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Splanchnic erythrocyte content decreases during hemodialysis: A new compensatory mechanism for hypovolemia

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Splanchnic erythrocyte content decreases during hemodialysis: A new compensatory mechanism for hypovolemia. Splanchnic and splenic erythrocyte volumes decrease during postural changes and exercise to help maintain central blood volume and cardiac output. The contribution of this compensatory mechanism to hemodynamic stability during dialysis has not been studied, however. In 8 ESRD patients, age 51.0 ± 4.5 years old, we measured changes in the splanchnic/splenic erythrocyte volume during dialysis by tagging the patients' erythrocytes with technetium and following abdominal radioactivity over time. Splanchnic radioactivity decreased to 90.2 ± 3.8% (mean ± SEM) of the baseline value after 2 hr of accelerated fluid removal (3.7 ± 0.4 liters) during dialysis (DUF), while it remained relatively unchanged after two hours of dialysis without fluid removal (DD) [106.5 ± 2.3%, *P* (DUF vs. DD) = 0.03]. Splenic radioactivity decreased to 89.2 ± 5.0% of the initial value during DUF versus 103 ± 3.8% during DD, but the decrease was noted only during the last 30 minutes of DUF and did not attain statistical significance. Autonomic nervous system integrity was measured by the spontaneous variation of the R-R interval during deep respiration (E/I ratio) and by the Valsalva ratio. The mean E/I and Valsalva ratios in the eight patients were 1.13 ± 0.03 (± SEM) and 1.42 ± 0.1 respectively, suggesting reasonably adequate autonomic nervous system functioning. The results suggest that contraction of the splanchnic, and possibly the splenic, vascular beds occurs during fluid removal associated with hemodialysis. The resultant addition of erythrocytes to the circulation may help maintain central blood volume and cardiac output.

The hemodynamic causes of hypotension during dialysis are multifactorial. Compensatory responses to acute hypovolemia include mechanisms that decrease venous capacity, mechanisms that increase cardiac contractility and rate, and mechanisms that increase vascular resistance [1]. A substantial percentage of the total blood volume is located in the venous system, the capacity of which can change markedly [2]. Translocation of this blood volume centrally during hypovolemia can result in a relative increase in the rate of venous return [3].

The splanchnic/splenic vascular bed is composed of the circulation to the spleen, liver and intestines. It is well established that splanchnic/splenic capacity decreases during hypovolemia [4–6]. Splanchnic veins are extensively innervated with both alpha- and beta-adrenergic fibers. Reduction in splanchnic/splenic capacity during hypovolemia can be due either to reduced inflow or to active venoconstriction. Early reductions in splanchnic capacity may take place due simply to reduced inflow (De Jager-Krogh effect), whereas increases in plasma epinephrine levels during severe hypovolemia might act to further reduce splanchnic capacity [7, 8].

As there was no information about changes in splanchnic/splenic capacity during hemodialysis, we undertook a study to examine the changes in the splanchnic/splenic erythrocyte blood volume while fluid was being removed during dialysis as compared to when no fluid was removed during dialysis. We also studied the integrity of the autonomic nervous system in the patients that underwent splanchnic blood pool monitoring, as we anticipated that changes in splanchnic/splenic capacity might be impaired in patients with autonomic nervous system (ANS) dysfunction. However, patients selected for this study were not expected to have ANS dysfunction.

Methods

Dialysis study

Patients were selected from among those undergoing chronic hemodialysis at our medical center. Eight patients were studied. Informed consent was obtained and the protocol was approved by the Hines VAMC Human Investigations Subcommittee. All patients were male, with an average age of 51.0 ± 4.5 years. The patients selected for this study were specifically selected to be normal controls, that is, none were diabetic, and none were hypotension prone. The mean dry weight was 76.4 ± 19 kg. Almost all were using a blood flow rate of 350 ml/min, and all had an AV access. Anti-hypertensive medicines were being taken by 4 of the patients (3 CCBs, one ACE inhibitors). These medications were held the day of the study.

Each patient was studied twice. On one occasion, fluid removal was accelerated during the initial two hours of dialysis, and zero during the last two hours. On another occasion, diffusion dialysis was performed during the initial two hours, and with accelerated fluid removal during the last two hours. The order of these two treatments was randomized.

