinants and DBV (top) and SBV (bottom) in healthy male and female adults.

For SBV, effect sizes were generally smaller but maintained similar sex-specific patterns. HCT again displayed a higher slope in men (0.174) than in women (0.074). Protein-related determinants continued to show sex divergence: men exhibited positive associations for total protein (0.178), albumin (0.178), and γ-gap (0.434), whereas women showed attenuated or negative slopes (–0.063 for total protein and albumin; 0.073 for γ-gap). Enzymatic markers (AST and ALT) and inflammatory markers (WBC and ESR) again demonstrated modest associations, with consistently small but positive slopes in both sexes. Taken together, these findings demonstrate that non-lipid biochemical factors influence blood

viscosity differently in men and women, with protein-related determinants showing the largest sex-specific divergence.

4. Discussion

In the present study, WBV showed clear relationships with several hematologic and biochemical variables, emphasizing its dependence on both cellular and metabolic factors.

4.1. WBV vs. Age

The greater standard deviation in male WBV across the age range suggests that aging interacts differently with hemorheological variability in men compared with women. Although WBV remains essentially age-independent in both sexes, the markedly wider dispersion among men indicates that inter-individual physiological differences—such as variability in erythrocyte mechanical properties, plasma protein concentrations, iron status, or hormonal influences—may broaden the range of viscosity responses to aging within the male population.

In contrast, the much tighter clustering of WBV among women, reflected by smaller SDs across age groups, suggests more uniform regulation of factors governing blood viscosity, consistent with the observation that female WBV differs only modestly from male WBV at any given age. This pattern appears distinct from reports in many Western cohorts [7], where women frequently show equal or greater variability, raising the possibility that the narrow dispersion observed here reflects population-specific physiological characteristics—particularly among healthy Korean women. Taken together, these findings highlight that sex differences in WBV may be driven more by differences in variability than by age-related trends themselves, emphasizing the importance of considering population-specific and sex-specific physiological diversity when interpreting viscosity measures in clinical or epidemiological contexts.

4.2. HCT and Ferritin

The present analysis highlights distinct sex-specific determinants of blood viscosity, with hematocrit emerging as the dominant and uniform rheological driver across measurement conditions, while ferritin demonstrates divergent associations between males and females. Consistent with established hemorheological principles, rising hematocrit was strongly and positively associated with both DBV and SBV; however, this relationship was considerably steeper in males, indicating that male blood has greater sensitivity to changes in red cell volume fraction. In contrast, ferritin displayed opposite directional relationships with viscosity depending on sex. Among females, higher ferritin levels were accompanied by modest increases in both DBV and SBV, whereas in males, increasing ferritin was associated with slight decreases in both DBV and SBV. These opposing slopes suggest that iron stores may influence rheology through sex-dependent biological pathways, potentially involving differences in iron handling, inflammatory milieu, erythrocyte deformability, or plasma protein composition. Collectively, these findings underscore that although hematocrit exerts a predictable influence on blood viscosity in both sexes, ferritin reflects more complex, sex-specific physiology that may have implications for vascular risk stratification and the interpretation of iron biomarkers in clinical and epidemiologic research.

4.3. TODI and ODI

The behavior of the ODI and TODI in this healthy cohort provides insights into sex-independent regulation of oxygen transport dynamics. The ODI decreased progressively as SBV increased for both men and women (male $\beta = -1.2023$; female $\beta = -0.9646$), indicating that higher viscosity at physiologic shear rates is associated with reduced oxygen delivery

efficiency. Similarly, the TODI showed nearly identical negative slopes in both sexes (male $\beta = -0.1443$; female $\beta = -0.1568$), demonstrating that as DBV rises, the capacity for microvascular oxygen delivery correspondingly diminishes.

The close parallelism of male and female regression lines for both the ODI and TODI suggests that the mechanical determinants of oxygen transport and microvascular perfusion stability are fundamentally similar across sexes in healthy adults. Moreover, the reference value framework described in the dataset supports using these indices as sensitive benchmarks for detecting impaired oxygen delivery in clinical populations, given their tight clustering and consistent behavior in healthy populations. Collectively, these findings imply that while viscosity exerts predictable constraints on oxygen delivery, the regulatory mechanisms maintaining the ODI and TODI appear robust and not strongly influenced by sex under healthy physiologic conditions.

