Plasma exchange in acute and chronic hyperviscosity syndrome: a rheological approach and guidelines study

Marco Ballestri[a], Federica Ferrari[a], Riccardo Magistroni[a], Maria Mariano[b], Giovanni Battista Ceccherelli[b], Giorgio Milanti[b], Marisa De Palma[b] and Alberto Albertazzi[a]

[a] Divisione e Cattedra di Nefrologia Dialisi e Trapianto renale; [b] Medicina Trasfusionale, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy

Summary. Therapeutic plasma exchange is an extra-corporeal technique able to remove from blood macromolecules and/or replace deficient plasma factors. It is the treatment of choice in hyperviscosity syndrome, due to the presence of quantitatively or qualitatively abnormal plasma proteins such as paraproteins. In spite of a general consensus on the indications to therapeutic plasma exchange in hyperviscosity syndrome, data or guide lines about the criteria to plan the treatment are still lacking. We studied the rheological effect of plasma exchange in 20 patients with plasma hyperviscosity aiming to give data useful for a rational planning of the treatment. Moreover, we verified the clinical applicability of the estimation of plasma viscosity by means of Kawai's equation. Plasma exchange decreases plasma viscosity about 20-30% for session. Only one session is required to normalize plasma viscosity when it is < 2.2 mPas, whereas a maximum of 3 sessions are required when it is > 2.2 till to 6 mPas. A fourth session is useless, especially if the inter-session interval is < 15 days. By means of a polynomial equation, knowing basal-plasma viscosity and the disease of a patient, we can calculate the decrease of viscosity obtainable by each session of plasma exchange then the number of session required to normalize the viscosity. Kawai's equation is able to evaluate plasma viscosity in healthy volunteers, but it is not clinically reliable in paraproteinemias.

Key words: therapeutic apheresis, plasma viscosity, hyperviscosity syndrome, plasma exchange.

Riassunto *(*Plasma exchange *nella sindrome da iperviscosità acuta e cronica: approccio reologico e studio di linee guida)*. Il *plasma exchange* è una tecnica terapeutica extracorporea che consente di rimuovere dal sangue macromolecole lesive e/o supplementare fattori plasmatici carenti. Costituisce il trattamento di elezione della sindrome da iperviscosità, dovuta alla presenza nel plasma di proteine quantitativamente o qualitativamente anomale. Nonostante l'ampio consenso all'impiego del *plasma exchange* nella sindrome da iperviscosità, non vi sono al momento istruzioni operative o linee guida per la pianificazione del trattamento. Abbiamo studiato gli effetti emoreologici del *plasma exchange* in 20 pazienti con iperviscosità plasmatica al fine di ricavare dati utili per una pianificazione razionale della terapia aferetica. Abbiamo inoltre verificato l'applicabilità clinica della formula di Kawai per il calcolo teorico della viscosità plasmatica. Una singola seduta di *plasma exchange* riduce la viscosità plasmatica del 20-30%. Una sola seduta normalizza la viscosità plasmatica quando questa è < 2.2 mPas, mentre sono necessarie 3 sedute quando la viscosità è > 2.2, fino a 6 mPas. Una quarta seduta non risulta utile, specie se eseguita ad un intervallo < 15 giorni. Conoscendo la viscosità plasmatica iniziale e la patologia del paziente, utilizzando un'equazione polinomiale, è possibile calcolare il decremento di viscosità per ogni seduta ed il numero di sedute necessarie per normalizzarla. L'equazione di Kawai non consente un calcolo attendibile della viscosità plasmatica nei pazienti con paraproteinemia.

Parole chiave: aferesi terapeutica, viscosità plasmatica, sindrome da iperviscosità, *plasma exchange*.