Blood was drawn before dialysis and the erythrocytes in the sample were tagged with technetium using sterile technique. The blood was then re-injected into the patient. After equilibration,

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with the patient supine on an examination table, baseline posterior and anterior images of the abdomen were obtained by gamma camera to assess the radioactivity of the area concerned. This was followed by extracorporeal circulation (no dialysate flow, no fluid removal, patient remaining supine) for 30 minutes. A second set of images was then obtained. Then, the patient, based on randomization assignment, received two hours of either dialytic ultrafiltration (dialysis with fluid removal) or diffusion dialysis (dialysis without fluid removal), both given with the patient on the examining table in the supine position. When fluid was removed, the total amount of required fluid removal (initial weight less "dry weight") was performed during the initial two hour period. Posterior and anterior images were obtained every 30 minutes during the two-hour study period. Blood samples were also taken every 30 minutes for hematocrit and measurement of blood radioactivity. At the end of the two-hour study period, an additional two hours of dialysis was performed. When no fluid removal had been removed during the initial two hours, the required amount of fluid removal was performed during the second two-hour period. When fluid was removed during the initial two hours, no fluid was removed during the second two-hour period.

The dialysis treatments were performed with the patients' usual dialyzers, such as hemophan (HG400) or cuprophan (SCE135). Bicarbonate dialysis solutions was used for all treatments. It contained (in mM): sodium 140, calcium 1.75, magnesium 0.5, potassium 2.0 or 3.0, bicarbonate 40, and dextrose 11.1. Dialysate flow rate was 500 ml/min. The patient's usual blood flow rate (between 300 ml/min to 400 ml/min) was used for all treatments.

Radionuclide studies

Red blood cells were labeled *in vivo* using stannous pyrophosphate followed by 20 to 25 mCi of technetium-99m pertechnetate. Images were obtained using a low energy scintillation camera interfaced to a computer. A region of interest (ROI) was drawn to include the spleen and a background region medial to the spleen that avoided major organs and vascular pools. The splanchnic ROI included the entire region from the diaphragm to the bifurcation of the abdominal aorta, excluding the spleen and liver. All ROI counts were corrected for radioactivity decay.

Blood samples for blood and plasma radioactivity were drawn from a site other than that used for isotope injection. Radioactivity in 0.25 ml aliquots of blood and plasma was determined using a gamma counter. At the end of two hours and four hours of dialysis, after mixing, three samples of dialysate were obtained for counting for radioactivity. In the data analysis, all initial values were taken at the point 30 minutes after hooking up to the dialyzer, after extracorporeal circulation without fluid removal. Initial blood volume was computed from an anthropometric equation: $BV = 1993 + 39.8 \times W$, where W was the patient's dry weight in kg [9]. The estimated initial total Tc content was obtained by multiplying specific activity of the t30 blood sample times the estimated initial blood volume. The estimated final total Tc content was obtained by first computing the t150 blood volume, as the initial BV $\times$ the ratio of the initial to final hematocrits. The final BV was then multiplied by the t150 specific activity to obtain final total Tc content. The percent removed was then computed as 100 $\times$ (initial content $-$ final content)/initial content. The percent removed was also computed from the dialysate side. The dialysate specific activity was multiplied by 60 liters, and the total Tc removed was subtracted from the estimated initial Tc content. When blood samples were taken for counting, both whole blood and plasma samples were counted. From the average plasma level during dialysis and the total amount removed in the dialysate, a plasma Tc clearance was calculated.

Table 1. Baseline values at 0 and 30 minutes (mean ± SEM)

	DUF		DD	
	0 min[a]	30 min[b]	0 min[c]	30 min[d]
MAP *mm Hg*	108.7 ± 5.7	110.7 ± 4.4	108.8 ± 7.9	108.2 ± 8.7
HR *beats/min*	81.4 ± 3.0	80.8 ± 3.4	84.1 ± 3.4	81.1 ± 3.4
Pre-dialysis weight gain	3.7 ± 0.4	—	3.4 ± 0.5	—

P for a vs. b, a vs. c, and b vs. d and c vs. d were non-significant.

Autonomic nervous system testing

Autonomic nervous system testing focused primarily on cardiac parasympathetic activity, as measured by the spontaneous variation of the R-R interval during deep respiration and by the Valsalva ratio as outlined in a prior study [10]. After 10 minutes in the supine position, a constant ECG was recorded during a deep breathing procedure for one minute: 5 maximal expirations and 5 inspirations per minute, using six second inhale and six second exhale periods. The E/I ratio was calculated from the mean values of the longest R-R interval during expiration (E) and the shortest R-R interval during inspiration (I).

