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RESEARCH ARTICLE

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Plasmapheresis for hypertriglyceridemia: The association between blood viscosity and triglyceride clearance rate

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Objectives: Several factors in double filtration plasmapheresis (DFPP) were associated with triglyceride (TG) clearance rate. This study examines whether baseline whole blood viscosity was a predictor for efficient TG removal.

Methods: Adult subjects who receiving DFPP for hyperlipidemia in Taoyuan General Hospital from January 2015 to March 2018 were classified into efficient and inefficient TG removal according to TG removal rate ≥50% vs <50%. TG removal rate was defined as following formula: (pre-apheresis TG - post-apheresis TG)/pre-apheresis TG. Whole blood viscosity (WBV) was estimated by following equation: WBV = 0.12 × hematocrit +0.17 × (total protein −2.07). Univariate linear regression was used to assess the association between TG removal rate and WBV. Odds ratios (ORs) and 95% confidence interval (95%CI) for associations between variables and efficient TG removal were evaluated by logistic regression model to including univariate and multivariate adjustment.

Results: From a total of 66 subjects receiving DFPP, 37 subjects reached efficient TG removal. The difference in pre-apheresis TG levels, hematocrit, and WBV between efficient vs. inefficient TG removal groups was 4.1 vs 6.7 mmol/L; 43.1% vs 39.5%; and 6.0cP vs 5.cP (Ps <0.05). After multivariate adjustment, WBC was a significant predictor for efficient TG removal (ORs and 95% CI were 3.192 (1.300-7.838), $P < 0.05$). The correlation between WBV and extraction of TG was significant ($r = -0.255$, $P = 0.039$).

Conclusion: Hyperviscosity reduced the efficiency of TG removal in those receiving DFPP.

KEYWORDS

double filtration plasmapheresis, hematocrit, removal rate, triglyceride, viscosity

1 | INTRODUCTION

Hypertriglyceridemia was a well-known risk factor for pancreatitis and coronary artery disease.[1,2] The prevalence of hyperlipidemia was 12% in men and 7% in women in Taiwan (fasting triglyceride (TG)>2.26 mmol/L), whereas those for United States was 32.2% (fasting TG>1.7 mmol/L).[3,4] Hypertriglyceridemia could be divided into primary and secondary hyperlipidemia. Primary hypertriglyceridemia manifested with eruptive xanthoma, lipemia retinalis, hepatosplenomegaly, and focal neurologic symptoms. Secondary hyperlipidemia were owing to obesity, metabolic syndrome, positive energy intake balance, alcohol consumption, hypothyroidism, autoimmune disease, and certain drugs, such as steroid and estrogen.[5,6] It was important to treat hypertriglyceridemia, especially in those with high risk of major cardiovascular event, since reduction in serum triglyceride was associated with fewer death from atherosclerotic cardiovascular disease, nonfatal myocardial infarction and insulin resistance.[7,8] Traditional treatment recommendation included adequate exercise, lipid-lowering drug, diet and nutrition and modification as well as life style modification, such as smoking cessation

and weight reduction.[9] However, plasma exchange and double filtration variant(DFPP) were also contributory to reducing triglyceride levels in acute stage.

Plasma exchange and double filtration variant were two common methods to remove lipid, immunoglobulin as well as specific proteins. Plasma exchange was theoretically superior to DFPP in triglyceride removal because it had less filtration-saturation problem.[10] Despite of better extraction of triglyceride, loss of high-density lipoprotein cholesterol (HDL) and some important protein such as albumin were more common in plasma exchange. In DFPP, the plasma was filtrated and then return to the patient avoiding the need for replacement fluid. This technique required a hollow fiber filter to separate plasma from blood cells (primary plasma separation). Plasma is processed through a second hollow fiber filter, permeable for particles with a molecular weight below 50 000-100 000 Da, allowing HDL, albumin, and smaller immunoglobulins to pass, whereas low-density lipoprotein cholesterol (LDL), lipoprotein (a), and chylomicrons, as well as larger immunoglobulins like IgM, were retained. The loss of HDL and albumin were negligible.[11] Averagely, the reported triglyceride clearance rate was 50%, ranged from 38% to 56% in single session of lipid filtration.[11] Higher blood and plasma flow rate, higher plasma volume processed and lower transmembrane pressure (TMP) were associated with better triglyceride clearance in the modality. Whole blood viscosity (WBV), reflected by hematocrit and total protein, could be evaluated prior to commencing lipid filtration, whereas the blood flow rate, plasma flow rate, and transmembrane pressure were technical parameters and were measured during apheresis. Hematocrit was not only a parameter for plasma volume estimation but also a surrogate for blood viscosity, which was associated with the transmembrane pressure gradient.[12,13] Nevertheless, the association between baseline WBV and the clearance rate of triglyceride was not well investigated.