INTRODUCTION

Therapeutic plasma exchange (TPE) is an extracorporeal blood purification technique able to remove from plasma macromolecules not removable by means of haemodialysis and/or to replace deficient plasma factors [1]. About twenty years after the birth and the empirical application of TPE [2], authoritative studies typed the diseases in which TPE may be useful and looked for guidelines in indications for TPE. Four categories of diseases had been identified [1, 3, 4]: the first category includes the diseases in which controlled trials suggested TPE as the

Indirizzo per la corrispondenza (Address for correspondence): Marco Ballestri, Divisione e Cattedra di Nefrologia Dialisi e Trapianto Renale, Azienda Ospedaliero-Universitaria di Modena, Via del Pozzo 79, 41100 Modena, Italy. E-mail: ballestri.marco@unimore.it.

standard therapy *i.e.* thrombotic thrombocytopenic purpura or hyperviscosity; second category includes the diseases for which there is available evidence suggesting efficacy of TPE, *i.e.* systemic vasculitis, or myeloma-paraproteinemias; third category includes the disorders which have not adequately tests of efficacy of TPE at this time, *i.e.* progressive systemic sclerosis or multiple sclerosis; fourth category includes the disease for which it's not demonstrated efficacy of TPE in controlled trials, *i.e.* psoriasis or amyotrophic lateral sclerosis. Despite of a large consensus on guidelines concerning the indications to TPE, data or guidelines about the criteria to plan the treatment are still lacking [4].

We studied the use of TPE in dysproteinemias which can cause different kidney lesions (*i.e.* cast nephropathy, light chain deposition disease) and/or plasma hyperviscosity. Acute hyperviscosity syndrome (HS) can occur when the normal plasma viscosity (PV) of 1.4 mPas increse up to 4-5 mPas and it is more common in Waldenström's macroglobulinemia, than multiple myeloma or cryoglobulins [5]. In particular, acute HS can appear when plasmatic IgM is > 5 gr/dL or IgG3 and monomeric IgA > 4-5 gr/dL or polimeric IgA > 10-11 gr/dL. Clinical manifestations of acute HS are due to both vascular occlusion and impaired haemostasis; it includes ocular, neurological and cardiovascular dysfunctions and bleeding [6]. Really, acute HS is a very rare event whereas we often observe patients with asimptomatic light or mild plasma hyperviscosity, 2-3 mPas, due to paraproteins, high levels of immunoglobulins, alfaglobulin or lipids. TPE is the tratment of choice of acute HS and it is however able to effectively and rapidly correct plasma viscosity during the period that other therapeutic interventions such as chemotherapy take effect. It's well known that the efficiency of TPE is different for different molecules and ranges from 15 to 75%; it is highest for IgM because of their prevalent intravascular distribution and is 4-5 fold lower for IgG because of their wide extravascular distribution [1, 7]. In spite of this, quantitative data about the rheological effect of TPE are lacking and parameters regarding the start, the frequency and the end point of TPE are usually empirically settled.

Aims of the study were: a) to get a status-report of our clinical behaviour; b) to quantify the rheological efficacy of TPE; c) to give data useful in planning TPE; d) to create a model for computation the number of TPE-sessions required to normalizing PV in each patient on the basis of his basal PV and his disease; e) to verify the clinical applicability of the estimation of PV by means of Kawai's equation (KE). In fact, KE could be very helpful in hospital units where viscometers or rheometers are unavailable.

METHODS

We studied 20 patients undergone to TPE for a total of 51 treatments. The mean age of the patients was 65±14 years. They were undergoing to TPE because of multiple myeloma (MM) 30%, Waldenström's macroglobulinemia (WM) 25%, monoclonal gammopathy of undetermined significance (MGUS) 5%, cryoglobulinemia (CG) 25%, other inflammatory disease (ID) 15% with increased alfa-globulins and/or polyclonal immunoglobulins, such as collagenopathies.

The technique of plasma exchange was: continuous flow system; mean volume of exchange 40 ml/kg/session; acid-citrate-dextrose as anticoagulant. Replacement solution composition: albumin 3.3%, Na 154 mEq/L, K 3 mEq/L, Ca 2.5 mEq/L.