After another 10 minutes of rest, the subject performed a Valsalva maneuver by blowing through a mouth-piece attached to a manometer and maintaining a pressure of 40 mm Hg for 15 seconds. The test was performed three times during continuous ECG recording. Between each blowing, the subject rested for three minutes. The Valsalva ratio was calculated as the mean longest R-R interval after the maneuvers to the mean shortest during the maneuvers from 3 ECG recordings. The deep breathing test and Valsalva maneuvers were also performed in 5 healthy volunteers (age range 25 to 45 years).

Statistical methods and analysis of results

Statistical analysis was performed using the SPSS Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL, USA) PC computer software package. All the data at different time points were expressed as the percentage change from baseline. As there were multiple time points for each treatment, a two-factor (time $\times$ treatment) repeated measures analysis of variance design was used. If a treatment or a time $\times$ treatment effect was found, then the treatment effect at each time point was further explored by paired *t*-testing of that time point versus baseline.

Results

Both dialysis treatments were well tolerated without symptomatic hypotension. The baseline hemodynamic measurements at 0 minutes and 30 minutes are listed in Table 1. There were no significant differences in any of these baseline values immediately prior to DUF versus DD.

By two-factor repeated measures ANOVA, time and treatment effects were significant for splanchnic erythrocyte content, hematocrit, and blood radioactivity. Significant treatment-time interactions were seen with splanchnic erythrocyte content and MAP. Analysis of the individual time points indicated that splanchnic

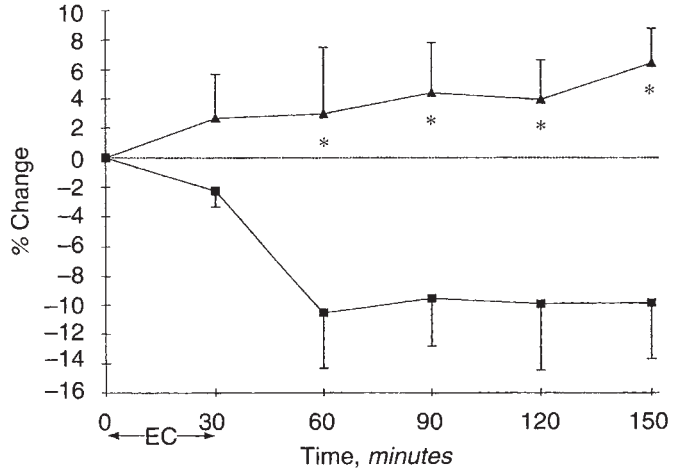

Fig. 1. *Changes in baseline splanchnic erythrocyte radioactivity over time during the 2 hr study period.* Symbols are: (■) dialysis plus fluid removal (dialytic ultrafiltration, DUF); (▲) dialysis without fluid removal (diffusion dialysis, DD). Fluid was not removed and dialysate was not circulated during the initial 30-minute period, marked EC (extracorporeal circulation) on the graph. Asterisks represent a P value < 0.05.

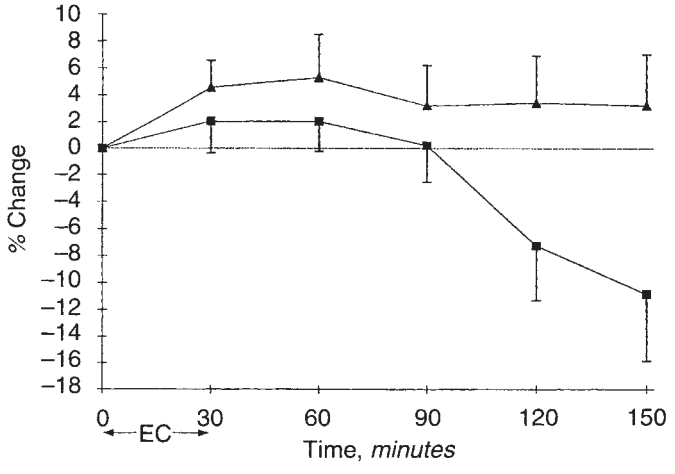

Fig. 2. *Same graph in Figure 1, except that the region of interest was the spleen.* In contrast to total splanchnic radioactivity (Fig. 1), splenic radioactivity began to decrease only late during dialytic ultrafiltration (DUF, squares), and the decrease failed to quite reach the 0.05 level of statistical significance. Symbols are: (■) DUF; (▲) DD.

