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ORIGINAL PAPER

Effect of Dielectric Barrier Discharge Treatment of Blood Plasma to Improve Rheological Properties of Blood

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Abstract The whole blood viscosity (WBV) is one of the major independent indicators for the risk of cardiovascular disease, stroke, and peripheral arterial diseases. Furthermore, oxidized LDL molecules are known to cause atherosclerotic plaques in arteries, and it is one of the key components that increase WBV. The present study attempted to reduce WBV by coagulating plasma proteins and lipid molecules from blood plasma using non-thermal dielectric barrier discharge (DBD) and removing them through filtration. The DBD treatment was found to produce coagulated particles in blood plasma. After filtration of the coagulated particles, WBV decreased by 9.1 and 17.7% for both systolic and diastolic blood viscosities, respectively. The present results suggest that the removal of excess plasma proteins and lipid molecules might be feasible using DBD treatment.

Keywords Dielectric barrier discharge (DBD) · Blood viscosity · Filtration · Fibrinogen · LDL

Introduction

The viscosity of a fluid represents the frictional resistance between a moving fluid and stationary wall. Blood viscosity is the inherent resistance of blood to flow and represents the thickness and stickiness of blood. Since about 45% of blood volume is made up of suspended cellular particles, primarily red blood cells, the blood behaves as a non-Newtonian fluid where its viscosity varies with shear rate (i.e., the ratio of flow velocity to lumen diameter). The dynamic range of the whole blood viscosity (WBV) is relatively

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large, i.e., 40–450 millipoise (mP) (or 4–45 centipoise), which highlights the potential utility of this parameter as a biomarker—to the degree that viscosity provides additional incremental prediction of clinical outcomes and is modifiable by therapeutic modalities.

WBV has been strongly associated with cardiovascular disease [1–5], stroke [6–11], and peripheral arterial disease [12–14]. Mechanical interaction between blood and blood vessels mediated by the increase of WBV has a crucial pathogenic role in the release of endothelium-derived mediators (NO and endothelia), thus causing subsequent vascular remodeling by activation of endothelium, initiation of inflammation, alteration of lipid metabolism, and finally progression of atherosclerotic vascular disease [15–19].

There are a number of variables for the WBV, which include hematocrit, plasma proteins (i.e., fibrinogen, immunoglobulin, and albumin), total cholesterol, low-density-lipoprotein (LDL) cholesterol, high-density-lipoprotein (HDL) cholesterol and triglyceride [20–22]. In addition, the aggregation and deformability of erythrocytes critically affect the WBV [22, 23]. Since both the plasma proteins and LDL molecules influence the aggregation of erythrocytes [24–27], it is important to keep both levels within the respective normal ranges. For example, lipid-lowering statin drugs have been widely used to keep the LDL cholesterol within the normal range (i.e., 62–130 mg/dl) [28–34]. Statins are powerful cholesterol-lowering drugs in clinical practice and have a life-saving potential in properly selected patients, particularly those with severe hyperlipidemia and atherosclerotic disease [28, 35]. Results from randomized clinical trials have demonstrated a decrease in congested heart diseases (CHD) and total mortality, reductions in myocardial infarctions, revascularization procedures, stroke, and peripheral vascular disease [28, 36]. However, statins are prescribed for less than half of the patients who should receive this therapy, unfortunately, because of fear of liver and muscle toxicity, a side effect which remains a major impediment to the appropriate use of these drugs [37, 38].

In recent years, many new medical applications, including the sterilization of living tissue without damage, blood coagulation, the induction of apoptosis in malignant tissues, and the modulation of cell attachment are being developed utilizing non-thermal plasma discharges in atmospheric pressure [39–47]. It was demonstrated that selective coagulation of fibrinogen, which is one of the major viscosity determinants in blood, could be induced by the application of dielectric barrier discharges (DBD) in air [39]. Hence it is hypothesized that the hemorheological properties of blood may be improved by lowering the levels of fibrinogen and LDL molecules in blood plasma through DBD-assisted coagulation and the subsequent filtration of the coagulated particles from the treated blood plasma. Hence, the objective of the present study was to investigate the feasibility of reducing whole blood viscosity through DBD treatment of blood plasma and subsequent filtration.