We measured PV with the rheometer Hakke-CV100 (Hakke GmbH, Karlsruhe, Germany) at even temperature of 37 °C and shear rate 300 s^{-1}, accordingly with the indications of the International Committee for Standardization in Haematology standards [8]. The measures had been done pre and post TPE. In CG, the PV had been measured at temperature of 30 °C too.

Moreover, we estimated the rough PV pre and post TPE and in 30 healthy volunteers by means of the equation of Kawai [9, 10]:

$$PV = 0.204 + (0.177 \times PT)$$

where PV is plasma viscosity expressed as mPas and PT are plasma proteins expressed as g/dL.

All the data concerning PV were analyzed after the end point of TPE program, therefore results and values of PV did not influence planning and frequency of the treatments.

RESULTS AND DISCUSSION

First of all, we could obtain a status-report of our clinical behaviour at this time. Empirically, we prescribed 3 TPE for patients with MGUS, 4 for MM and 5 for WM. In CG and ID we tend to prescribe a major number of treatments, till to 7. The interval between the treatments was less than a week (from 1 to 5 days) for the first 4 sessions, and usually above 15 days for following sessions. The end point of TPE was empirically decided for patients with paraproteinemias, whereas for the other diseases, included CG, it was determined especially on the basis of laboratory and clinical signs of remission.

Figure 1 shows the rheological effects of each TPE-session. The rheological efficiency (RE) of TPE in decreasing PV was major when major was basal-PV. By the analysis of the figure we can roughly foresee that the normalization of a basal-PV < 2.2 mPas requires only one TPE-session; whereas, the required sessions are almost 2 when basal-PV is > 2.2 till up to 6 mPas. Nevertheless, it must be considered that the RE of each session is varying during a TPE program. In fact, the RE tended to progressively decrease in relation to the progressive decrease of PV. Really, as shown in *Figure 2a*, a significant fall of RE appeared only during the fourth consecutive