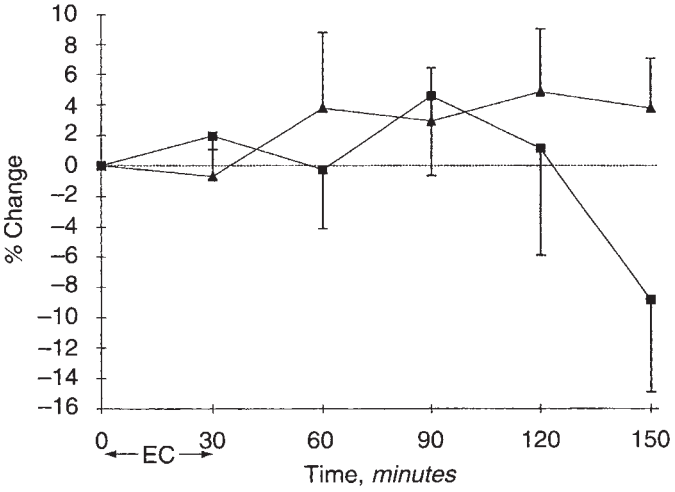

Fig. 3. *Change in mean arterial pressure during dialytic ultrafiltration (DUF, ■) and diffusion dialysis (DD, ▲).* There were no significant differences, although there was a strong trend for a decrease in MAP during the last 30 minutes of DUF.

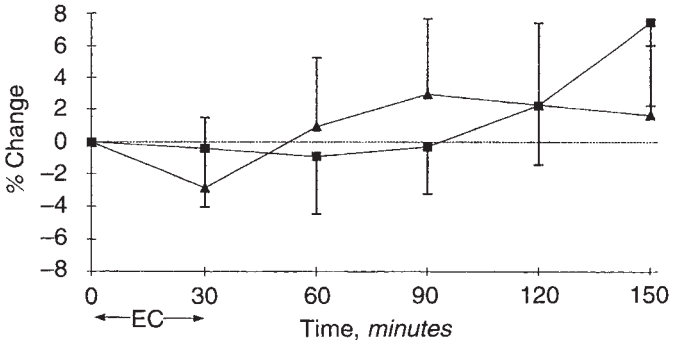

Fig. 4. *As shown, there were no significant changes in heart rate with either dialytic ultrafiltration (DUF, ■) or diffusion dialysis (DD, ▲).*

erythrocyte content decreased significantly during dialytic ultrafiltration (DUF, Fig. 1). At the same time points, no changes in the splanchnic erythrocyte content during diffusional dialysis (DD) were observed. Splenic erythrocyte content remained unchanged in both DUF and DD during the initial 60 minutes (Fig. 2). Splenic radioactivity decreased when the blood pressure started to drop during the second hour of DUF, although the reduction of both the radioactivity of the spleen and MAP did not reach statistical significance.

There was no significant difference in interdialysis weight gain prior to the study (DUF) compared to the control (DD) sessions: 3.7 ± 0.4 kg versus 3.4 ± 0.5 kg, $P = 0.67$. Mean arterial pressure (MAP) remained relatively unchanged during the first 90 minutes of DUF and then it decreased to 91.2 ± 6.1% (mean ± SEM; Fig. 3) of the baseline value in the last 30 minutes. MAP remained unchanged throughout DD. There were no changes in heart rate during DUF or DD (Fig. 4).

Radioactivity per unit volume of the whole blood increased by an average of 9.2 ± 10.5% during DUF while it decreased by 9.6 ± 4.6% during DD. The decrease in specific activity with DD was due to loss of technetium to the dialysate by diffusion during dialysis. During DUF, the loss of the radioactivity was compensated by hemoconcentration (hematocrit increased by 14.4% during DUF while it decreased by 0.64% (P = NS) during DD. The radioactivity of the plasma was about 3 to 4% of that of whole blood and this proportion did not change over the duration of the dialysis treatment. Plasma Tc counts were unchanged during DUF, but fell significantly, by 18 ± 15% during DD (Table 2). The reason for the lack of decrease in plasma counts during DUF was unclear. It may have been related to a higher proportion of red cells in the blood, with a higher equilibrating mass of Tc associated with erythrocytes.