The aim of the study was to evaluate whether baseline blood viscosity, estimated by hematocrit and total protein, was a predictor for TG removal rate or not (defined as removal rate of TG ≥50%). We analyzed multiple factors associated with TG clearance before apheresis, including volume of plasma processed, blood and plasma flow rate, as well as maximal TMP in a single center.

2 | MATERIALS AND METHODS

2.1 | Participants

The retrospective observational study included 75 patients aged from 38 to 72 years, who paid for DFPP owing to hypertriglyceridemia (TG>2.26 mmol/L) in Taoyuan General Hospital from January of 2015 to March of 2018. Participants were followed up until June 30, 2018. We reviewed clinical characteristics and biochemical data 48 hours before apheresis and obtained blood samples after apheresis. All of them received single session of DFPP. Lipid-lowering agents were continued throughout treatment period. Thirteen subjects had history of acute pancreatitis owing to hypertriglyceridemia. None of them received interventions for coronary artery reperfusion. Nine participants without data on serum total protein were excluded. Finally, 66 participants were assessed and analyzed.

2.2 | Ethics

This study was conducted in accordance with the Declaration of Helsinki (2000) of the World Medical Association, and the protocol was approved by the institutional review board of Taoyuan General Hospital (TYGH107018). This study was investigated in a single center, and all patients in the study were directly diagnosed and followed up at Taoyuan General Hospital.

2.3 | Apheresis and Outcome ascertainment

Demographic data, clinical characteristics, and biochemical data were reviewed according to electronic medical records. Pretreatment blood samples were obtained in fasting status. DFPP was performed using the all-in-one blood purification device (HF440, Informed SA, Geneva, Switzerland). Plasma separators were used to separate plasma from blood with surface area 0.3 square meters (LF-030, Informed SA, Geneva, Switzerland), whereas the second hallow fibers were made of polyethersulfone with maximal pore size 30 nanometer (Medopen 30, INFOMED SA, Geneva, Switzerland). During apheresis, blood flow rate, plasma flow rate, TMP, arterial and venous pressures were monitored. Posttreatment blood samples were obtained at end of apheresis. One and a half estimated plasma volume was processed, which was estimated through the following equation: estimated plasma volume = (0.065 × wt(kg)]) × (1-Hct).[13] Normal saline 0.1 liters flushing in the circuit was launched automatically when TMP was higher than 150 mm Hg. Heparin was used as an anticoagulant. The plasma flow rate was 25% of blood flow rate. Since reducing effective apheresis duration could improve the clearance of TG and minimize the loss of albumin, we terminated apheresis when estimated plasma volume was fully processed or just after second normal saline flushing.[10] We used 18-gauge needles as vascular access in both antecubital veins.

2.4 | Laboratory test

Serum cholesterol, triglyceride, creatinine, LDL, albumin as well as total protein (reference range (60-83 g/L) and hematocrit (reference range: 39%-53% for men and 33%-47% for women) were measured before commencing apheresis (ADVIA 1800, Siemens, Germany and XN9000, Sysmex, Japan). The inter-assay coefficients of variance (CV%) for hematocrit and total protein were <2% and 1.4%, respectively; whereas intra-individual CV% for total protein and triglyceride were 2.8% and <10%. The triglyceride measurement was based on the enzymatic determination of glycerol using the enzyme glycerol phosphate oxidase (GPO) after hydrolysis by lipoprotein lipase, whereas hematocrit was measured by direct current detection method on microscopy. Total protein was measured by biuret reference method. WBV was estimated in centipoises (cP) at high shear rate (208 s^{-1}) according to following equation as previous study[14]: WBV = 0.12 × Hct + 0.17 × (total protein −2.07). The removal rate of

triglyceride was calculated using the following formula: (pre-apheresis TG - post-apheresis TG)/pre-apheresis TG. Besides, the removal rate of cholesterol and LDL were also calculated as previous equation. Since the TG clearance rate in single session of lipid filtration was 50% on average, we defined those with a removal rate of TG less than 50% as inefficient TG removal in the modality. Technical parameters, such as total heparin dose, duration of apheresis, filtrated plasma volume, maximal transmembrane pressure, blood flow rate, plasma flow rate and volume of plasma processed, reflected by filtrated-to-estimated plasma volume ratio, were also recorded.