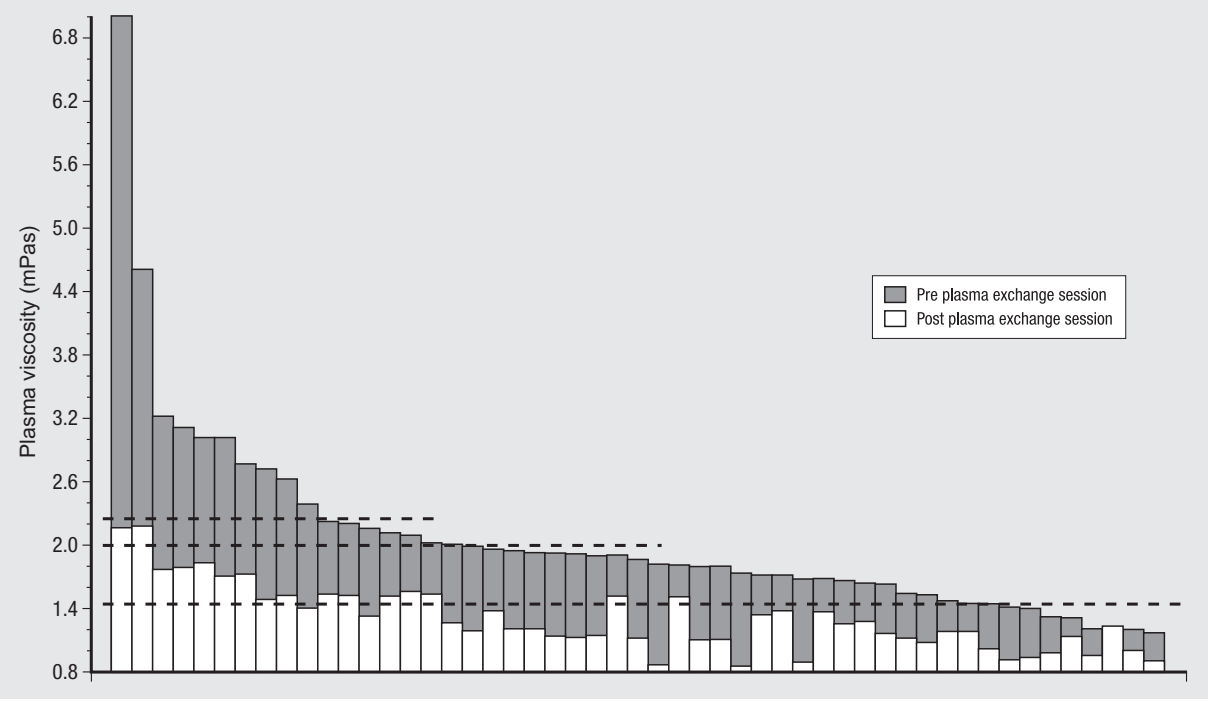

Fig. 1 | *Rheological effects of each therapeutic plasma exchange session. Higher is basal plasma viscosity therefore grater is the decrease of viscosity post apheresis. A single one session of plasma exchange normalizes plasma viscosity when it is < 2.2 mPas. Whereas 2 sessions sare required when plasma viscosity is > 2.2 till to 6 mPas.*

session of TPE. Moreover, TPE is very able to remove molecules, but it don't stop their production and PV could tend to rise during the break between the sessions. *Figure 2b* shows the mean increasing of PV between consecutive sessions of TPE, due to redistribution and/or neo-production of plasma proteins and/or paraproteins. Really, PV reached again to the starting levels only in occasion of the

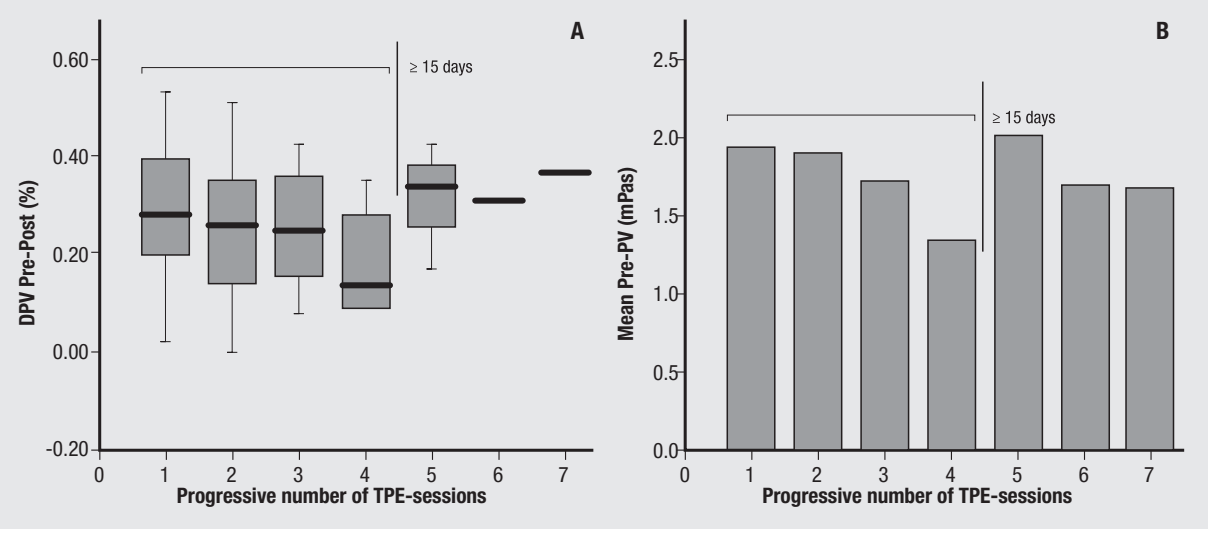

Fig. 2 | *a) the fall in rheological efficiency of plasma exchange (DPV pre-post) was significant only during the fourth consecutive session. It increased again after an interval ≥15 days, when plasma viscosity (PV) was increased too. Whereas, the break between the first four sessions was ≤ 5 days. b) mean plasma viscosity pre-plasma exchange (PrePV) during consecutive session. PrePV progressively decreased till to a nadir after the third session and increase again after the break ≥15 days.*

