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# La rhéophérèse réalisée chez les patients hémodialysés chroniques cible l'endothélium et exerce un effet anti-inflammatoire

Justine Solignac

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**La rhéophérèse réalisée chez les patients hémodialysés chroniques cible  
l'endothélium et exerce un effet anti-inflammatoire**

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**LA FACULTÉ DES SCIENCES MEDICALES ET PARAMEDICALES  
DE MARSEILLE**

**Le 28 Mai 2021**

**Par Madame Justine SOLIGNAC**

**Née le 31 mars 1991 à Paris 19eme (75)**

**Pour obtenir le grade de Docteur en Médecine**

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 GRIMAUD Jean-Charles (PU-PH)  
 LAUGIER René (PU-PH)  
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 LECHEVALLIER Eric (PU-PH)  
 ROSSI Dominique (PU-PH)  
 SERMENT Gérard (PU-PH) *sumombre*



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## ABSTRACT

**Background:** Rheopheresis is a double filtration plasmapheresis which removes a defined spectrum of high molecular weight proteins to lower plasma viscosity and improve microcirculation disorders. It can be performed in hemodialysis (HD) patients with severe micro-ischemia. Interestingly, some studies have shown that rheopheresis sessions improve endothelial function.

**Methods:** Our study evaluated the inflammatory and endothelial biomarker evolution (circulating endothelial adhesion molecules, cytokines, angiogenic factor, and circulating endothelial cells [CECs]) in 23 HD patients treated with or without rheopheresis. A p value  $\leq$  0.001 was considered statistically significant.

**Results:** We analyzed 13 HD patients treated by rheopheresis either for a severe peripheral arterial disease (N=8) or calciphylaxis (N=5). We also included 10 control HD patients to rule out any rheopheresis effects from the HD circuit. Circulating endothelial adhesion molecules, cytokines, angiogenic factor concentrations and CEC levels were not modified in the no rheopheresis HD group. In the HD with rheopheresis group, the circulating endothelial adhesion molecules sVCAM-1, sP-selectin and sE-selectin, but not sICAM-1, were significantly reduced. For pro-inflammatory cytokines, TNF- $\alpha$  was significantly reduced by 32.6% [(-42.2)–(-22.5)] (p<0.0001), while the anti-inflammatory cytokine IL-10 increased by 674% [306–1299] (p<0.0001). Among angiogenic factors, only sEndoglin was significantly reduced. CEC level increased from 13 [3–33] to 43 [8–140]cells/mL (p=0.002). We observed no difference in pre-session values of the molecules of interest between the first and last rheopheresis sessions.

**Conclusions:** This is the first study to demonstrate that rheopheresis immediately modified inflammation balance and endothelial injury biomarkers. Further studies are needed to understand the mechanism underlying these biological observations.

**Keywords:**

Rheopheresis, double filtration plasmapheresis, vascular endothelium, cytokines, cell adhesion molecules.



# GRAPHICAL ABSTRACT

## RHEOPHERESIS BIOLOGICAL EFFECTS : Assay of inflammatory and endothelial markers

Extracorporeal circulation effects ? Rheopheresis in tandem with hemodialysis



Hemodialysis patients not treated by rheopheresis (N=10)

Pre and post dialysis session



No effect of dialysis sessions

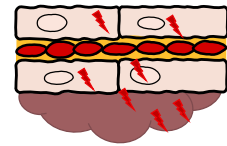


- Chronic critical limb ischemia (N= 8)
- Calciphylaxis (N=5)

Pre and post rheopheresis session



ANTI-INFLAMMATORY SIGNAL



Plasmatic viscosity

PRO-ANGIOGENIC SIGNAL ?

- ↓ Fibrinogen
- ↓ CRP
- ↓ TNF- $\alpha$
- ↓ VCAM-1
- ↓ sE-Selectin
- ↓ sP-Selectin



↑↑ IL-10

ACUTE EFFECT

↑↑ CEC

↑ sEndoglin

## THE RHEOPHERESIS TARGETS ENDOTHELIUM AND HAS ACUTE ANTI-INFLAMMATORY EFFECT

## INTRODUCTION

Rheopheresis is an apheresis treatment which removes 30 to 60% of the value of a defined spectrum of high molecular weight proteins (such as LDL-cholesterol, fibrinogen,  $\alpha_2$ -macroglobulin, immunoglobulin M [IgM], von Willebrand factor [vWF], and fibronectin) from human plasma, lowering blood plasma viscosity as well as reducing erythrocyte and thrombocyte aggregation [1, 2]. Rheopheresis is a double filtration plasmapheresis, using membrane technology configured in a differential filtration array with two single-use membrane filters. By reducing crucial determinants of plasma viscosity [3], this technique aims to improve microcirculation disorders.

Microcirculation operates at the interfaces between blood cells, plasma, and the endothelial cells from the vascular wall. The quality of the exchanges between these components is essential for the proper oxygenation of tissues. Plasma viscosity and its determinants are major factors in capillary blood flow [3], as are shear stress signaling and endothelial cell activation status [4]. Modulating plasma viscosity therefore appears to be a relevant therapeutic target.