Methods

Experimental Setup for DBD Treatment

The DBD system used in the present study was the identical to the one used by Kalghatgi et al. [39], which was atmospheric pressure dielectric barrier discharge and is illustrated in Figs. 1 and 2. The DBD system was operated with one dielectric-covered powered electrode and the other grounded electrode. Discharge was ignited when the powered electrode approached the surface of the sample to be treated at a distance of less than 3 mm, the phenomenon which depended on the waveform, duration, and polarity of the driving voltage [40]. A pulsed high voltage of 35 kV (peak to peak) with alternating polarity at

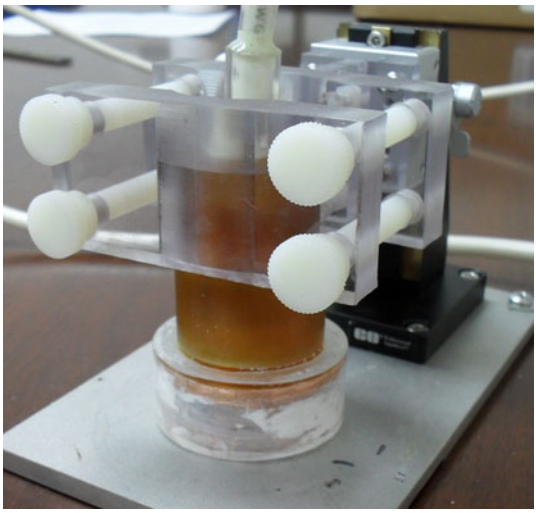


Fig. 1 Application of DBD to blood plasma sample

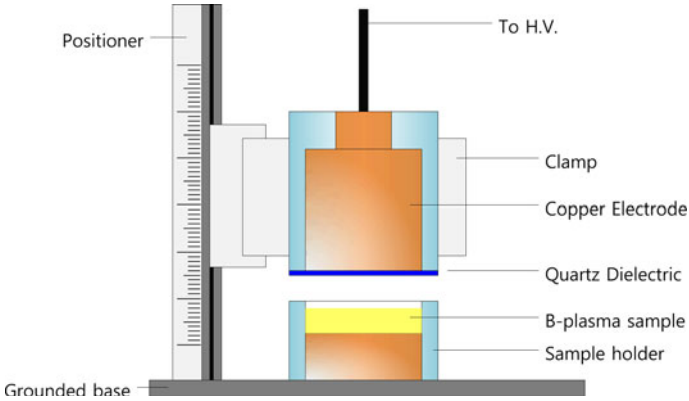


Fig. 2 Schematic of the experimental setup for the DBD treatment of blood plasma

1 kHz frequency was applied between the quartz insulated copper electrode and the surface of the sample (blood plasma) to generate DBD. The power applied to the present DBD system was analyzed by measuring the current passing through the discharge gap and the voltage drop in the gap when the discharge was generated. The current and voltage signals were acquired and recorded by a two-channel digital phosphor oscilloscope (DPS) (TDS5052B, 500 MHz bandwidth, 5 GS/s sample rate, Tektronix, Inc). The surface power density which corresponded to the applied power was around 1.5 W/cm^2 [39, 40, 48].

The electrode was constructed of a 25 mm diameter copper rod enclosed in polytherimide (Ultem®). A 1 mm thick fused quartz was used to prevent an arc formation by limiting the current in the DBD discharge. The presence of the insulating layer prevented the buildup of high current and subsequent heating of the gas in the discharge gap so that biological samples could be treated without thermal damage. The gap between the bottom of the dielectric quartz glass covering the copper electrode and the surface of the blood

plasma sample was adjusted to be 2 mm using a precision vertical positioner shown in Fig. 2. To treat the sample with DBD, 4 mL of blood plasma were placed in the sample holder (see Fig. 2) which was composed of a 25-mm-diameter copper rod inserted into polytherimide (Ultem®) shell. The bottom of the copper rod inside the sample holder was placed on a 21 mm thick polycarbonate plate as the grounded base electrode [39, 48].

Experimental Procedure

Human whole blood of 150 mL with 1.5 mL of ethylene diaminetetraacetic acid (EDTA) as an anti-coagulant was obtained from Lampire Biological Laboratories (Pipersville, PA) in a glass bottle. Both the WBV and hematocrit for the blood sample were measured to determine the baseline data prior to the DBD treatment. The whole blood in the 150 mL of bottle was then transferred to several 10 mL-polyethylene tubes to prepare blood plasma from whole blood using a centrifuge (VanGuard V6500, Hamilton Bell Co.) with 1200 G of relative centrifugal force (RCF) for 15 min.