Given the dominant influence of hematocrit on WBV, simple recalibration strategies may enhance interpretability across subgroups. Notably, ODI and TODI inherently normalize viscosity by hematocrit and demonstrated tighter distributions than raw viscosity measures, supporting their utility as hematocrit-adjusted indices. These ratio-based parameters may be preferable for cross-sex or cross-population comparisons, and future work should formally evaluate optimized recalibration approaches in diverse clinical settings.

4.4. Lipid Markers

Sex-specific differences in the relationship between lipid markers and blood viscosity likely reflect underlying hormonal and metabolic distinctions. Estrogen favorably modifies lipid handling and vascular function, which may dampen the viscosity-increasing effects of certain lipids in females, particularly before menopause. Menopausal status was not systematically collected at enrollment and therefore could not be reliably incorporated into sex-stratified analyses. Although estrogen-mediated effects on lipid metabolism and vascular rheology are well recognized, inference of menopausal state based solely on age would risk misclassification. Future studies incorporating confirmed menopausal status and hormonal profiling may further elucidate female-specific hemorheological transitions across the adult lifespan.

In contrast, males typically have greater visceral adiposity and higher VLDL and triglyceride production, which helps explain the stronger TG–viscosity association observed in men. Differences in lipoprotein particle size, inflammatory profiles, and erythrocyte properties between sexes may further influence how lipid fractions affect hemorheology. These findings suggest that lipid-driven changes in blood viscosity contribute differently to cardiovascular risk in men and women, underscoring the importance of considering sex as a biological variable when interpreting lipid–viscosity relationships.

4.5. Non-Lipid Biochemical Determinants

In this study, we observed clear sex-specific patterns in how non-lipid biochemical determinants relate to both DBV and SBV. The most striking differences emerged in protein-related parameters—total protein, albumin, and the γ-gap—each of which demonstrated strong positive associations with viscosity in men but markedly attenuated or even negative associations in women. These findings suggest fundamental sex differences in the contribution of circulating proteins to rheological behavior, potentially reflecting differences in plasma protein composition, hydration status, or immunoglobulin distribution. HCT also consistently showed a stronger viscosity-raising effect in men, aligning with known male–female differences in erythrocyte mass and microvascular flow dynamics.

In contrast, inflammatory markers (WBC and ESR) and liver-derived enzymes (AST and ALT) exhibited only small slopes in both sexes, indicating comparatively modest

roles in determining blood viscosity under physiologic conditions. Together, these results highlight that the determinants of blood viscosity are not uniform across sexes; instead, they reveal sex-specific rheological phenotypes in which protein-related factors dominate viscosity behavior in men, whereas women exhibit a more muted or qualitatively different response. These findings underscore the importance of considering sex as a biological variable in viscosity-related research and may help explain previously reported sex differences in microcirculatory function, oxygen delivery, and cardiovascular risk.

Hydration status represents a potential confounder in blood viscosity measurement. In this study, surrogate indicators such as blood urea nitrogen (BUN) and creatinine were available; however, BUN showed no significant association with WBV, and creatinine demonstrated only modest correlations likely reflecting sex-related differences in muscle mass rather than plasma volume. Given the standardized donor screening environment and the generally healthy population studied, clinically significant dehydration was unlikely. Nonetheless, future studies incorporating direct hydration metrics such as plasma osmolality may further refine interpretation, particularly for low-shear viscosity.

4.6. Methodological Context

Direct head-to-head comparison between the scanning capillary tube viscometer and legacy rotational viscometers was not performed in the present study. Nevertheless, the magnitude and shear-dependent trends of WBV observed here are consistent with values previously reported using cone-and-plate and Couette viscometers in healthy adults [17]. We further discuss methodological differences between capillary-based and rotational viscometry, emphasizing the advantage of SCTV in providing reproducible shear-dependent viscosity using disposable flow paths.

Unlike rotational systems, the SCTV allows automated determination of shear-dependent apparent viscosity using disposable flow paths, reducing contamination risk and handling variability. These features support its suitability for routine clinical and reference interval applications while preserving physiologic concordance with established measurement approaches.

Recently, Choe et al. reported the measurements of WBV with a newly introduced capillary viscometer at the EHA 2025 European Hematology Association Congress [18]. The capillary viscometer utilized a wavy channel with a square cross-section, as shown in Figure 9. Since the velocity profile in the wavy channel does not exist in a single direction (see the x_1-coordinate in Figure 2), the shear rate $\dot{\gamma}$ cannot be determined [12]. Therefore, the non-Newtonian blood viscosity cannot be measured in such capillary viscometer using the wavy channel.