End stage renal disease patients display both severe macrovascular and microvascular diseases, resulting in high cardiovascular morbi-mortality, not entirely explained by the traditional cardiovascular risk factors [5, 6]. One way of understanding this is through the accumulation of uremic toxins, especially indolic uremic toxins, which are factors of microvascular aggression, and which impair the ability to repair injury [7–11]. These compounds are usually excreted by the kidney but indolic uremic toxins in particular are protein-bound so are poorly removed by dialysis. However, hemodialysis (HD) patients are characterized by a chronic inflammatory and pro-thrombotic state, reflected by increased levels of TNF- $\alpha$ , IL-6, IL-1 $\beta$  [12], sCD40L [13], vWF [14], fibrinogen [15], PAI-1 [16], tissue factor [17], and Factors VII and VIII [18]. Moreover, HD patients have an increased level of circulating adhesion molecules ICAM-1, VCAM-1, E-selectin and P-selectin [19, 20]. All these biological alterations can be related to endothelial dysfunction, described as a switch from a protective endothelial phenotype to a chronic pro-coagulant, pro-adhesive and pro-inflammatory phenotype.

Rheopheresis effectiveness on microcirculation disorders has been demonstrated in a few clinical trials. According to the 2019 American Society for Apheresis (AFSA) guidelines, rheopheresis is a first-line treatment for dry age-related macular degeneration and sudden hearing loss [21]. Randomized controlled trials have indeed shown the clinical efficiency of rheopheresis treatment in these indications [22, 23]. Smaller clinical series evaluating rheopheresis in chronic limb threatening ischemia resulting from peripheral arterial disease (PAD-CLTI) and calciphylaxis have shown promising results [24–27]. Our team is currently conducting a randomized controlled trial on PAD-CLTI in HD patients (RHEOPAD; Clinical trial number:03975946).

Interestingly, some studies showed that rheopheresis sessions led to an acute improvement of endothelial function. Control of vascular tone was indeed enhanced after rheopheresis treatment, assessed by flow-mediated vasodilation and skin vasodilator response to acetylcholine iontophoresis and to ischemia [28, 29]. However, no studies have evaluated the biological effects of rheopheresis on endothelium dysfunction markers, including inflammation mediators. Our study assesses the evolution of inflammation and endothelial lesion / regeneration markers in 23 HD patients treated with or without rheopheresis.

## MATERIAL AND METHODS

### Population

13 HD patients treated by rheopheresis (HD with rheopheresis group) in the dialysis center of the Hospital of La Conception (Marseille, France) were consecutively included between 01/02/2018 and 01/09/2019. The indication for rheopheresis therapy was either PAD-CLTI or calciphylaxis. 10 HD patients not treated by rheopheresis (HD without rheopheresis group) with peripheral artery disease history and micro-inflammatory status, defined as C-reactive protein (CRP) > 5 ng/mL without infection, were also included as a control group. All patients received at least three weekly dialysis sessions. The data included in this study was anonymized, approved and registered at the Health Data Portal of Assistance Publique – Hôpitaux de Marseille. All patients included were informed and consent was obtained.

### Rheopheresis treatment

Rheopheresis technology was performed using Plasauto  $\Sigma$  supplied by Hema.T Medical (Ramonville-Saint-Agne, France), and manufactured by Asahi Medical Co, Ltd (Tokyo, Japan). The rheopheresis extracorporeal circuits has two filters, one after the other, a first plasma-separator (Plasmaflo OP-05W[L]) which separates the plasma from blood cells, and a second rheofilter (Rheofilter ER-4000), which separates high molecular weight plasma proteins from the plasma, with a theoretical threshold of 200 KiloDalton (KDa). The rheopheresis and dialysis circuits were connected together, so that treatment was performed during the first hours of the dialysis session, usually over 1 hour (**Figure 1**). The patients received a two-phase treatment regimen of rheopheresis, a first phase with two weekly sessions followed by a second phase with one weekly session for at least 8 weeks. Thereafter, treatment was continued once a week if the lesions were not healed. The plasma volume target was 40 mL/kg during the first phase, and 60 mL/kg during the second phase.

## Blood assays

We performed blood assays immediately before (pre) and after (post) the following rheopheresis sessions: first, mid-protocol and last sessions. Anticoagulation of the circuit was performed with citrate. As control, we performed the same blood assays immediately before (pre) and after (post) HD sessions without rheopheresis. In this case, anticoagulation of the circuit was performed with heparin.

Assays of circulating endothelial adhesion molecules (sVCAM-1, sICAM-1, sE-Selectin, sP-Selectin), cytokines (TNF- $\alpha$ , sCD40-L, IL-1 $\beta$ , IL-6, IL-8, IL-10), and angiogenic factors (angiopoietin 2, sEndoglin, VEGF-A) were performed by the Multiplex immunoassays: Adhesion Mag LxPA 4-plex Kit from Bio-Techne, Milliplex Catalog ID.HCYTOMAG-COK-09.Human Cytokine and Catalog IO.1-IAGP1MAG-12K-04.Hu Angiogenesis/GF MAG 1 kits from Merck Millipore, respectively.

Circulating endothelial cells (CECs) were counted according to a previously published standardized protocol [30]. Briefly, the first 2 mL of drawn blood was discarded to avoid contamination by mural endothelial cells dislodged by venipuncture. CECs were isolated by immunomagnetic separation with magnetic beads (Dynabeads M-450, Thermo Fisher, Carlsbad, CA) coated with CD146 (clone S-endo1, Biocytex, Marseille, France) and enumerated by fluorescence microscopy after acridine orange labeling at 490 nm. The stability of the microscope (Nikon Eclipse TE2000-S, Nikon, Tokyo, Japan) was regularly monitored with an Argo-Check Intensity LSG 130 (Argolight, Pessac, France). CECs were counted by an operator blinded to the patients' clinical features and were identified according to the following consensus criteria: rosette cell staining with acridine orange, size over 15  $\mu$ m, bearing more than five beads.

