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New method of hematocrit correction of whole blood viscosity☆

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ABSTRACT

Hematocrit (HCT), the volume fraction of cells in whole blood, is one of the most important variables that affect the viscosity of whole blood. Matrai's HCT-correction model (Matrai model) provides a method of HCT-correction so that the blood viscosity can be compared at a standard HCT of 45%. Since the Matrai model requires the plasma viscosity, there is a need to have another method for HCT correction of the blood viscosity in cases when the plasma viscosity is not available. The present study introduced a new method of HCT correction using the whole blood viscosity measured over a range of shear rates without plasma viscosity. For validation of the new method, three different human blood samples were used. Each blood sample was reconstituted to eight different HCT levels (from 25 to 60%) and the blood viscosity at each HCT level was measured over a range of shear rates, including the blood viscosity at HCT 45%. HCT-correction results from the Matrai model and the present model were compared with the blood viscosity measured at HCT 45%. The present model gave significantly better HCT corrections (i.e., about 3 times less error) than the Matrai model.

1. Introduction

The viscosity of whole blood exhibits shear-thinning non-Newtonian behavior due to a large amount of suspended cells in plasma. In particular, the volume fraction of erythrocytes in whole blood, which is called hematocrit (HCT, %), varies over a wide range, and it is one of the most important variables that determine the magnitude of whole blood viscosity (WBV). For example, the normal HCT ranges of women and men are from 36 to 45% and from 39 to 50%, respectively [1]. A ten-percent increase in HCT (i.e., from HCT 40 to 44%) increases high-shear blood viscosity by around 5% [2], whereas the same increase in HCT increases low-shear blood viscosity by approximately 30% [3].

In addition to HCT, plasma proteins such as fibrinogen and immunoglobulins are also important determinants of viscosity. These proteins are instrumental in erythrocyte aggregation in the microcirculation and Rouleaux formation [4–7]. Both fibrinogen and immunoglobulins are relatively long chain molecules that promote aggregation [4,7,8]. In contrast, albumin has been reported to suppress aggregation [9]. Low-density lipoprotein (LDL) molecules have also been shown to promote erythrocyte aggregation, increasing blood viscosity at low shear rates, whereas HDL molecules have been reported to suppress aggregation [6,7,10–12].

When the blood viscosity is measured at a specific HCT (i.e., 40%), it is not easy to compare it with that measured at a different HCT (i.e., 49%). Matrai's HCT-correction model (Matrai model) provides a method of HCT-correction so that the blood viscosity can be compared at a standard HCT of 45% [13] as shown below:

$$\frac{\mu_{45\%\ \mathrm{hct}}}{\mu_{PV}} = \left[\frac{\mu_{\mathrm{native\ hct}}}{\mu_{PV}}\right]^{\frac{45}{H}} \tag{1}$$

where $\mu_{\mathrm{native\ hct}}$ is the measured WBV at a native HCT, $\mu_{45\%\ \mathrm{hct}}$ is the corrected WBV to a standard HCT of 45%, μ_{PV} is the measured plasma viscosity (PV; i.e., blood viscosity at HCT 0%), and H is the measured native HCT.

In the past, the Matrai model has been widely used by a number of researchers. For example, Lowe et al. [14] investigated the association between blood rheological parameters and peripheral arterial narrowing in lower limb ischemia using the corrected WBVs to HCT 45% (1581 men and women aged 55 to 74 years). Amanda et al. [15] reported the relationship between rheological factors and carotid intima–media thickness (IMT) by correcting the measured WBVs to HCT 45%. Lee et al. [16,17] also utilized the Matrai model to evaluate the pathophysiological abnormalities of acute coronary syndromes (ACS) and cardiac syndrome X (CSX) promoted by circulatory dysfunction of blood. Michalska-Malecka et al. [18] correlated the pathogenic factors with the hemorheological parameters in age-related macular degeneration (AMD) by comparing the HCT-corrected WBVs. However, when PV is not available, the Matrai model cannot be used.

Recently, various new techniques in determining WBVs over a wide range of shear rates (i.e., from 1 to 1000 s^{-1}) have been introduced

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[19–21]. Hence, if one can perform HCT correction utilizing the WBV measured over a wide range of shear rates without the use of PV, it will be quite useful in comparing WBVs measured at different HCTs to those at HCT 45%.

Therefore, the objective of the present study was to investigate a feasibility of correcting the WBV measured at a native HCT level to a standard HCT of 45% without PV. In order to validate the present model, WBV measurements were conducted with three different human blood samples, and the HCT-corrected blood viscosities obtained with the present model was compared to those obtained with the Matrai model [13] in terms of error and standard deviations.

2. Methods

2.1. HCT-reconstituted whole blood samples

Human whole blood samples used in the present study were obtained from Lampire Biological Laboratory (Pipersville, PA). Anti-coagulant, K_2 ethylenediaminetetraacetic acid (EDTA), was used to prevent the coagulation of whole blood. Whole blood was transferred into 200-mL glass containers and stirred gently for homogeneous distribution of the erythrocytes. HCT of whole blood was determined using a micro-centrifuge (StatSpin MP, Iris Sample Processing, MA).