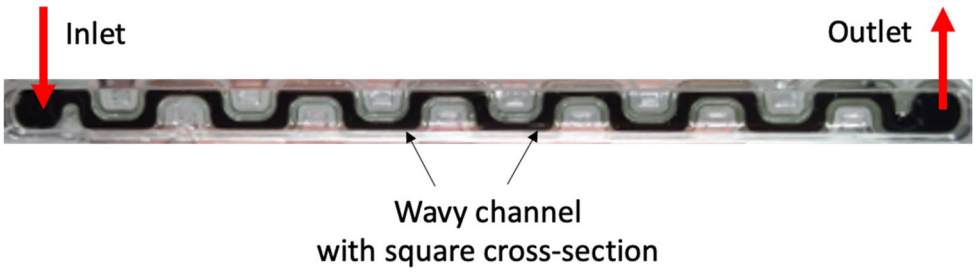


Figure 9. The configuration of the viscometer utilizing a wavy channel with a square cross-section.

4.7. Limitations and Clinical Implications

This study has several limitations. First, the analysis was restricted to healthy adults, and the determinants of WBV, ODI, and TODI may differ substantially in individuals with inflammatory, metabolic, or cardiovascular disorders, where elevated fibrinogen,

acute-phase proteins, or altered lipid profiles could disproportionately influence low-shear viscosity responses.

Second, although the cohort was large, participants were drawn from a single national population, which may limit generalizability, as hemorheological parameters can vary by ethnicity, lifestyle, and environmental factors. Thus, we emphasize that these reference intervals were derived from healthy Korean adults, and that WBV is known to vary with ethnicity, hematologic distributions, diet, and cardiometabolic risk burden. Thus, the reference intervals presented here may not be directly generalizable to populations with differing ethnic background, hematologic distributions, dietary patterns, or cardiometabolic risk profiles. Clinicians should therefore interpret WBV, ODI, and TODI values in conjunction with patient-specific characteristics such as hematocrit, lipid profile, inflammatory burden, and comorbid disease. In populations with altered baseline physiology, relative deviations from expected sex-specific patterns may be more informative than absolute comparison to reference limits alone.

Third, despite comprehensive biochemical profiling, some potentially relevant determinants—such as fibrinogen, immunoglobulin subclasses, and detailed erythrocyte deformability metrics—were not measured and therefore could not be evaluated for their rheological contributions.

Finally, the cross-sectional design precludes assessment of temporal variability or longitudinal changes in viscosity and oxygen delivery indices, which may be clinically important in conditions involving evolving inflammation, iron status, or metabolic disturbance. These limitations highlight the need for future multicenter, multiethnic, and disease-specific studies using standardized viscometry methods.

5. Conclusions

This study establishes the first comprehensive sex-specific reference intervals for WBV across key shear rates, along with normative ranges for the ODI and TODI in healthy male and female adults. WBV remained stable with age, while sex differences were driven mainly by variability rather than mean levels. Hematocrit was the dominant determinant of viscosity in both sexes, whereas lipid and protein-related factors showed pronounced sex-specific effects: triglycerides and plasma proteins contributed more strongly in men, and multiple lipid fractions influenced viscosity in women. Ferritin demonstrated opposite viscosity relationships between sexes, reflecting underlying biological differences. Both the ODI and TODI showed consistent inverse relationships with blood viscosity and exhibited only modest sex differences. These findings provide clinically useful benchmarks and highlight distinct rheological phenotypes that may inform future studies of microcirculatory and cardiovascular risk.

Author Contributions: Y.H.: Conceptualization, Literature search, Formal analysis, Methodology. K.N.L.: Literature search, Methodology, Writing—review and editing. J.K.: Conceptualization, Literature search, Formal analysis. I.T.K.: Conceptualization, Formal analysis, Methodology. Y.I.C.: Literature search, Methodology, Writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Hanmaeum Blood Center (2 September 2025).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in the manuscript:

ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
cP	centiPoise
CV	coefficient of variation
CLSI	clinical and laboratory standards institute
DBV	diastolic blood viscosity
ESR	erythrocyte sedimentation rate
Hb	hemoglobin
HCT	hematocrit
HDL	high-density lipoprotein
LDL	low-density lipoprotein
ODI	oxygen delivery index
RBC	red blood cell
RDW	red blood cell distribution width
SAS	statistical analysis system
SBV	systolic blood viscosity
SCTV	scanning capillary tube viscometer
SD	standard deviation
TG	triglyceride
TODI	tissue oxygen delivery index
TP	total protein
VLDL	very-low-density lipoprotein
WBC	white blood cell
WBV	whole blood viscosity