Upper values of the reference interval provided by the laboratory based on a healthy donor were: 300 ng/mL for sICAM-1; 2500 ng/mL for sVCAM-1; 50 ng/mL for sE-Selectin; 44 ng/mL for sP-Selectin; 140 pg/mL for sCD40L; 12 pg/mL for TNF- $\alpha$ ; 3 pg/mL for IL-1 $\beta$ ; 3.5 pg/mL for IL-6; 11 pg/mL for IL-8; 13 pg/mL for IL-10; 4.3 pg/mL for angiopoietin 2; 7100 pg/mL for sEndoglin; 115 pg/mL for VEGF-A, and 20 cells /mL for CECs.

The measurement of the biological parameters after the apheresis and the dialysis sessions was corrected according to the modification of the plasma hemoconcentration. We used the Von Beaumont equation based on hematocrit measurement before (H1) and after (H2) the

sessions to correct the values of the biological parameters by a factor (FC) to take into account

the plasma volume reduction [31]:  $FC = \frac{H1(1-H2)}{H2(1-H1)}$

We calculated the molecule concentration percentage change in patient blood measured immediately before (pre value) and after (post value) rheopheresis therapy as follows:

$$\frac{\text{pre value} - \text{post value}}{\text{pre value}} .$$

### Statistical analysis

Continuous variables were expressed as medians [interquartile range]. Categorical variables were presented as number (%). Values have been rounded up to the tenth. We used a Student paired t-test when values were > 30 and Wilcoxon paired test when values were < 30 for comparative analyses. A p value ≤ 0.001 was considered statistically significant.

## RESULTS

### Study population

Baseline clinical and biological features of the HD with rheopheresis group and the HD without rheopheresis group are summarized in **Tables 1 and 2**. 13 HD patients treated by rheopheresis were included, 8 for PAD-CLTI and 5 for calciphylaxis. HD patients treated by rheopheresis had diabetes (n=8;62%), hypertension (n=13;100%), coronary artery disease (n=7;54%), and peripheral artery disease (n=9;69%). They experienced a pronounced inflammatory syndrome with median fibrinogen concentration of 5.9 g/L [5.2 – 6.5] and CRP of 33.8 mg/L [14.0 – 47.5]. The median CEC level at inclusion was high, at 16 cells/mL [2 – 34]. 10 HD patients not treated by rheopheresis were included. Most had diabetes (n=8;80%), hypertension (n=8;80%), coronary disease (n=6;60%) and peripheral artery disease (n=9;90%). They displayed an inflammatory syndrome with a median concentration CRP of 7.9 mg/L [6.3 – 12.3]. Compared to the HD with rheopheresis group, HD patients not treated by rheopheresis had higher TNF- $\alpha$  concentration at inclusion (p=0.0008).

### Acute effect of hemodialysis sessions on inflammatory and endothelial markers

In the HD without rheopheresis group, the circulating endothelial adhesion molecules, cytokines, angiogenic factors concentrations and CECs levels were not modified (**Table 3**) post-HD, except for sCD40L which trended to increase significantly from 81.9 pg/mL [27.8 – 179] pre-HD to 669pg/mL [195 – 881] post-HD (p=0.002).

### Acute effect of rheopheresis sessions

In all patients in the HD with rheopheresis group, there was a reduction of the high molecular weight protein. The median percentage reduction in fibrinogen was 53.4% [(-59.2) – (-45.4)], total cholesterol 48.1% [(-55.4) – (-40.3)], triglycerides 34.7% [(-43.4) – (-16.6)], LDLc 68.3% [(-75.8) – (-59.8)], IgM 54.1% [(-59.3) – (-46.1)], and  $\alpha$ 2-macroglobulin 51.2% [(-62.9) – (-43.5)]. CRP was also reduced by 39.5% [(-48.1) – (-34.2)] (p=0.01) (**Table 4**).

Circulating endothelial adhesion molecules (sVCAM-1, sP-selectin and sE-selectin) showed a significant reduction except sICAM-1 (**Figure 2A** and **Table 4**). Of the pro-inflammatory cytokines, TNF- $\alpha$  was significantly reduced by 32.6% [(-42.2) – (-22.5)] ( $p < 0.0001$ ), while the anti-inflammatory cytokine IL-10 increased by 674% [306 – 1299] ( $p < 0.0001$ , **Figure 2B** and **Table 4**). Among angiogenic factors, only sEndoglin demonstrated a significant reduction of -31.5% [(-43.1) – (-17.2)] ( $p < 0.0001$ , **Figure 2C** and **Table 4**). There was a trend for CECs levels to increase from 13 [3 – 33] cells/mL to 43 [8 – 140] cells/mL ( $p = 0.002$ , **Figure 2D** and **Table 4**).

#### Long-term effect of rheopheresis sessions

After a median 18 [12– 30] rheopheresis sessions, pre-rheopheresis only fibrinogen concentrations were significantly reduced, from a median 5.9 g/L [5.2 – 6.5] to 3.7 g/L [2.7 – 4.6] ( $p = 0.0007$ , **Table 5**). IL-10 reduced from 9.6 pg/mL [5.1–13.1] to 3.4 pg/mL [1.4 – 8.2] ( $p = 0.01$ , **Table 5**). We observed no difference in the values of the other molecules of interest and the CECs between the first and last sessions.