The blood plasma viscosity was measured before DBD treatment for the baseline data. Each blood plasma sample separated from whole blood was then treated with DBD for 1, 2, 4, and 8 min to investigate the effect of DBD treatment on the rheological properties of blood plasma and whole blood. Temperature change was monitored before and after the DBD treatment.

The viscosity of the blood plasma after DBD treatment was measured again with viscometers (see below) to compare the change in the plasma viscosity before and after DBD treatment.

In order to evaluate the change in the WBV due to the coagulated particles generated by DBD treatment, some of the DBD-treated blood plasma samples were mixed back with the original erythrocytes which had been separated in the previous step, and the WBV was measured. For the last step, to investigate whether or not the WBV could be reduced by the filtration of the coagulated particles from the DBD-treated blood plasma, some of the DBD-treated blood plasma samples was filtered using a syringe filter (25 mm, pore size 0.20 μm, Nylon, Millipore) and then mixed back with the centrifuged erythrocytes, and the viscosities of the mixed whole blood samples were measured.

Here, hematocrit concentration was also measured to examine any possible plasma loss or hemolysis during the transfer of blood, the centrifugation of blood cells, the DBD treatment, the filtration process of DBD-treated blood plasma, and the remixing of the DBD-treated blood plasma with the centrifuged erythrocytes.

Laboratory Analyses

WBV was measured at 37°C using Hemathix viscometer (Health OnVector, Inc.) over a range of shear rates from 1 to 1,000 s^{-1}. Detail test and viscosity calculation procedures are given elsewhere [49]. The viscosity of the DBD-treated blood plasma was also measured using Brookfield viscometer (LV-III with CP-42, Brookfield Engineering Lab.) at two different shear rates of 225 and 450 s^{-1}. The temperature of the test sample at Brookfield viscometer was maintained at a constant temperature of 37°C with a constant temperature water bath and circulator. Since some plasma volume could be lost during the DBD treatment and filtration, the WBV was normalized to a standard hematocrit of 45% using a standard hematocrit-correction method [50].

Statistical Analyses

The mean and standard deviations for both whole blood and blood plasma viscosities were calculated. WBV was reported both at the observed (native) hematocrit and normalized hematocrit of 45% [51].

Results

The WBVs of blood samples were measured using Hemathix Analyzer at five different shear rates of 1,000, 300, 100, 10, 1 s^{-1} before DBD treatment and the obtained WBVs including the baseline mean and standard deviation values were normalized to standardized hematocrit of 45%. The normalized WBV of untreated blood varied from 35.38 to 301.01 mP when shear rate decreased from 1,000 to 1 s^{-1}.

When blood plasma was treated with DBD, a white layer formation was found on the top surface of the treated blood plasma samples and at the interfacing edge with a copper surface, whereas the blood plasma without DBD treatment did not exhibit any white particle formation on the sample surface after being exposed to open atmosphere for the same duration (see Fig. 3). The viscosity of blood plasma treated with DBD measured with Brookfield viscometer at two different shear rates, 225 and 450 s^{-1}, is shown in Fig. 4. The viscosity of blood plasma showed irregular values in accordance with the DBD treatment time for both shear rates.

The values of WBV for the blood samples mixed with blood plasma treated by DBD are given in Fig. 5 at five different shear rates at each treatment time (i.e., 1, 2, 4, and 8 min). Over the range of shear rates, the normalized WBV increased with increasing DBD treatment time. WBV measured at a high shear rate of 300 s^{-1} is usually termed as systolic whole blood viscosity (SBV), whereas WBV measured at a low shear rate of 1 s^{-1} is termed as diastolic whole blood viscosity (DBV) as WBV varies during a cardiac cycle like blood pressure. As shown in Fig. 5, DBV values were significantly higher in DBD-treated samples (i.e. 368.10 $\pm$ 65.41 mP for 8-min DBD treatment case) than untreated control samples (301.02 $\pm$ 56.17 mP). SBV values were also elevated from 38.60 $\pm$ 3.39 mP for control to 49.30 $\pm$ 9.92 mP (for 8-min DBD treatment case).