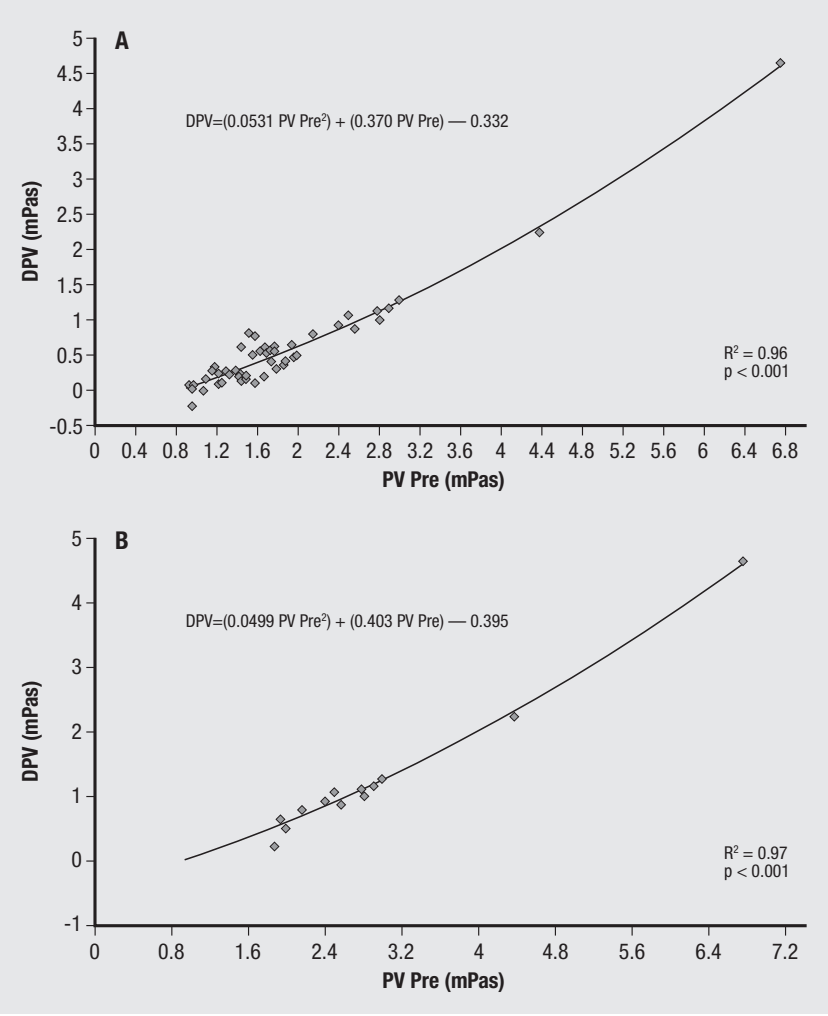

Fig. 3 | *Correlation between gradient of plasma viscosity pre and post apheresis (DPV) in function of basal plasma viscosity (PV). It's possible to roughly calculate a polynomial relation by mean of which the DPV of each plasma exchange can be predicted. Then, the number of sessions required to normalize PV can be estimated. a) Curve calculated on the basis of the overall cases. b) Curve calculated on the basis of GM and MM patients.*

fifth session, usually performed ≥15 days after the fourth. Nevertheless, we take into account that rate of productions can be very variable and depending to type and severity of the disease and to medical treatments such as chemotherapy.