## DISCUSSION

This is the first study to demonstrate that a rheopheresis session modifies the inflammation balance. Rheopheresis treatment lowered plasma viscosity, a major determinant of capillary blood flow, especially when vasomotor functions are impaired [1]. The rheopheresis effect on rheological parameters has been explored [1, 2]; nevertheless, previous studies did not assess the effects on cytokines and endothelial biomarkers. We chose a stringent alpha risk at 0.001 to limit the statistical bias induced by the exploratory nature of our study [32, 33]. We observed a clear immediate anti-inflammatory-induced rheopheresis process highlighted by the decrease of fibrinogen, CRP, TNF- $\alpha$ , and the increase of IL-10 at a median more than 6-fold the baseline value. The spectrum of inflammation and endothelial markers with statistically significant changes by rheopheresis sessions is summarized in **Figure 3**. We also observed that pre-rheopheresis fibrinogen is reduced as a long-term effect, which may reflect an improvement in the micro-inflammatory and pro-thrombotic state of our patients.

The effect of rheopheresis sessions is not explained by the HD procedure. HD sessions had no effect on circulating endothelial adhesion molecules, cytokines, angiogenic factors, and CECs. This result is consistent with some studies in the literature [19, 34–36]. There was a trend for levels of sCD40L to increase after dialysis sessions but this needs to be confirmed in a larger sample size. Platelet activation by extracorporeal circuit may explain the increase of sCD40L which is a key factor in thrombi stabilization and is produced almost entirely by activated platelets [37, 38].

The mechanism by which rheopheresis produces such a rapid pulse lowering effect has yet to be clarified. The rapid post-rheopheresis increase of IL-10, which obviously cannot be removed by the rheofilter, indicates an immediate modulation of the immune system. The modification of inflammatory markers can occur through immediate mechanisms such as shedding of soluble forms or release from vesicular stock, independently of gene expression. One hypothesis may be that the removal of LDL, and especially oxidized LDL, induces the anti-inflammatory signal. Interestingly, statin therapy exerts anti-inflammatory effects on the innate and adaptive immune response [39, 40]. Similarly, some studies evaluating LDL

apheresis performed in patients with familial hypercholesterolemia, have shown a decrease of TNF- $\alpha$  and soluble cell adhesion molecules, and an increase of IL-10 [41–44].

It is well established that cytokines and circulating endothelial adhesion molecules represent a complex network interconnected with endothelial cell function [45]. These molecules are highly interrelated, as suggested by the correlations in clinical studies [20, 46, 47]. Endothelial cells express cytokine receptors of TNF- $\alpha$ , IL-1, IL-6 and IL-8, and are able to self-produce cytokines [48]. Several studies showed that TNF- $\alpha$  and IL-1 $\beta$  induce endothelial cell expression of VCAM-1, ICAM-1, E-selectin and P-selectin which are shed in circulation in a soluble form. In turn, circulating endothelial adhesion molecules, thought to have chemo-attractant and angiogenic effects [49], but whose biological role has not been fully elucidated, stimulate the secretion of various cytokines in different cell types and perpetuate a chronic pro-inflammatory state [50, 51].

Cytokines and circulating endothelial adhesion molecules reflect a state of endothelial cell activation, involving a switch from a quiescent to a pro-inflammatory phenotype, and resulting in endothelial dysfunction [37, 52]. These circulating molecules are considered biomarkers for endothelial injury and vascular disease prognosis, including in HD patients [13, 47, 53, 54]. Rheopheresis thus targets the endothelium and might therefore have a beneficial effect on endothelial cell stress.

We observed that post-rheopheresis CECs levels increased in our patients, reflecting an active endothelial phenomenon. Rheopheresis treatment could induce reperfusion of the occluded capillary bed releasing detached dead endothelial cells into circulation. It is well-known that CEC levels are associated with cardiovascular disease severity and endothelial dysfunction [55, 56] and are predictive of serious cardiovascular events, including in HD patients [57]. In our cohort with active vascular disease, pre-rheopheresis CEC levels remained stable, but the significance of this is unexplained.

Our study presents some limitations. First, the outcomes are purely biological and their consequences for patients are unknown. The data should be correlated to clinical endpoints. Second, it is a small cohort, and the results should be confirmed in a larger population, with assays performed in patients who are their own controls in order to obtain a strictly comparable population. These answers will be provided by the ongoing national project conducted by our team (RHEOPAD; Clinical trial number: 03975946). Third, interactions between the different mediators measured in the blood and the control of their production

are complex. There is a myriad of mediators not measured in this study, or not yet discovered. Moreover, the values are measured at a specific timepoint, at the end of the session, with no data on what occurs in the hours following the sessions. An apparently acute anti-inflammatory effect should therefore be viewed cautiously.

To conclude, besides its purifying and its rheological aspects, rheopheresis therapy can now demonstrate an immunological effect. Further studies are required to understand the mechanism underlying these biological observations.