WBVs of blood samples remixed with DBD-treated blood plasma, which was filtered before being mixed with the original red blood cells are shown in Figs. 6 and 7. For SBV values shown in Fig. 6, the systolic blood viscosity after 8-min DBD treatment without filtration increased by 5.5% from the baseline value of 41.0 mP. When the DBD-treated plasma was filtered and then remixed with red blood cells, the systolic blood viscosity decreased by 9.1% from the baseline SBV of 41.0 mP. The diastolic blood viscosity of blood treated by DBD but without filtration was elevated with increasing DBD treatment time. For example, the DBV of blood increased by 29.9% from the baseline value of 340.7 mP (see Fig. 7). When the DBD-treated plasma was filtered then remixed with red blood cells, the DBV of blood for 8-min treatment case decreased by 17.7% from the baseline value of 340.7 mP.

Discussion

When blood plasma was treated by DBD, a white clot layer was formed at the top of blood plasma sample (see Fig. 3), suggesting that the plasma proteins and lipids in blood plasma might have precipitated into coagulated particles through DBD treatment. Accordingly, if

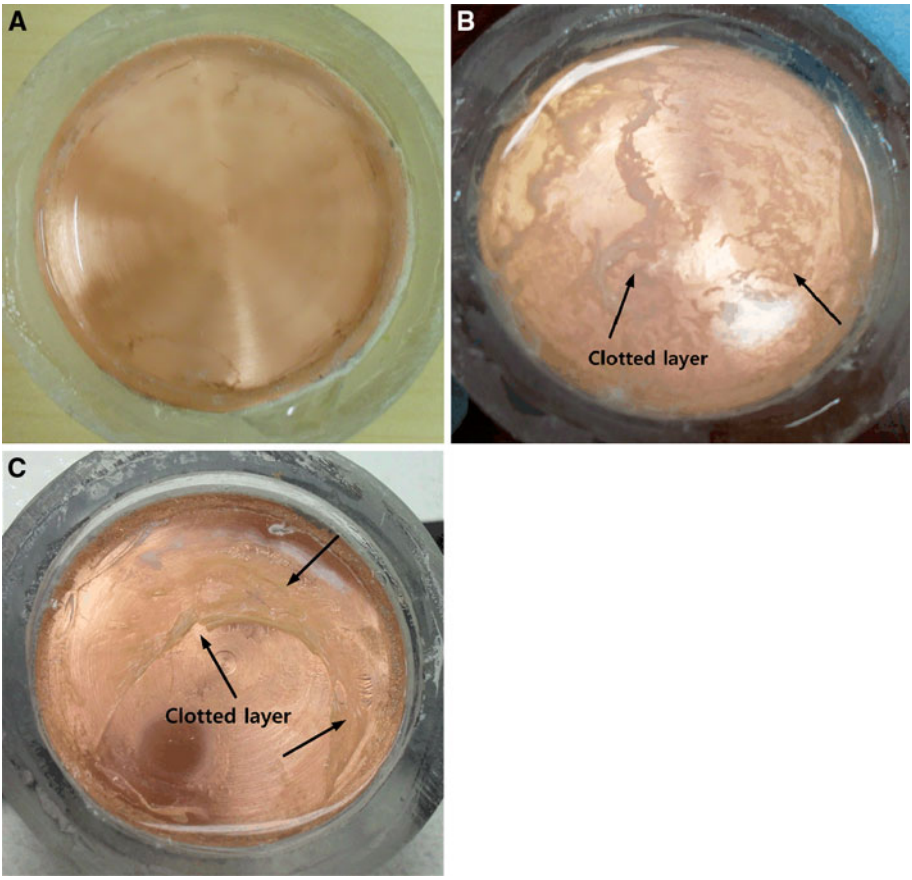


Fig. 3 Photographs of the formation of white layer in blood plasma sample with DBD treatment: **a** blood plasma before DBD treatment showed no coagulation, **b** blood plasma treated with DBD for 4 min. exhibited a partially coagulated layer, and **c** blood plasma treated with DBD for 8 min. Showed *white clotted layer* on the surface of copper surface

these coagulated particles are removed, one may anticipate some improvement in the rheological properties of whole blood. Note that the size of fibrinogen (diameter of 5–7 nm and length of 48 nm) and LDL molecules (approximately 22 nm) are too small to be removed by filter [52–54].

Although DBD discharge employed in this study is non-thermal, there could be about 20% of thermal energy to be transferred from filamentary discharge to the blood plasma sample due to energy distribution of input power to the metallic electrode [55, 56], a phenomenon which could create the white layer of coagulated particles by heating effect. To test this possibility, temperature measurement was performed before and after the treatment of the samples with DBD, and no significant change in temperature was observed, suggesting that the coagulated particles must have come from the oxidation and subsequent coagulation by active species generated by DBD. In addition, there was no change in hematocrit between before and after DBD treatment, indicating no significant evaporation in blood plasma during the DBD treatment procedure.