2.5 | Statistical analysis

Participants were divided into two groups, efficient TG removal (≥50%) vs inefficient TG removal (<50%), according to the removal rate of TG. Continuous variables with a normal distribution were summarized as mean ±SD unless otherwise stated. Variables with a non-normal distribution are expressed as a median (interquartile range (IQR)). Pearson's chi-square, independent student *t* test, or Mann-Whitney *U* test is used to determine the differences in the demographic data, the laboratory variables, and clinical characteristics among two groups. Univariate linear regression was used for assessing the association between continuous parameters and TG removal rate. Associations between variables and efficient TG removal were assessed using logistic regression analysis, including univariate and multivariate analysis. To avoid missing possible important predictors for efficient TG removal, predictors with $P < 0.2$ were enrolled in multivariate logistic regression. We chose "Enter" method for multivariable adjustment; thus, all variables were entered together. Hematocrit and total protein had collinearity with WBV. Besides, WBV was more predictive than hematocrit and total protein alone in TG removal. Therefore, we added WBV into the multivariate logistic regression model instead of hematocrit and total protein. Finally, age, gender cholesterol, triglyceride, WBV, duration of DFPP, and total heparin were added into model. All statistical analyses were performed using PASW Statistics 18 (SPSS Inc, Chicago, IL, USA). A two-tailed p value of less than 0.05 was considered statistically significant.

TABLE 1 Baseline characteristics for study population

Parameters at apheresis	TG removal <50% n = 29	TG removal ≥50% N = 37	*P* value
Age (y)	58.5 (53.0-60.6)	52.0 (44.5-60.9)	0.153
BW(kg)	76.4 ± 12.1	80 ± 13.6	0.266
Men(%)	22 (75.9)	33 (89.2)	0.191
DM(%)	14 (48.3)	18 (48.6)	1.000
Creatinine (μmol/L)	88.4 (61.9-106.1)	88.4 (61.9-106.1)	0.904
eGFR(mL/min)	78.3 (65.6-105.0)	87.5 (61.4-116.1)	0.620
Cholesterol (mmol/L)	4.9 (4.1-5.3)	5.2 (4.1-7.1)	0.620
TG (mmol/L)	4.1 (3.1-5.4)	6.7 (4.1-14.3)	<0.001*
LDL (mmol/L)	4.1 (3.4-4.4)	3.8 (3.4-4.3)	0.475
Hemoglobin(g/L)	147 (134-153)	133 (117-148)	0.047*
Albumin(g/L)	40.0 (39.0-42.5)	41.0 (37.0-45.0)	0.403
Total protein(g/L)	68.0 (66.0-70.1)	67.7 (64.9-73.4)	0.492
Hematocrit(%)	43.1 ± 4.25	39.5 ± 6.93	0.015*
WBV(cP)	6.0 (5.6-6.3)	5.6 (5.0-6.2)	0.047*
Volume of plasma processed	0.96 (0.87-1.03)	0.92 (0.84-1.01)	0.137
Duration of DFPP (hr)	2.1 (2.0-2.5)	2.0 (1.9-2.1)	0.184
Total heparin (1000 μ)	1.5 (1.4-1.5)	1.5 (1.4-1.5)	0.475
Blood flow (mL/min)	68 (64-70)	64 (64-70)	0.827
Plasma flow (mL/min)	17 (15-22)	17 (14-21)	0.703
Maximal TMP(mm Hg)	85.2 (36.5-128.0)	64.7 (49.5-116.7)	0.620
Removal rate of TG (%)	35 (13-42)	59 (54-66)	<0.001*
Removal rate of LDL (%)	47 (39-50)	50 (34-59)	1.000
Removal rate of Cholesterol (%)	41 (34-47)	49 (39-53)	0.137

DM, diabetes mellitus; TG, triglyceride; BW, body weight; LDL, low-density lipoprotein cholesterol; WBV, whole blood viscosity; DFPP, double filtration plasmapheresis, TMP, transmembrane pressure; eGFR, estimated glomerular filtration rate, MDRD 4 variable equation.
*$P < 0.05$, Data are percentage, mean ±standard deviation, median(interquartile range(IQR)).

