Blood Flow, Negative Pressure, and Hemolysis During Hemodialysis

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Blood flow, measured by an ultrasound flowmeter, and the extent of hemolysis were assessed during a single, routine dialysis in 100 patients. Before and after the hemodialysis session, blood was drawn for measurements of haptoglobin (HPT), hemoglobin (HGB), albumin (ALB), and lactate dehydrogenase (LDH).

The average values were as follows: pump speed 510 mL/min, real blood flow 422 mL/min, arterial chamber pressure –350 mm Hg, and venous chamber pressure 279 mm Hg. Haptoglobin concentrations were higher in patients with central vein catheters compared to patients with arterio-venous access. The meaning of this finding is unclear. Mean HPT concentrations increased significantly less during hemodialysis (2.37%) than concentrations of ALB (11.3%), HGB (9.17%), and LDH (18.2%), indicating that some hemolysis is present in all dialyses. In dialyses with arterial chamber pressures more negative than –350 the median concentration of ALB (8.70%) increased significantly more than the median concentration of HGB (7.99%). This indicates significantly more hemolysis in dialyses with more negative pressures compared to those with less negative arterial chamber pressures. Median LDH increased more in dialyses with more negative prepump chamber pressures (16.19% vs 13.78%), but not significantly; however, LDH increases were significantly higher than either HGB or ALB, thus indicating significantly more hemolysis in dialyses with more negative pressures compared to those with less negative arterial chamber pressures. Erythropoietin dose was not significantly different in patients dialyzed with more or less negative arterial chamber pressures (17 645 ± 1226 U/week vs 16 308 ± 1506 U/week).

We conclude that dialyses with negative arterial chamber pressures greater than –350 mm Hg cause slightly higher hemolysis than dialyses with less negative arterial chamber pressures, but this increased hemolysis is not associated with an increased requirement of erythropoietin dose. Whether this increased hemolysis is of clinical significance is uncertain.

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Key words

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Introduction

The most widely used pumps in hemodialysis machines are composed of a rotor with rollers, a stator, and a tubing compressed between the rollers and the stator. These are called flow-regulated pumps, since the flow depends mostly on the rotation speed of rollers. Negative pressure before the pump and positive pressure after the pump have only a small influence on the blood flow. In pressure-dependent pumps the pump tubing is stretched upon a vertical rotor without a stator. In this system blood flow is mostly dependent on the pre- and post-pump pressures and less dependent on the pump speed. Some hemolysis occurs in all extracorporeal circuits using pumps. The higher the blood flow, the higher the hemolysis. Significant hemolysis was found after each use of heart–lung machines [1,2]. In an *in vitro* study of various pumps, hemolysis was higher in systems where the tubing is occluded between a rotor and a stator (flow-regulated pumps) as compared to pressure-dependent pumps [3]. At blood flows of 5 L/min, hemolysis was higher than at flow rates of 0.5 L/min or less [3].

Fresenius hemodialysis machines, which we use in our outpatient dialysis facility, are equipped with flow-regulated pumps of the Sarns type, which have two rollers on a rotor. The occlusion of the tubing between the rollers and the stator is subtotal (some backflow is present if the pump is stopped) and is set by the manufacturer. The tightness of compression is regulated by the strength of special springs. The subtotal occlusion of the pump tubing decreases hemolysis [4].

With the use of roller pumps, blood flow rates are dependent on the blood pump speed, the size and the collapsibility of the pump tubing, negative pressure in the arterial line chamber located before the pump, and the pressure after the pump. For high dialysis efficiency, the highest possible blood flows are desirable. On the other hand, dialysis needles or catheters must have limited diameters to decrease blood access complications. These limited diameters cause high pressure gradients in the blood lines and high blood velocities in narrow segments. High blood velocities increase shear forces, which can hemolyze red blood cells. Hemolysis has been observed in high-flow single-needle dialysis [5], partial thrombotic occlusion of intravenous catheters [6], and with very low inflow pressures and complete collapse of the arterial line [7].

The subtotal occlusion of the tubing not only decreases hemolysis, but also prevents rupture of the outlet tubing in case the outflow pressure is excessively augmented. However, if the tubing is kinked between the pump and the venous chamber pressure gauge, the velocity of blood may be increased so much that, without any warning, massive hemolysis may occur [8–11]. Symptoms include malaise, nausea, chest pain, shortness of breath, abdominal pain, back pain, emesis, cyanosis, headache, and increased blood pressure. Gallstones and pancreatitis frequently develop after a hemolytic episode. Massive hemolysis is associated with a positive "pink test" (pink-appearing serum), due to the presence of free hemoglobin, a very high concentration of serum lactate dehydrogenase, and almost complete disappearance of haptoglobin [7–11].