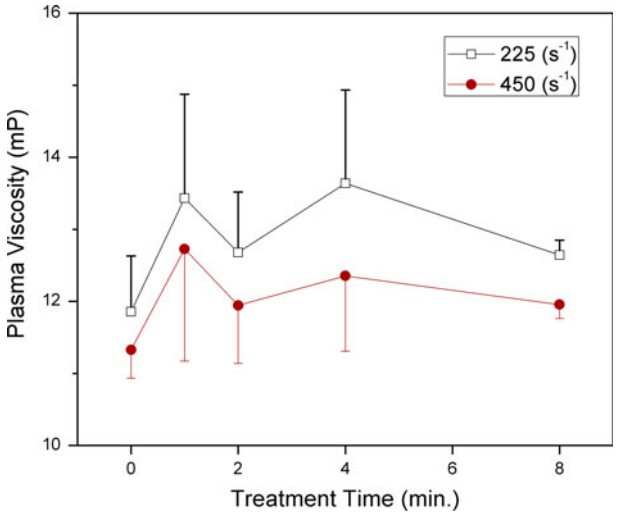


Fig. 4 Variations in the viscosity of blood plasma at two different shear rates, 225 and 450 s^{-1} at four different DBD treatment times together with baseline data

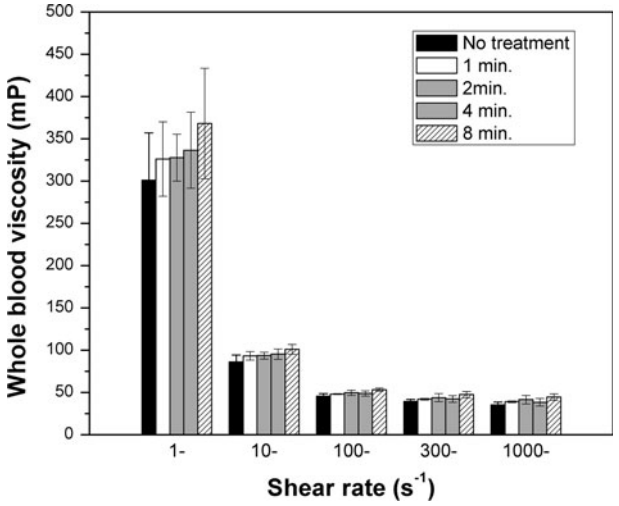


Fig. 5 Variations in the viscosity of whole blood at four different DBD treatment times together with baseline data

Two important buffer systems exist in blood plasma, dihydrogen phosphate buffer and carbonic acid buffer. The dihydrogen phosphate buffer resists a drop in pH, while the carbonic acid buffer resists a rise in pH [57]. It has been known that when non-thermal plasma discharge is applied to liquids, it generates a siginificant amount of hydrogen ions, which can change the acidity of liquids. The effect of DBD discharge on phosphate buffered liquids which is similar to the buffering system of blood plsama has been investigated and confirmed that when about 5-mL phosphate buffered solution was treated with DBD discharge, the phosphate buffer system prevented the acidification of the liquids,

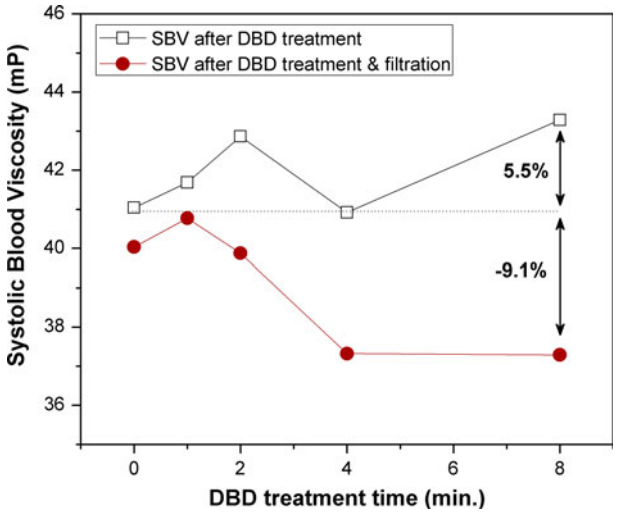


Fig. 6 Variations in the systolic blood viscosity of whole blood after DBD treatment with and without filtration