3 | RESULTS

In total, 66 participants receiving DFPP were enrolled between January 2016 and December 2017. The median age of study group was 57.0 years old, ranged from 38 to 72 years old, whereas the mean level of hematocrit was 41.9%, ranged from 26% to 54%. None of these subjects had history of apheresis, including plasma exchange and double filtration variant. Lipid-lowering agents, such as fenofibrate (51.5%), gemfibrozil (16.7%), and statin (30.3%), were used in study group. The median time of apheresis was 2.0 hour, ranged from 1.75 to 3.5 months. The median levels of triglyceride dropped from 5.43 to 2.78 mmol/L. Besides, the median value of whole blood viscosity was 5.84cP (5.33cP ~ 6.27cP), whereas the median removal rate of TG was 52.0% (8.9% ~ 91.3%). The removal rate of albumin was 10.6%. One event of allergy with skin rash and chemosis was reported. The majority (78.8%) of subjects had albumin supplement after apheresis.

Table 1 shows the comparisons of baseline characteristics, biochemical data, and DFPP-related parameters between efficient and inefficient TG removal defined by the removal rate of TG. The proportion of severe hypertriglyceridemia, defined as TG>5.65 mmol/L, was 42.4% (n = 28). Those with efficient TG removal had higher levels of pre-apheresis triglyceride (6.7 vs 4.1 mmol/L, respectively), whereas hematocrit, hemoglobin, and WBV were lower in the efficient TG removal group (39.5% vs 43.1%, 133 g/L vs 147 g/L and 5.6 cP vs 6.0 cP; *P*s < 0.05). There was no difference between two groups in age, body weight, proportion of diabetes and gender, creatinine, total protein, pretreatment cholesterol, albumin and LDL as well as technical parameters, such as duration of apheresis, total heparin dose, maximal TMP, volume of plasma processed, blood and plasma flow rate, removal of cholesterol and LDL (*P*s > 0.05). Besides, there was no difference between the use of fenofibrate (48% vs 54%), gemfibrozil (20.7% vs 13.5%), and statin (27.6% vs 32.4%).

In univariate linear regression analysis, improved extraction of TG was well correlated with younger age, (R^2 = 0.053, *P* = 0.047), lower hematocrit (R^2 = 0.091, *P* = 0.007), and hypoviscosity, reflected by lower WBV(R^2 = 0.098, *P* = 0.001) as well as higher pre-apheresis TG(R^2 = 0.184, *P* = <0.001) and cholesterol(R^2 = 0.134, *P* = 0.001) (Table 2). The univariate logistic regression demonstrated older age, higher hematocrit, and hyperviscosity were significant predictors for inefficient TG removal (odds ratio (ORs) and 95% confidence interval (95% CI) were 1.069 (1.003-1.140), 1.117(1.017-1.226), and 2.129 (1.052-4.310), *P*s < 0.05), whereas higher pre-apheresis level of TG and cholesterol could predict efficient TG removal (ORs (95%CI): 0.681(0.482-0.960) and 0.756(0.616-0.927), *P*s < 0.05) (Model *P* < 0.001, Cox and Snell *R* square = 0.458)(Table 3). In multivariate logistic regression analysis, hyperviscosity and hypertriglyceridemia remained predictors for the efficient TG removal (OR (95% CI): 3.192 (1.300-7.838) and 0.730(0.587-0.907)) (Table 3). Figure 1 demonstrated the correlation between WBV and extraction of TG (*r* = −0.255, *P* = 0.039), whereas Figure 2 demonstrated associations between parameters and TG removal rate <50%.