The whole blood in the 200-mL glass container was then transferred to 10-mL polypropylene transparent tubes and centrifuged with a relative centrifugal force of 1500 *g* for 15 min (Fleta 5, Hanil, South Korea). As shown in Fig. 1, after centrifugation, the blood samples were manually reconstituted to eight different HCT levels of 25, 30, 35, 40, 45, 50, 55, and 60% by either adding plasma to the centrifuged whole blood samples or removing it. The required volume of blood plasma, $V_{required}$, in reconstituting the whole blood samples to the target-HCT levels was calculated as:

$$V_{required} = \frac{\left(100 - HCT_{target}\right) \times HCT_{native}}{10 \times HCT_{target}} - \frac{V_{whole\ blood} \times (100 - HCT_{native})}{100} \quad (2)$$

where HCT_{target} is the target HCT to reconstitute, and HCT_{native} is the native HCT of the whole blood sample. After the completion of a manual reconstitution, reconstituted blood samples were gently mixed using a tube shaker (Labquake, Thermo Fisher Scientific, Inc., MA) to disperse packed red blood cells evenly within the blood samples. Then, HCT levels were measured again to verify whether or not the whole blood samples were correctly reconstituted to the target-HCT levels. The experiment was conducted using three different whole blood samples, which were randomly chosen without considering their native HCTs.

2.2. Measurement of WBV and PV

WBV of the reconstituted whole blood samples was measured over a wide range of shear rates from 1 to 1000 s^{-1} using a scanning capillary tube viscometer (SCTV) (Hemathix, Health Onvector, NJ) at the core body temperature of 36.5 ± 0.5 °C. PV was measured using a Brookfield cone-and-plate rotating viscometer (LV-III with CP-40; Engineering, MA) at a shear rate of 300 s^{-1}. PV was also measured using the SCTV.

2.3. Determination of the yield stress and the Casson constant

Whole blood is known to have a yield stress defined as the minimum shear stress required to maintain a continuous blood flow [22–24]. Although other non-Newtonian models could have been used, the present study utilized the Casson model to describe the non-Newtonian characteristics of whole blood, which is given as [22,25]:

$$\begin{aligned} \sqrt{\tau} &= \sqrt{\tau_y} + \sqrt{k}\sqrt{\dot{\gamma}} \ \text{ when } \ \tau \geq \tau_y \\ \dot{\gamma} &= 0 \ \text{ when } \ \tau < \tau_y \end{aligned} \quad (3)$$

where τ denotes the shear stress (Pa), $\dot{\gamma}$ is the shear rate (s^{-1}), τ_y is the yield stress (Pa), and k is the Casson constant (Pa·s). Both the yield stress and the Casson constant were determined by the curve fitting of the WBV profile over a range of shear rate using the following equation, which was obtained by re-arranging the Casson model, Eq. (3):

$$\eta(t) = k + \frac{\tau_y}{\dot{\gamma}} + \frac{\sqrt{k \cdot \tau_y}}{\sqrt{\dot{\gamma}}}. \quad (4)$$

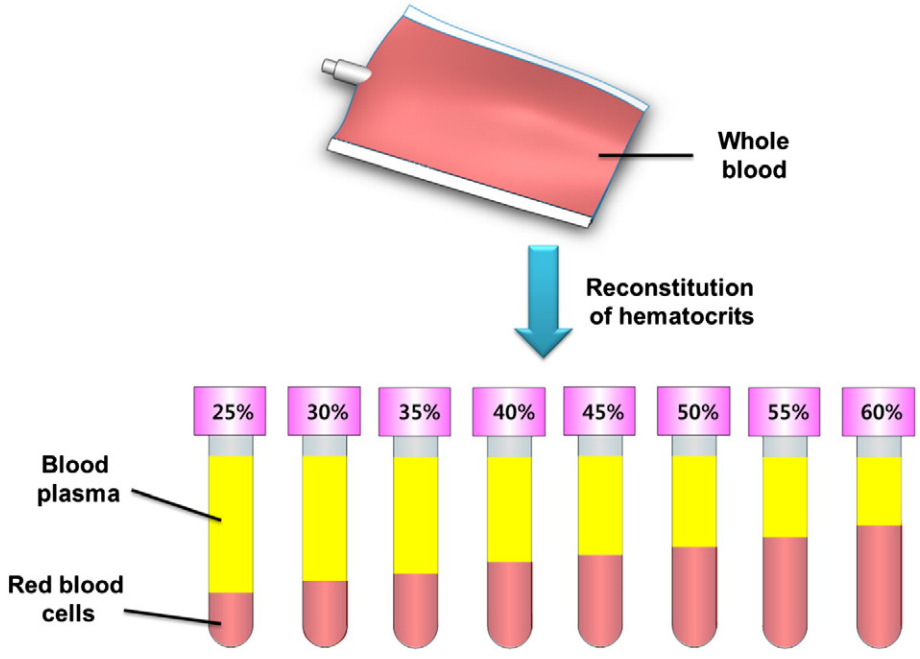

Fig. 1. Procedure to reconstitute whole blood to target-HCT levels ranging from 25 to 60%.