To assess mass balance and Tc removal, the computations described in the methods section were done. These results are

Table 2. Blood and dialysate technetium counts during dialytic ultrafitration (DUF) and diffusion dialysis (DD) (mean ± SD)

	Pre-dialysis	Post-dialysis	*P*
DUF-hematocrit %	31.9 ± 5.0	36.6 ± 6.7	0.008
DD-hematocrit %	32.6 ± 5.2	32.5 ± 5.3	NS
DUF-blood Tc counts × 10^6/ml	2.52 ± 0.68	2.74 ± 0.71	0.004
DD-blood Tc counts × 10^6/ml	2.52 ± 1.4	2.24 ± 1.2	0.003
DUF-plasma Tc counts × 10^4/ml	9.68 ± 2.1	9.70 ± 1.8	NS
DD-plasma Tc counts × 10^4/ml	10.6 ± 5.7	8.6 ± 4.5	0.049
DUF-blood volume *ml*	5032 ± 766	4411 ± 587	0.008
DD-blood volume *ml*	5032 ± 766	5056 ± 677	NS
DUF-total Tc blood × 10^{10}	1.25 ± 0.33	1.19 ± 0.33	NS (0.065)
DD-Total Tc blood × 10^{10}	1.26 ± 0.67	1.12 ± 0.59	0.007

Table 3. Technetium removal measures

	DUF	DD	*P*
2 Hour values			
Total Tc dialysate × 10^{10}	0.065 ± 0.023	0.066 ± 0.30	NS
% Removed (blood initial − final)	4.4 ± 4.4	8.8 ± 6.8	NS (0.084)
% Removed (initial − dialysate)/initial	5.9 ± 1.9	6.2 ± 1.2	NS
Plasma cleared of Tc in 2 hours (ml)	6994 ± 2731	7370 ± 1241	NS
Clearance (plasma cleared/120)	58 ± 23	61 ± 10	NS
4 Hour values			
Total Tc dialysate × 10^{10}	0.12 ± 0.043	0.14 ± 0.59	NS
% Removed (initial − dialysate)/initial	11.4 ± 3.9	13.0 ± 12.7	NS

presented in Table 3. It can be seen that, by both blood and dialysate side methods, the removal of Tc was about 6% over a two hour period, and this did not differ significantly during the DUF and DD sessions. The plasma Tc clearance was about 60 ml/min. Four-hour Tc removal and clearances gave quite consistent results, with an average of 12% of initial Tc content being removed over a four hours period.

The expiratory/inspiratory (E/I) and Valsalva heart rate ratios of the eight patients studied were 1.13 ± 0.03 and 1.42 ± 0.1, respectively. These values are considered within the normal range, although they were somewhat lower than in the non-uremic healthy controls.

Discussion

Dialysis hypotension is an important clinical problem. In the course of an "average" hemodialysis, 2 to 4 liters of ultrafiltrate must be removed, representing a volume close that of the plasma. Although such rapid fluid removal can often be achieved without hypotension, in a substantial percentage of dialysis patients intradialytic hypotension does occur. The causes of hemodialysis hypotension are multifactorial, and the hemodynamic mechanisms are likewise varied [1].

During acute hypovolemia, several mechanisms are involved to maintain cardiac output and thus hemodynamic stability. A substantial percentage of the total blood volume is located in the venous system. During acute hypovolemia, venous capacity will decrease to help to maintain cardiac filling [2, 3]. The splanchnic circulation is one of the most important vascular beds that participate in maintaining hemodynamic stability. Although the relative contributions of spleen, liver and intestines to splanchnic-mediated volume redistribution are not known, the decrease of splanchnic capacity during hypovolemia in other clinical conditions are well known [4–6]. The human spleen can contract on change to upright posture and during exercise, with the addition of previously sequestered erythrocytes to the circulation [11].

Our results suggest that splanchnic blood volume did indeed decrease during dialysis, but only when fluid was removed. The extent of the reduction in splanchnic red cell radioactivity was on the order of 10%. This splanchnic erythrocyte shift began during the first 30 minutes of dialytic ultrafiltration and persisted throughout the study (Fig. 1). With more fluid removal and a progressive drop in blood pressure (Fig. 3), our data suggest that contraction of the spleen may also have occurred (Fig. 2), although this finding needs to be interpreted cautiously, as the reduction in splenic radioactivity did not quite attain statistical significance.