## TABLES AND FIGURES

**Table 1: Main clinical and biological characteristics**

	<b>HD with rheopheresis group (N=13)</b>	<b>HD without rheopheresis group (N=10)</b>
Age (years old)	<b>68 [59 – 71]</b>	<b>78.5 [73.5 – 80.5]</b>
Male gender	<b>8 (62%)</b>	<b>8 (80%)</b>
HD Vintage (Months)	<b>33 [18 – 39]</b>	<b>20 [16 – 35]</b>
BMI (kg/m <sup>2</sup> )	<b>26.0 [23.2 – 29.5]</b>	<b>30.1 [27 – 71]</b>
Diabetes	<b>8 (62%)</b>	<b>8 (80%)</b>
Hypertension	<b>13 (100%)</b>	<b>8 (80%)</b>
Dyslipidemia	<b>11 (85%)</b>	<b>6 (60%)</b>
Smoking history	<b>7 (54%)</b>	<b>7 (60%)</b>
Coronary disease	<b>7 (54%)</b>	<b>6 (60%)</b>
Ejection fraction (%)	<b>65 [53.7 – 65]</b>	<b>50[50 – 62.5]</b>
Peripheral occlusive arterial disease	<b>9 (69%)</b>	<b>9 (90%)</b>
Stroke history	<b>0</b>	<b>1 (10%)</b>
FAV	<b>9 (69%)</b>	<b>6 (60%)</b>
Indication of rheopheresis:		
PAD-CLTI	<b>8</b>	<b>-</b>
Calciphylaxis	<b>5</b>	<b>-</b>
Number of sessions	<b>18 [12 – 30]</b>	<b>-</b>
Albumin (g/L)	<b>31.9 [28.4 – 35.2]</b>	<b>35.8 [33.2 – 39.5]</b>

*Quantitative variables are expressed as median [quartile 1 – quartile 3].*

Table 2: Pre-session levels of endothelial adhesion molecules, cytokines, angiogenic factors and CECs at inclusion

	HD with rheopheresis group (N=13)	HD without rheopheresis group (N=10)	P value
Fibrinogen (g/L)	5.9 [5.2 – 6.5]	4.4 [4.3 – 5.6]	0.11
PCR (mg/L)	36.0 [12.0 – 49.0]	7.9 [6.3 – 12.3]	0.01
sICAM-1 (ng/mL)	243 [54.0 – 189]	220 [144 – 397]	0.1
sVCAM-1 (ng/mL)	1735 [1324 – 2150]	1146 [862 – 1442]	0.04
sE-Selectin (ng/mL)	25.0 [19.0 – 35.5]	34.0 [31.0 – 49.7]	0.36
sP-Selectin (ng/mL)	45.0 [27.5 – 53.0]	42.0 [40.0 – 46.7]	0.68
sCD40L (pg/mL)	46.3 [33.9 – 81.1]	82.0 [31.0 – 115]	0.68
IL-1 $\beta$ (pg/ml)	1.0 [1.0 – 1.5]	1.0 [1.0 – 4.6]	0.4
IL-6 (pg/ml)	6.2 [1.0 – 17.3]	1.0 [1.0 – 1.0]	0.01
IL-8 (pg/ml)	11.9 [8.7– 17.7]	9.0 [6.0 – 15.5]	0.23
TNF- $\alpha$ (pg/mL)	37.8 [29.0 – 45.1]	58.0 [50.0 – 62.0]	0.0008
IL-10 (pg/ml)	9.6 [5.1 – 13.1]	2.0 [1.0 – 7.5]	0.01
Angiopoietin 2 (ng/mL)	4.1 [3.0 – 6.9]	3.0 [3.0 – 3.9]	0.18
sEndoglin (pg/mL)	662 [574 – 971]	1347 [912 – 1455]	0.01
VEGF-A (pg/mL)	42.0 [25.0 – 56.0]	62.0 [25.0 – 104]	0.52
CEC (n/mL)	16 [2 – 34]	1 [1 – 4]	0.02

Quantitative variables are expressed as median [quartile 1 – quartile 3].

The Mann-Whitney test was used for statistical analysis.  $p < 0.001$  was considered statistically significant.

Table 3: Circulating adhesion molecules, cytokines, angiogenic factors and CECs before and after dialysis sessions

Variables are expressed as median [Quartile 1 – Quartile 3].

	Pre-dialysis (N=10)	Post-dialysis (N=10)	P value
ICAM-1 (ng/mL)	222 [146 – 347]	193 [130 – 317]	0.04
VCAM-1 (ng/mL)	1146 [801 – 1556]	1120 [701 – 1629]	0.49
E-Selectin (ng/mL)	30.3 [26.6 – 45.6]	30.7 [24.5 – 45.4]	0.62
P-Selectin (ng/mL)	41.8 [39.8 – 48.7]	48.0 [46.3 – 64.2]	0.004
sCD40L (pg/mL)	81.9 [27.8 – 179]	669 [195 – 881]	0.002
IL-1 $\beta$ (pg/mL)	1.6 [1.0 – 4.6]	8.7 [0.9 – 11.6]	0.027
IL-6 (pg/mL)	1.0 [1.0 – 1.0]	0.9 [0.8 – 1.5]	0.57
IL-8 (pg/mL)	9.3 [5.0 – 17.4]	6.9 [4.2 – 16.6]	0.08
TNF- $\alpha$ (pg/mL)	57.8 [49.2 – 67.3]	38.8 [31.3 – 49.8]	0.009
IL-10 (pg/ml)	2.2 [1.0 – 7.5]	7.0 [1.7 – 9.8]	0.19
Angiopoietin (ng/mL)	3.0 [3.0 – 4.0]	2.68 [2.4 – 3.2]	0.04
sEndoglin (pg/mL)	1347 [873 – 1474]	1061 [766 – 1536]	0.19
VEGF-A (pg/mL)	59.8 [25.0 – 113]	114 [24.0 – 250]	0.43
CEC (n/mL)	1 [1.0 – 4.0]	1 [1.0 – 2.0]	0.13

Values after dialysis sessions were corrected according to the hemoconcentration using the Van Beaumont equation. Wilcoxon test was used for statistical analysis.  $P < 0.001$  was considered statistically significant.