TABLE 2 Univariate linear regression between removal rate of triglyceride and other variables

Parameters	β	R^2	*F*	*P*
Age	−0.007	0.053	4.076	0.047*
BW	−0.001	0.001	0.001	1.000
eGFR	0.001	0.016	1.196	0.278
Hematocrit	−0.012	0.091	7.297	0.007*
Cholesterol	0.035	0.134	11.303	0.001*
LDL	0.016	0.005	0.359	0.551
Triglyceride	0.010	0.184	16.481	<0.001*
Albumin	−0.002	0.001	0.085	0.772
Total protein	−0.022	0.006	0.442	0.508
WBV	−0.088	0.098	7.336	0.006*
Blood flow	−0.001	0.001	0.078	0.781
Plasma flow	0.001	0.002	0.102	0.751
Maximal TMP	0.471	0.005	0.349	0.557
Duration of DFPP	−0.075	0.013	0.947	0.334
Total heparin	−0.052	0.011	0.817	0.369
Volume of plasma processed	0.136	0.013	0.939	0.336

β, regression coefficient; R^2, coefficient of determination; F, F ratio in analysis of variance (ANOVA).
BW, body weight; eGFR, estimated glomerular filtration rate, MDRD 4 variables equation; WBV, whole blood viscosity; LDL, low-density lipoprotein cholesterol; TMP, transmembrane pressure; DFPP, double filtration plasmapheresis.
[a]*P* < 0.05.

4 | DISCUSSION

This cross-sectional observational study demonstrated not only pre-apheresis triglyceride but also whole blood viscosity, estimated by hematocrit and total protein, was associated with the efficiency of lipid apheresis after multivariable logistic regression analysis. The TG removal rates between high WBV(>5.83cP) vs low WBC(<5.83cP) were 56.8% vs 46%.

Several studies had demonstrated the associations between efficiency of lipid apheresis and blood flow rate, plasma flow rate, TMP as well as filtrated plasma volume.[10,15] However, the association between pre-apheresis whole blood viscosity and efficiency of lipid apheresis has not been well investigated. Blood viscosity, reflected by hematocrit and total protein, might be associated with elevated TMP during apheresis.[12] Conceptually, TMP was different from viscosity. TMP was an indicator monitored during apheresis for patency of circuit and was influenced by length of circuit, blood viscosity, pore size of plasma separator or fractionator, arterial and venous pressures,[12] whereas blood viscosity could be estimated by hematocrit, total protein, lipid, temperature, and shear rate of blood vessel.[16-18] Moreover, blood viscosity was associated with gender, obesity, sodium intake, age, race, plasma renin activity, mean blood pressure, RBC aggregation, platelet activation

TABLE 3 Logistic regression analysis for removal rate of TG <50%

Parameter	β coefficient	SE	Odds ratio	95% CI	*P* value
Univariate regression					
Age	0.066	0.033	1.069	1.003-1.140	0.044*
BW	−0.023	0.021	0.977	0.939-1.018	0.267
eGFR	−0.004	0.008	0.996	0.980-1.012	0.625
Hematocrit	0.110	0.048	1.117	1.017-1.226	0.021*
Cholesterol	−0.385	0.176	0.681	0.482-0.960	0.029*
LDL	−0.252	0.264	0.777	0.463-1.204	0.340
Triglyceride	−0.280	0.104	0.756	0.616-0.927	0.007*
Albumin	0.008	0.048	0.992	0.903-1.089	0.861
Total protein	−0.023	0.302	0.978	0.541-1.766	0.940
WBV	0.756	0.360	2.129	1.052-4.310	0.036*
Blood flow	0.011	0.027	1.011	0.958-1.066	0.676
Plasma flow	−0.047	0.043	0.954	0.876-1.039	0.282
Maximal TMP	0.002	0.005	1.002	0.992-1.011	0.712
Duration of DFPP	1.328	0.803	3.773	0.782-18.210	0.098
Total heparin	1.161	0.742	3.193	0.757-13.460	0.114
Volume of plasma processed	0.774	1.150	2.168	0.112-41.830	0.608
Men	−0.965	0.685	0.381	0.100-1.457	0.159
DM	−0.015	0.496	0.985	0.372-2.606	0.976
Multivariate regression					
Age	0.042	0.042	1.043	0.959-1.133	0.324
Men	−0.696	0.792	0.498	0.126-2.352	0.379
cholesterol	−0.243	0.285	0.784	0.449-1.370	0.393
Triglyceride	−0.315	0.111	0.730	0.587-0.907	0.004*
WBV	1.161	0.458	3.192	1.300-7.838	0.011*
Constant	7.241	4.983	-	-	-

SE, standard error; BW, body weight; LDL, low-density lipoprotein cholesterol; WBV, whole blood viscosity; DFPP, double filtration plasmapheresis; TMP, transmembrane pressure; DM, diabetes mellitus.