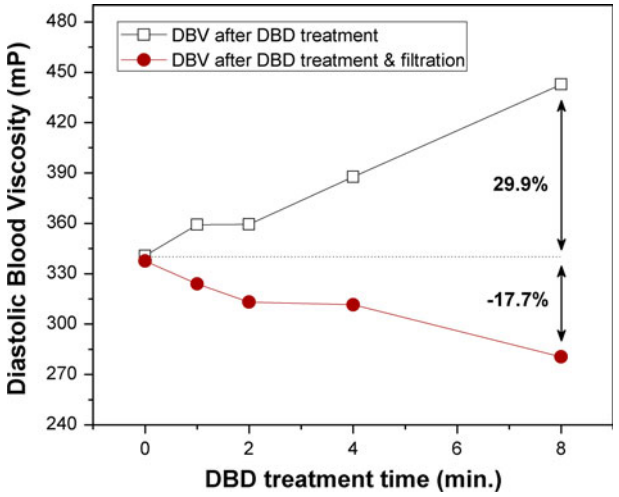


Fig. 7 Variations in the diastolic blood viscosity of whole blood after DBD treatment with and without filtration

while treating smaller volume (i.e. less than about 1.5 mL) for longer than about 10 min. could be susceptible to the acidification of DBD discharge [43, 58]. In the present study, the 4-mL blood plasma sample was treated with DBD discharge for maximum 8 min., thus we assumed that the acidification of 4-mL blood plasma sample could not be significantly affected by DBD plasma discharge.

The blood mixed with the blood plasma treated by DBD without filtration showed significant increase in WBV. This can be attributed to the fact that plasma proteins and lipids formed large groups of coagulated particles of micron size, increasing frictional

resistance to flow over the entire range of shear rates. Since the coagulated particles are visible (i.e., large in size), they could be relatively easily removed with filtration, a process which helped reducing WBV as the plasma proteins and lipids are the key determinants of WBV.

The SBV of blood with DBD treatment and filtration decreased by about 9.1%, whereas the DBV dropped by 17.7% from the respective baseline values, both representing significant improvements in rheological properties. The reason why the DBD treatment improved the DBV more than the SBV is as follows: The SBV is usually affected by erythrocyte deformability while DBV is affected by the erythrocyte aggregation. Since the plasma proteins (i.e., fibrinogen and immunoglobulins) and LDL molecules are instrumental in the RBC aggregation [26, 27], their removal by the DBD treatment and filtration should mitigate the erythrocyte aggregation, subsequently reducing the DBV.

In terms of the mechanism of DBD treatment in the precipitation of plasma proteins and lipids from blood plasma, Kalghatgi et al. [39] reported that DBD treatment might have activated some of protein coagulation process which resulted in rapid fibrinogen aggregation. It was also mentioned that the selective coagulation of proteins was observed—not of albumin but of fibrinogen only [39]. We can hypothesize that this coagulated fibrinogen and subsequent removal might have affected the WBV of blood with DBD-treated blood plasma.

In addition, oxidized LDL molecules are known adhere to arterial wall surfaces, playing a key role in the progression of atherosclerosis [59, 60]. In a similar manner, from the reduction of DBV, we can indirectly hypothesize that LDL molecules in blood plasma might have been oxidized by DBD treatment, and the oxidized LDL molecules may tend to precipitate and coagulate, a phenomenon which requires further investigation. Since LDL molecules are one of the important variables in WBV [61–63], their removal with DBD treatment and filtration should not only help reducing WBV [64] but also reducing the progression of atherosclerosis.

Conclusions

The present study utilized DBD treatment and filtration to reduce blood viscosity. The results presented in this paper indicated that the non-thermal DBD treatment could precipitate and coagulate plasma proteins (i.e., fibrinogen) and LDL molecules in blood plasma. The formation of white layer on the surface of blood plasma after DBD treatment confirmed the precipitation and coagulation of plasma proteins and lipids in blood plasma. The present study showed that WBV could be significantly reduced by 9.1 and 17.7% for SBV and DBV, respectively, from the respective baseline values when DBD-treated blood plasma was filtered prior to mixing. Further investigation is necessary to determine the mechanisms of the precipitation and coagulation of plasma proteins and lipids by DBD non-thermal plasma treatment.

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