Table 4: Inflammatory parameters, circulating adhesion molecules, cytokines, angiogenic factors and CECs before and after rheopheresis sessions

	Pre-rheopheresis (N=37)	Post-rheopheresis (N=37)	Percentage change (%)	P value
Fibrinogen (g/L)	4.72 [3.0 – 6.0]	1.9[1.4 – 2.7]	-53.4 [(-59.2) – (-45.4)]	<0.0001
CRP (mg/L)	15.3[5.2 – 36.9]	9.0 [2.8 –21.5]	-39.5 [(-48.1) – (-34.2)]	0.001
ICAM-1 (ng/mL)	148 [116 – 182]	132 [102 – 175]	- 10 [(-20.7) – (-3.1)]	0.02
VCAM-1 (ng/mL)	1856 [1257 – 2707]	1330 [908 – 1654]	-34.7 [(-45.0) – (-23.2)]	<0.0001
E-Selectin (ng/mL)	21.0 [15.5 – 30.5]	12.3 [7.3 – 20.3]	-38.6 [(-54.8) – (-31.8)]	<0.0001
P-Selectin (ng/mL)	44.0 [26.5 – 53.0]	21.8 [16.1 – 33.8]	-38.3 [(-48.1) – (-29.1)]	<0.0001
sCD40L (pg/mL)	44.9 [31.3 – 64.3]	61.6 [34.3 – 96.1]	38.0 [7.7 – 104]	0.06
IL-1 $\beta$ (pg/mL)	1.0 [1.0 – 1.0]	0.9 [0.9 – 1.07]	-9.1 [(-22.1) – 0]	0.04
IL-6 (pg/mL)	1.0 [1.0 – 11.3]	2.6 [0.9 – 13.5]	0 [(-12.4) – 37.7]	0.93
IL-8 (pg/mL)	10.4 [7.7– 15.6]	9.6 [7.1 – 15.1]	-19.4 [(-32.1) – (-6.0)]	0.99
TNF- $\alpha$ (pg/mL)	39.1 [30.1 – 47.0]	25.7 [22.2 – 30.4]	-32.6 [(-42.2) – (-22.5)]	<0.0001
IL-10 (pg/mL)	5.6 [2.1 – 10.9]	60.9 [31.3 – 64.3]	674 [306 – 1299]	<0.0001
Angiopoietin2 (ng/mL)	3.5 [3.0 – 6.8]	3.3 [2.8 – 6.3]	-9.2 [(-14.8) – (-1.6)]	0.37
sEndoglin (pg/mL)	694 [353 – 1018]	474 [224 – 697]	-31.5 [(-43.1) – (-17.2)]	<0.0001
VEGF-A (pg/mL)	25.0 [25.0 – 56.0]	26.1 [23.7 – 46.0]	0 [(-29.0) – 0]	0.6
CEC (n/mL)	13[3 – 33]	43 [8 – 140]	317 [14.6 – 574]	0.002

Variables are expressed as median [Quartile 1 – Quartile 3].

Values after rheopheresis sessions were corrected according to the hemoconcentration using the Van Beaumont equation. Student t test was used for statistical analysis.  $P < 0.001$  was considered statistically significant.

Table 5: Inflammatory parameters, circulating adhesion molecules, cytokines, angiogenic factors and CECs before the first and the last rheopheresis sessions

	Pre-rheopheresis first session (N=13)	Pre-rheopheresis last session (N=13)	P value
Fibrinogen (g/L)	5.9 [5.2 – 6.5]	3.7 [2.7 – 4.6]	0.0007
CRP (mg/L)	36.0 [12.0 – 49.0]	11.5 [2.3 – 23.1]	0.12
ICAM-1 (ng/mL)	243 [54.0 – 189]	213 [54.0 – 159]	0.04
VCAM-1 (ng/mL)	1735 [1324 – 2150]	2485 [1172 – 3337]	0.05
E-Selectin (ng/mL)	25.0 [19.0 – 35.5]	18.0 [14.5 – 27.5]	0.009
P-Selectin (ng/mL)	45.0 [27.5 – 53.0]	44.0 [26.0 – 53.5]	0.69
sCD40L (pg/mL)	46.3 [33.9 – 81.1]	43.2 [29.9 – 75.2]	0.83
IL-1 $\beta$ (pg/mL)	1.0 [1.0 – 1.5]	1.0 [1.0 – 1.0]	0.99
IL-6 (pg/mL)	6.2 [1.0 – 17.3]	1.0 [1.0 – 5.4]	0.32
IL-8 (pg/mL)	11.9 [8.7– 17.7]	10.4 [6.2 – 14.4]	0.26
TNF- $\alpha$ (pg/mL)	37.8 [29.0 – 45.1]	40.4 [32.3 – 50.4]	0.73
IL-10 (pg/mL)	9.6 [5.1 – 13.1]	3.4 [1.4 – 8.2]	0.01
Angiopoietin2 (ng/mL)	4.1 [3.0 – 6.9]	3.0 [3.0 – 5.8]	0.71
sEndoglin (pg/mL)	662 [574 – 971]	740 [202.0 – 1117]	0.73
VEGF-A (pg/mL)	42.0 [25.0 – 56.0]	30.0 [25.0 – 53.5]	0.9
CEC (n/mL)	16 [2 – 34]	10 [2 – 27]	0.44

Variables are expressed as median [Quartile 1 – Quartile 3].

Wilcoxon test was used for statistical analysis.  $p < 0.001$  was considered statistically significant.



Figure 1: Diagram of the connection in tandem of the rheopheresis and dialysis extracorporeal circuit.