[a]$P < 0.05$.

and microcirculation status.[17-19] It was difficult to separate plasma from whole blood under hyperviscosity status, since blood viscosity was representative not only for high red blood cell mass but also hydrodynamics and macromolecule induced red blood cell aggregation.[19-21] On the other hand, the plasma from subjects with blood hyperviscosity but normal hematocrit was easily separated from blood cell via primary separator. However, the hyperviscosity was attributed not only to high hematocrit but also to high total protein. The protein-rich plasma would make second hallow fiber early saturated and reduced the efficiency of target molecule removal. Not surprisingly, high TG value was associated with high TMP during apheresis because of high blood viscosity with early saturation of plasma separator.[22] Nonetheless, the amplitude of rebound of TG was higher in those with higher TG removal rate than that of those with lower TG removal rate.[23,24] Median recovery half times for lipid and lipoprotein range from 2.3 to 4 days.[23] Inefficient TG removal was not uncommon for those with low baseline TG values. Thus, whether higher triglyceride was associated, better extraction of TG remained controversy since hypertriglyceridemia was associated with high TMP and hyperviscosity but lower lipid was associated with higher amplitude of lipid rebound. Sigmoidal shape between serum triglyceride and TG removal rate might be reasonable. In the study, we demonstrated high pre-apheresis whole blood viscosity was a significant predictor for inefficient apheresis. Since we could adjust the ratio of plasma-to-blood flow rate during apheresis, lower ratio of plasma-to-blood flow rate with lower blood viscosity might be necessary in those with higher pre-apheresis blood component, such as lipid, protein, and immunoglobulin.

The reported TG removal rate ranged from 38% to 58% in double filtration variant, whereas it was only 52% in our study.[10,11] There were several reasons why the TG removal rate was lower and varied widely (8.9% ~ 91.3%) in our study. First, the estimated plasma volume was not totally processed. Some treatments were early

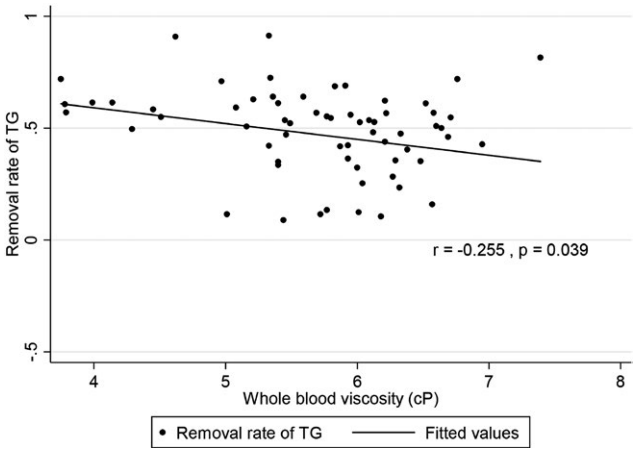

FIGURE 1 The correlation between WBV and extraction of TG. TG, triglyceride; cP, centipoise