References

1. Stoltz, J.F.; Singh, M.; Riha, P. *Hemorheology in Practice*; IOS Press: Wahington, DC, USA, 1999.
2. Lowe, G.D.O. *Clinical Blood Rheology*; CRC Press Inc.: Boca Raton, FL, USA, 1988.
3. Baskurt, O.K.; Meiselman, H.J. Erythrocyte aggregation: Basic aspects and clinical importance. *Clin. Hemorheol. Microcirc.* **2013**, *53*, 23–37. [CrossRef] [PubMed]
4. Başkurt, O.K.; Neh, B.; Meiselman, H.J. *Red Blood Cell Aggregation*; CRC Press: Boca Raton, FL, USA, 2012.
5. Chien, S. Determinants of blood viscosity and red cell deformability. *Scand. J. Clin. Lab. Investig.* **1981**, *41*, 7–12. [CrossRef] [PubMed]
6. Rosenson, R.S.; Lowe, G. Effects of lipids and lipoproteins on thrombosis and rheology. *Atherosclerosis* **1998**, *140*, 271–280. [CrossRef] [PubMed]
7. de Simone, G.; Devereux, R.B.; Chien, S.; Alderman, M.H.; Atlas, S.A.; Laragh, J.H. Relation of blood viscosity to demographic and physiologic variables and to cardiovascular risk factors in apparently normal adults. *Circulation* **1990**, *81*, 107–117. [CrossRef] [PubMed]
8. Yang, W. *Biothermal-Fluid Sciences: Principles and Applications*; Taylor and Francis: New York, NY, USA, 1989.
9. Cho, Y.I.; Cho, D.J. Hemorheology and microvascular disorders. *Korean Circ. J.* **2011**, *41*, 287–295. [CrossRef] [PubMed]
10. Kameneva, M.V.; Watach, M.J.; Borovetz, H.S. Gender difference in oxygen delivery index: Potential link to development of cardiovascular diseases. *Appl. Cardiopulm. Pathophysiol.* **2000**, *9*, 382–387.
11. Yi, J.-E.; Youn, H.-J. Hemorheological abnormalities and their associations with coronary blood flow in patients with cardiac syndrome X: A comparison between males and females. *Perfusion* **2017**, *32*, 57–67. [CrossRef] [PubMed]
12. Middleman, S. *Flow of High Polymers; Continuum and Molecular Rheology*; John Wiley & Sons, Inc.: New York, NY, USA, 1968.

13. Anderson, A.M.; Bruno, B.A.; Smith, L.S. Viscosity measurement. In *Materials and Engineering Mechanics*; Kurtz, M., Ed.; Wiley: Hoboken, NJ, USA, 2014; Chapter 23, Volume 1, pp. 809–836.
14. Baskurt, O.K.; Boynard, M.; Cokelet, G.C.; Connes, P.; Cooke, B.M.; Forconi, S.; Liao, F.; Hardeman, M.R.; Jung, F.; Meiselman, H.J. New guidelines for hemorheological laboratory techniques. *Clin. Hemorheol. Microcirc.* **2009**, *42*, 75–97. [CrossRef] [PubMed]
15. Kim, S.; Cho, Y.; Hogenauer, W.; Kensey, K. A method of isolating surface tension and yield stress effects in a U-shaped scanning capillary-tube viscometer using a Casson model. *J. Non-Newton. Fluid Mech.* **2002**, *103*, 205–219. [CrossRef]
16. Han, Y.; Kap, N.L.; Kim, J.; Kim, I.T.; Cho, Y.I. Analytical performance evaluation and reference intervals for Whole Blood Viscosity using a scanning capillary viscometer. *J. Clin. Chem. Lab. Med.* **2026**, *9*, 313.
17. Alexy, T.; Wenby, R.B.; Pais, E.; Goldstein, L.J.; Hogenauer, W.; Meiselman, H.J. An automated tube-type blood viscometer: Validation studies. *Biorheology* **2005**, *42*, 237–247. [CrossRef] [PubMed]
18. Choe, K.W.; Kim, H.; Lim, Y.K.; Kweon, O.J.; Kim, H.R.; Lee, M.-K.; Yoon, S. Analytical performance of the fully automated blood viscometer based on the scanning capillary method. In Proceedings of the EHA 2025 European Hematology Association Congress, Milan, Italy, 12 June 2025; Abstract number: 4162913, PB3840.

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