The study of rheological effect of the TPE-sessions in the different diseases confirmed the greatest efficacy in decreasing PV in WM (about 33 ± 0.12 %), because of the prevalent intravascular distribution of IgM [1]. The decrease was 20 ± 0.21% in MM, 17 ± 0.04 % in MGUS, 19 ± 0.12 % in CG and 33 ± 0.09 % in ID. The high rheological efficiency of TPE obtained in ID could be explained by the complex genesis of hyper-PV, probably due to synergic effect of alfa- and gamma-globulins. On the contrary, in CG, the influence of immunoglobulins became evident only when we measured PV at temperature 30 °C, whereas at 37 °C, the hyper-PV seemed mainly due to alfa-globulins. Nevertheless, because of the little number of cryoglobulinemic patients, we did not obtain the statistical significance.

The analysis of PV-decreasing in function of basal-PV showed a polynomial relation expressed by the following equation *(Figure 3)*:

$DPV = (0.0531\ PV\ Pre^2) + (0.370\ PV\ Pre) - 0{,}332$ where DVP is the gradient of PV pre-post a single session of TPE and PV Pre is PV at the start of the session.

The standard error of this equation is 0,1 ($R^2 = 0.96$; p = 000). The error lightly increases when PV Pre is < 2 mPas, but in this case only one session of TPE is sufficient to normalize PV and no long planning is request. Testing the correlation in the different diseases, we could confirmed a more closely correlation only in the lympho-immunoproliferative disorders and we could be define more specific numeric coefficients to reduce the standard error. In particular, $DPV = (0.045\ PV\ Pre^2) + (0.4485\ PV\ Pre) - 0.4533$ for MM ($R^2 = 0.99$; p = 0.000); $DPV = (0.0347\ PV\ Pre^2) + (0.4584\ PV\ Pre) - 0.4307$ for WM ($R^2 = 0.95$; p = 0.000) and $DPV = (0.0499\ PV\ Pre^2) + (0.403\ PV\ Pre) - 0.3949$ ($R^2 = 0.97$; p = 0.000) for MM + WM.

KE was perfectly reliable when applied to estimate PV in healthy volunteers and in patients affected by ID *(Table 1)*. On the contrary, it was not reliable in calculating PV pre-TPE in patients with paraproteinemias because of an evident undervaluation. KE was again reliable post TPE-session, that is after

Table 1 | *Difference between plasma viscosity (PV) measured (M) and roughly calculate with Kawai's equation (KE)*

		HV	All	MM	WM	MGUS	CG	ID
PV Pre	M (mPas)	1.47 ± 0.10	1.96 ± 0.99	2.94 ± 1.93	2.02 ± 0.43	1.42 ± 0.20	1.47 ± 0.27	1.70 ± 0.19
	KE	1.47 ± 0.06	1.58 ± 0.30	1.93 ± 0.26	1.66 ± 0.18	1.35 ± 0.01	1.25 ± 0.15	1.74 ± 0.12
	p	n.s.	0:03	n.s.	0.008	n.s.	0:02	n.s.
PV Post	M (mPas)		1.21 ± 0.23	1.20 ± 0.03	1.33 ± 0.27	1.18 ± 0.24	1.09 ± 0.21	1.22 ± 0.22
	KE		1.14 ± 0.18	1.64 ± 0.28	1.15 ± 0.03	1.07 ± 0.03	1.01 ± 0.08	1.19 ± 0.08
	p		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

PV Pre: PV pre plasma exchange; PV Post: PV post plasma exchange; HV: healthy volunteers; MM: multiple myeloma; WG: Waldenström's macroglobulinemia, MGUS; monoclonal gammopathy of undetermined significance; CG: cryoglobulinemia; ID: other inflammatory diseases. Kawai's equation (KE).

removal of paraproteins from plasma. The absence of statistic significance in MM and MGUS group was due respectively to the high variance and to the small dimension of the sample. These observations confirm that hyperviscosity in paraproteinemias is due not only to the concentrations of paraproteins [5], but also to their abnormal shape, abnormal polymerisation, and/or interaction with other plasmaproteins. On the contrary, the increase of PV in ID is due to an excess of normal plasma proteins (mainly alfa-globulins and/or polyclonal immunoglobulins) and only their concentration influences PV.