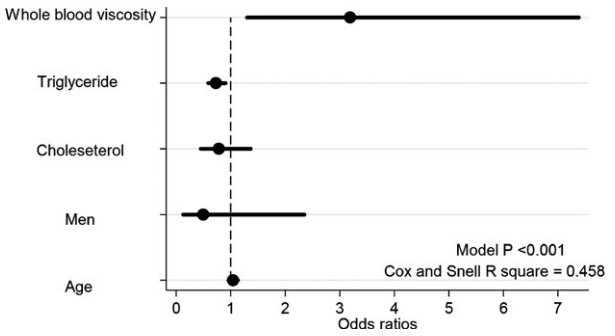

FIGURE 2 Associations between parameters and TG removal rate <50%

terminated owing to high TMP and unpredicted conditions. Besides, the blood flow rate was relatively lower than those in other studies owing to the different vascular access from previous studies since blood flow was a determinant of efficiency of TG removal.[10,15] We used 18-gauge needles as vascular access, whereas dialysis catheters or double lumen catheter were chosen in previous studies. Moreover, most participants in previous studies were with severe hyperlipidemia (>5.65 mmol/L) and the mean TG levels were higher than those of our participants. As noted, extremely high triglyceride was associated with good extraction of TG. In the DFPP modality, not only large immunoglobulin, but also fibrinogen, coagulation factor 11 and 13 were retained and discarded after plasma was processed through second hallow fiber. Albumin, LDL, antithrombin III, protein C, coagulation factor 2, 9, and 10 were recycled.[25] TG removal was more efficient using plasma exchange than using DFPP. Regardless of molecular size, plasma exchange removed substance with high protein-binding affinity and provided more efficient removal of substance. However, it required plasma supplement and had risk of allergic reaction and transfusion-related infection.[14,26] DFPP removed substance selectively according to molecular weight without need for plasma supplement.[14] Besides, the adverse effect in DFPP modality was rare.[27] Mounting evidence indicated that lipid apheresis removed not only lipid but also inflammatory makers and improved hemorheology, vasomotion, and plaque stable in arteries.[21,28]

There were several limitations in present study. First, it was an observational study within one medical center, and thus, the result might not be extrapolated into other areas or countries. Besides, the causal inference and temporal relationship was weak in cross-sectional study. Second, since the expenditure of DFPP was not covered in national health insurance, case and control selection bias were inevitable. Control group was not representative to general population. Hospital-based control, community-based control, and population-based control should be enrolled simultaneously to improve the statistical power. Third, overshoot of TMP might be related to circuit occlusion or saturation of plasma separators. Early termination of apheresis according to overshooting of TMP would induce inefficient clearance of TG. However, the volume of plasma processed was not different between two groups. The misclassification of inadequate process of filtrated plasma volume rather than saturation of plasma separators would be non-differential. Fourth, hematocrit was not only a surrogate of blood viscosity but also a marker for hemoconcentration. High hematocrit did not necessarily imply hyperviscosity. Nonetheless, the hematocrit-to-hemoglobin ratio was close to 3.0 in the study. Hemoconcentration was less likely when the ratio was close to 3.0. Finally, blood viscosity was estimated according to hematocrit only. Blood viscosity measured by viscometer might be necessary. Despite hematocrit and total protein-based blood viscosity formulae had be validated and hematocrit was the key factor, the influence of erythrocyte aggregation and deformity might be underestimated.[14,17,29] Although HDL, fibrinogen, TG may contribute to blood viscosity, their contribution and correlation to blood viscosity were minimal (Pearson's correlation coefficients <0.1). On the other hand, the correlation between hematocrit and viscosity as well as total protein was high (Pearson's correlation coefficients were 0.75 and 0.39). Total protein plus hematocrit could be a good surrogate for blood viscosity. Actually, real whole blood viscosity might had more impact on TG clearance since WBV was underestimated.[29,30] The association between estimated WBV and TG clearance rate remained conclusive.

To sum up, hematocrit, WBV, estimated according to hematocrit and total protein, was associated with the efficiency of lipid apheresis. The impact of hyperviscosity on TG clearance rate was mainly attributed to hematocrit and total protein. Adjustment of ratio of plasma-to-blood flow rate during apheresis might increase clearance of triglyceride. Applications of apheresis were not only for hyperlipidemia, but also for hypercholesterolemia, sudden onset hearing loss, acute inflammatory demyelinating polyneuropathy, acute fatty liver, rapid progressive glomerulonephritis, and hyperviscosity syndrome.[9] Optimal ratios of plasma-to-blood flow rate in different diseases and viscosity have not be established. This study was limited by the cross-sectional and observational nature and sample size. A multicenter observational study is warranted to confirm the relationship between pre-apheresis blood viscosity and clearance of different molecule. Optimal ratios of plasma-to-blood flow rate during apheresis will also need further investigation in different setting of diseases.

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DECLARATION OF INTEREST

The authors report no conflict of interests.

AUTHORS' CONTRIBUTIONS

H-CW and W-JW assisted with acquisition of data. L-CL and H-CW made contributions to conception and design of the study. L-CL also assisted with data organization. Both H-CW and L-CL contributed equally to this work.

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