The reduction in splanchnic radioisotope count observed during DUF was not due to loss of radioactivity by decay, as decay was accounted for in the computations. The reduction was not due to diffusional loss of radioactivity during dialysis, as the splanchnic erythrocyte content decreased significantly only during dialytic fluid removal and not during dialysis without fluid removal. During dialysis with or without fluid removal, some radioactivity of the peripheral blood was lost as a result of diffusion of the radioisotope to the dialysate. This was indicated by the decrease in the peripheral blood radioactivity count during the diffusional dialysis without fluid removal (Table 2). With DUF, of course, the peripheral blood radioactivity count increased (Table 2) as a result of the increase in hematocrit that occurred. The fact that overall Tc loss was consistent whether measured from the blood or dialysate side provides evidence that at 30 minutes, equilibration of Tc was relatively complete. If it had not been, one would have expected the percent Tc removed computed based on pre- and post-specific activities and hematocrits to be greater than percent Tc removed computed based on dialysate recovery. Such a discrepancy was not found, however.

Plasma Tc counts decreased by about 18% during DD, but were unchanged during DUF. Why this was so is not immediately apparent. Perhaps the increase in Hct during DUF caused more transfer of Tc from erythrocytes to plasma during DUF, increasing the plasma counts slightly. As plasma Tc counts were only 4% that of whole blood, any minor change in erythrocyte to plasma Tc transfer rate could account for marked changes in the plasma level. Tc removal was similar during DD and DUF, whereas one might have predicted increased removal during DUF due to convective transport. Again, as the total removal of Tc was only about 6% of the injected dose, small differences in Tc removal between DD and DUF could not be detected with the sample size used.

Evidence of hemodynamic changes during hemodialysis as a result of peripheral pooling of the blood was first provided by Chen et al [12]. The ratio of end-diastolic cardiac volume to total blood volume (EDV/TBV) was taken to be a measure of peripheral pooling. An increased EDV/TBV ratio would reflect a central shift of the blood volume whereas a decreased EDV/TBV ratio

would signal peripheral pooling. During regular acetate hemodialysis, EDV/TBV decreased, presumably due to venodilation and peripheral pooling, whereas during bicarbonate dialysis EDV/TBW increased, suggesting a central shift of the blood volume [12, 13]. It would be of interest to compare splanchnic volume shifts during bicarbonate versus acetate dialysis. As acetate causes selective splanchnic vasodilatation [14], it is possible that the peripheral pooling of blood noted by Chen et al may have been due to splanchnic sequestration of erythrocytes via a reverse DeJager-Krogh effect. Another area of interest to explore might be whether or not the hemodynamic benefits of isolated ultrafiltration or cool dialysate are partly mediated via enhanced mobilization of splanchnic erythrocytes.

One approach to the study of autonomic reflexes in patients is to focus primarily on cardiac parasympathetic activity, as measured by the spontaneous variation of the R-R interval during deep respiration and by the Valsalva ratio [10]. These tests have been proven to be a sensitive test of autonomic neuropathy in early diabetes [15–17]. This method is quite sensitive and reproducible for detecting autonomic nervous system defects. A Valsalva ratio of 1.25 or less or R-R variation with E/I ratio less than 1.05 is associated with autonomic neuropathy [10]. In the patients we studied, the autonomic reflexes controlling heart rate appeared to be relatively intact, with a mean Valsalva ratio of 1.43 and E/I ratio of 1.13. It is possible that their intact autonomic reflexes were required to effect a reduction in splanchnic vascular bed volume during dialysis.

The question remains: what about patients in whom the ANS is clearly impaired? Originally, we planned to identify and study patients with clearly impaired ANS function and assess their splanchnic volume changes during dialysis. We did manage to study one such patient, in whom the Valsalva and E/I ratios were close to unity. In this patient there was no evidence of a decrease in either splanchnic or splenic radioactivity during DUF, despite a considerable fall in MAP. Further study was made impossible, however, due to a change of mission of the hospital where these investigations were performed (outsourcing of dialysis). So the investigation of the relation between ANS dysfunction and splanchnic volume changes during dialysis remains an area for further investigation.

In summary, our results suggest that translocation of erythrocytes from the splanchnic circulation (and possibly from the spleen) may be one of the mechanisms whereby the body compensates for hypovolemic stress during dialytic ultrafiltration. This mechanism was demonstrated to occur in dialysis patients with a relatively intact autonomic nervous system. Whether patients with ANS dysfunction can also reduce splanchnic erythrocyte volume during dialysis remains a topic that requires further study. Other areas to explore are the effects of isolated ultrafiltration or cool dialysate on splanchnic volume during ultrafiltration.

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