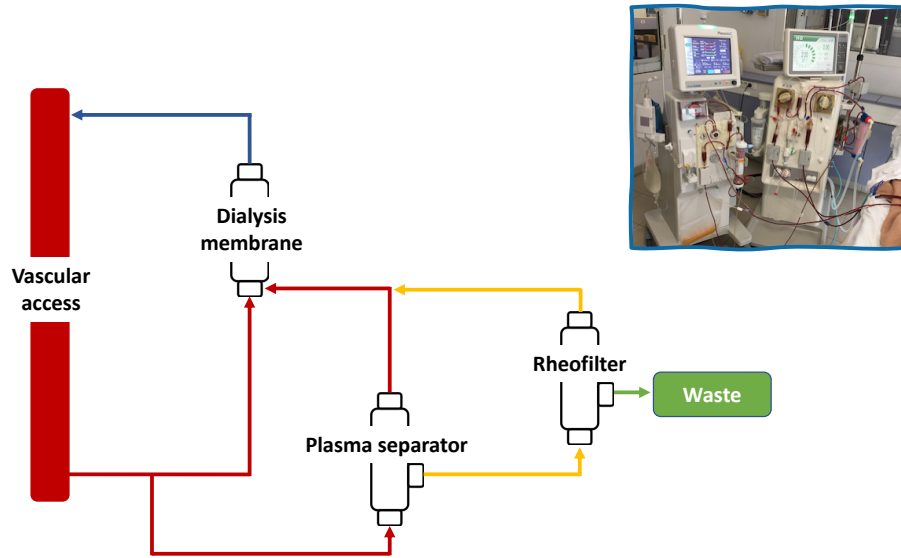
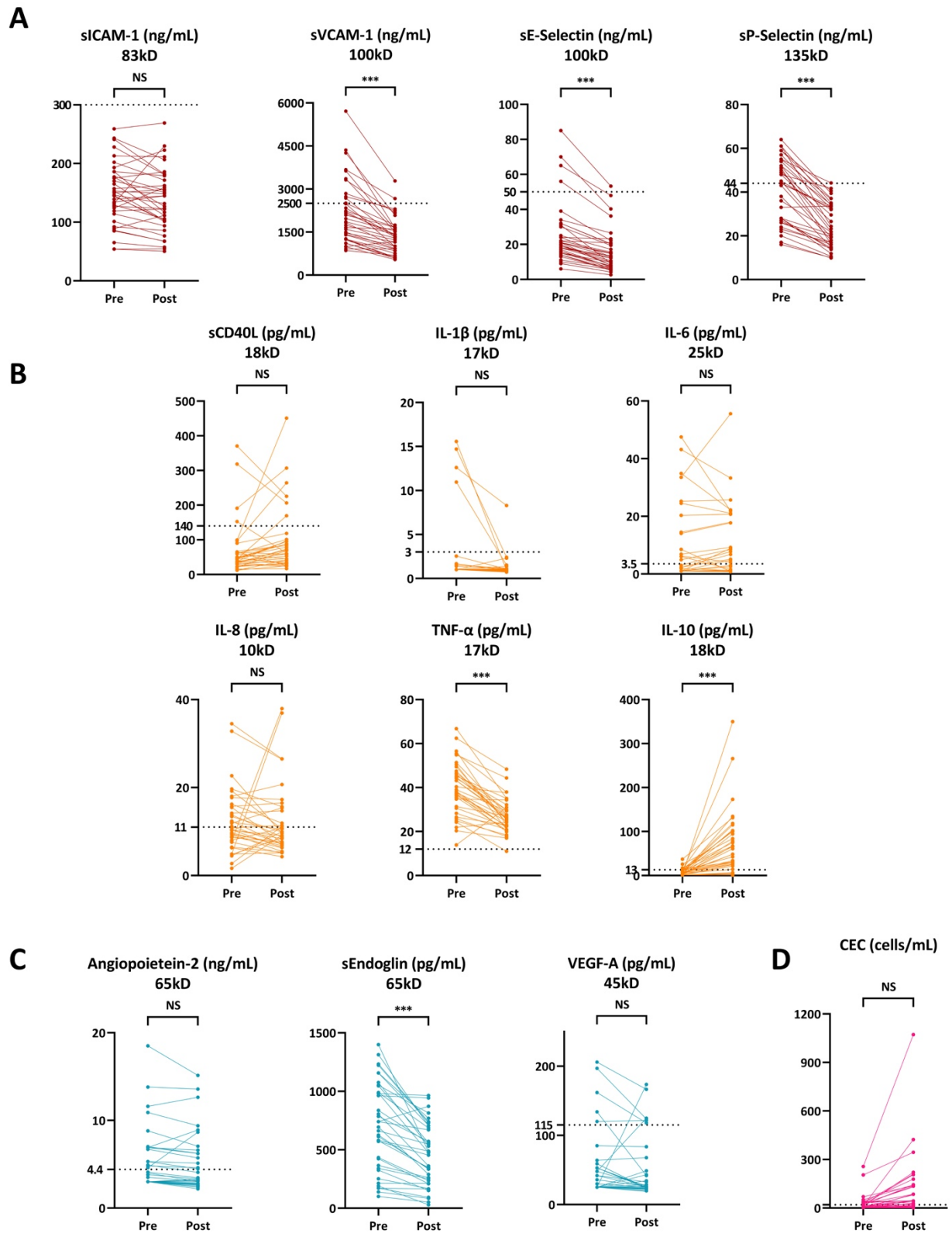
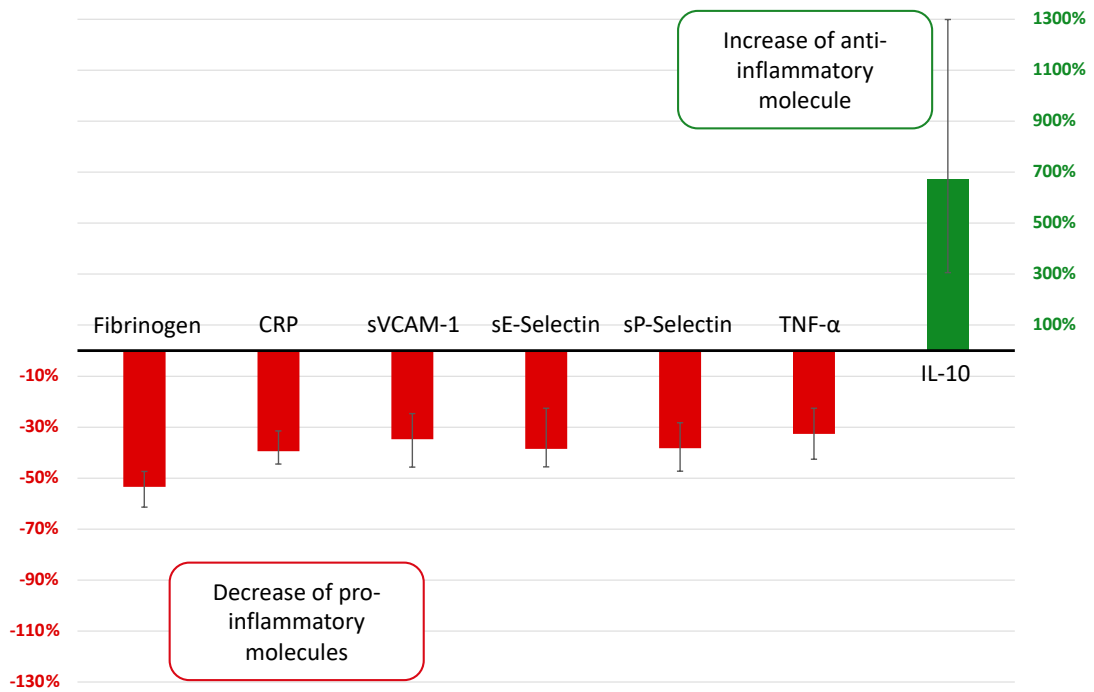