CONCLUSIONS

TPE is a useful technique able to rapidly correct HS and mainly decrease PV about 20-30% each session. Probably, the existing empirical approach to planning TPE-treatment in hyper-PV causes a little overdose of this therapy. Only one TPE-session is required to normalize PV when it is < 2.2 mPas, whereas a maximum of 2-3 session are required when it is > 2.2 till up to 6 mPas. In general, a fourth session is useless especially if the inter-session period is < 10-15 days.

We can roughly calculate the decrease of PV obtainable by each TPE-session and the number of session required to normalize PV, knowing basal-PV and the disease of a patient. The polynomial equation suggested is: $=(0.0499\ PV\ Pre^2)+(0.403\ PV\ Pre)-0.395$. However it is possible to use more disease's specific coefficients.

KE is not clinically reliable to evaluate PV in paraproteinemias because paraproteins can influence PV by means of interaction mechanisms and independently by their concentrations.

Actually we are performing studies on larger populations, this effort will permit to develop a simply software for automatic planning of TPE-treatment in HS.

Moreover, we need studies able to clarify when the correction of hyper-PV is indicated. Acute HS is of very rare occurrence, therefore light or mild chronic asymptomatic hyper-PV is of very frequent observation in patients with paraproteins, inflammation disorders, hyper-fibrinogenemia, hyper-lipoproteinemia, metabolic syndrome and so on. The rule of chronic hyperviscosity in stimulating endothelial responses is probably underestimated and we cannot exclude the existence of a chronic HS (CHS) able to impair microcirculation and promote progression of target organ-damage. Probably, TPE will not be the treatment of choice for CHS: it will be a new venture.

Submitted on invitation.
Accepted on 3 April 2007.

References

1. McCullogh J. Therapeutic apheresis In: McCullogh J. (Ed.) *Transfusion Medicine*. Philadelphia: Elsevier Churchill Livingstone, 2005; p. 517-47.
2. McCarthy L. Therapeutic apheresis: current prospectives. *Ther Apher* 2002;6:1.
3. Smith JV. Therapeutic apheresis in the United States: current indications and directions. *Ther Apher* 1999;3:1-3.
4. Teruya J. Practical isuues in therapeutic apheresis. *Ther Apher* 2002;6(4):288-9.
5. Metha J, Singhal S. Hyperviscosity syndrome in plasma cell dyscrasias. *Semin Thromb Hemost* 2003;29:467-71.
6. Rampling MW. Hyperviscosity as a complication in a variety of disorders. *Semin Thromb Hemost* 2003;29:459-65.
7. Zarkovic M, Kwaan HC. Correction of hyperviscosity by apheresis. *Sem Thromb Hemost* 2003;29:535-42.
8. International Committee for Standardization in Hematology. Guidelines for measurement of blood viscosity and erythrocyte deformability. *Clin Hemorheol* 1996;8:83-8.
9. H Kawai. Proceedings, *4th Congress on rheology*, New York, 1965.
10. Remuzzi A, Brenner BM, Pata V, Tebaldi G, Mariano R, Belloro A, Remuzzi G. Three-dimensional reconstructed glomerular capillary network: blood flow distribution and local filtration. *Am J Physiol* 1992;263(3 Pt 2):562-72.
11. Baskurt OK, Meiselman HJ. Blood rheology and hemodynamics. *Sem Thromb Hemost* 2003;29:435-50.
12. Lehoux S, Castier Y, Tedgui A. Molecular mechanisms of the vascular responses to haemodinamics forces. *J Int Med* 2006;259:381-92.