Figure 2: Circulating adhesion molecules (A), cytokines (B), angiogenic factors (C) and circulating endothelial cells before (pre) and after (post) rheopheresis sessions.



The dashed line represents the upper standard. NS: Not statistically significant. \*\*\*:  $p < 0.001$ .

Figure 3: The spectrum of molecules with statistically significant changes after rheopheresis sessions.



*Changes are expressed by median percentage change with interquartile range. The two axes have different scales.*

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## **RÉSUMÉ**

**Introduction :** La rhéophérèse est une technique de plasmaphérèse de double filtration en cascade qui élimine les protéines de haut poids moléculaire afin de diminuer la viscosité du plasma. La rhéophérèse peut être réalisée chez les patients hémodialysés (HD) qui présentent une ischémie micro-circulatoire sévère, en même temps que leur séance de dialyse. Certaines études indiquent que les séances de rhéophérèse améliorent la fonction endothéliale quant aux capacités de réponse vasodilatatrice.

**Objectif :** Notre étude a évalué l'évolution des biomarqueurs inflammatoires et endothéliaux (molécules d'adhésion endothéliales circulantes, cytokines, facteurs angiogéniques et cellules endothéliales circulantes (CEC)) chez 23 patients HD traités ou non par rhéophérèse. Une valeur  $p \leq 0,001$  a été considérée comme statistiquement significative.

**Résultats :** 13 patients HD traités par rhéophérèse soit pour une artériopathie périphérique sévère (N=8), soit pour une calciphylaxie (N=5) ont été analysés. 10 patients HD ont également été inclus en témoin, afin de s'affranchir des effets du circuit de dialyse. Dans ce groupe HD sans rhéophérèse, nous n'avons pas observé de modification après les séances des dosages des molécules d'adhésion endothéliales circulantes, des cytokines, des facteurs angiogéniques et des CEC. Dans le groupe HD avec rhéophérèse, les molécules d'adhésion endothéliales circulantes (sVCAM-1, sP-selectine et sE-selectine) diminuaient significativement après les séances, à l'exception de sICAM-1. Parmi les cytokines pro-inflammatoires, le TNF- $\alpha$  diminuait significativement de 32,6 % [(-42,2) - (-22,5)] ( $p < 0,0001$ ), tandis que la cytokine anti-inflammatoire IL-10 augmentait de 674 % [306 - 1299] ( $p < 0,0001$ ). Parmi les facteurs angiogéniques, seule l'endogline diminuait significativement. Le niveau de CEC avait tendance à augmenter de 13 [3 - 33] cellules/mL à 43 [8 - 140] cellules/mL ( $p = 0,002$ ). Nous n'avons pas observé de différence dans les valeurs des molécules d'intérêt au branchement entre la première et la dernière session de rhéophérèse.

**Conclusion :** Il s'agit de la première étude qui montre que la rhéophérèse a un effet immédiat sur la balance inflammatoire et sur les biomarqueurs endothéliaux. D'autres études sont nécessaires pour comprendre le mécanisme qui sous-tend ces observations biologiques.

**Mots clefs :** Rhéophérèse, plasmaphérèse, dysfonction endothéliale, molécules d'adhésion endothéliale, cytokines, cellules endothéliales circulantes, effet anti-inflammatoire.