In our hemodialysis unit high blood pump speeds [up to 600 on arteriovenous (AV) access and up to 590 on intravenous (IV) access] are used to achieve high-efficiency dialysis. Negative prepump pressures of –400 mm Hg or lower are sometimes needed to achieve such flows. There are no clinical symptoms of hemolysis and no signs of any detrimental effects of such flows by routine patient evaluation. There is no visible hemolysis in routine, monthly, postdialysis blood samples; however, the degree of hemolysis has not been determined by more sensitive methods.

The goal of the study was to determine the degree of hemolysis by changes in haptoglobin (HPT) and lactic dehydrogenase (LDH), concentrations in comparison with changes in albumin (ALB), hemoglobin (HGB) concentrations, and hematocrit (HCT) before and after hemodialysis sessions. The results of the changes in pre- and post-values were compared in relation to the blood flows and circuit pressures during dialysis.

Methods

Patients

The project was approved by the Institutional Review Board. The study was performed on 100 patients, selected at random from 143 patients treated at Dialysis Clinics, Inc., in Columbia, Missouri. All patients gave informed oral consent. There were 45 females, aged 23 – 86 years (mean 63.7 years) and 55 males, aged 26 – 89 years (mean 61.5 years). Forty-one patients were African-American, and 59 were white. None of the patients had hemoglobinopathy, red cell membrane abnormalities, or red cell enzyme defects. The average weekly dose of erythropoietin was taken from the records.

Blood access

Eighteen patients (2 females and 16 males) had primary AV fistulas, 51 patients (26 females and 25 males) had bridge AV grafts, and the remaining 31 patients (17 females and 14 males) had central vein catheters: 17 were PermCath (Kendall Healthcare Products Comp., Mansfield, MA, U.S.A.), one was AccessCath (MEDCOMP, Harleysville, PA, U.S.A.), 10 were Tesio (MEDCOMP), and 3 were VasCath (BARD, Salt Lake City, UT, U.S.A.). The needles were 1 1/4" back eye (Medisystems Corporation, Seattle, WA, U.S.A.). One male patient used a 14 G needle, 36 patients (8 females and 28 males) used 15 G needles, 31 patients (20 females and 11 males) used 16 G needles, and one male used 17 G needles.

Dialyses

Patients were dialyzed according to routine prescriptions by attending nephrologists. Seventy-three dialyses were performed on Fresenius A2008D machines (Fresenius Medical Care, Bad Homburg, Germany). Prepump chamber pressure gauges on these machines had been recalibrated to measure pressures from +100 to –450 mm Hg. The remaining 27 dialyses were performed on Fresenius 2008H machines (Fresenius). In these machines the prechamber pressure gauges were routinely disengaged. Nurses were alerted of a possible low prepump pressure by a low venous chamber pressure. The excessive negative pressure was confirmed by noting a low arterial chamber blood level. For study purposes a negative pressure aneroid manometer, able to measure negative pressures up to –500 mm Hg, was attached to the arterial chamber. Dialysis duration was between 3 and 4 hours.

Dialysate was prepared from tap water purified with deionizer, reverse osmosis, and carbon filter. Dialysate calcium ranged from 2.0 – 3.5 mEq/L, sodium 137 – 144 mEq/L, bicarbonate 35 – 40 mEq/L, and potassium 1 – 4 mEq/L.

Dialyzers were resterilized with bleach and glutaraldehyde. Twenty-three patients were dialyzed with single CA-210 dialyzers (Baxter Healthcare, Deerfield, IL, U.S.A.), two with double CA-210 dialyzers arranged in series (stack), one with F-60, one with F-70, 60 with F-80 dialyzers (Fresenius), and 13 with two F-80 dialyzers arranged in series. At the time of study, CA-210 dialyzers were at their first to forty-ninth use (mean 7.96), the F-60 dialyzer was at its seventh use, the F–70 was used for the first time, and single F-80 dialyzers were at their first to seventh use (mean 3.16), and stack F-80 dialyzers were at their first to seventh use (mean 4.34). Polysulfone dialyzers (F) were maximally reused 6 times (7 uses), CA dialyzers had limit of 99 reuses, but were discarded when a leak was present or capacity dropped below 96 mL. Before dialysis, all dialyzers passed the test for absence of glutaraldehyde.

ReadySet (Medisystems) blood lines with an 8 mm ID pump segment and a noncollapsible arterial chamber were used in all dialyses. Blood flows were measured by an ultrasound flowmeter (Transonic Systems Inc., Ithaca, NY, U.S.A.) at the start and at the end of dialysis.

Chemistry

Immediately before and after each hemodialysis session, blood was drawn for measurements of HPT, HCT, ALB, and LDH. Lactate dehydrogenase and ALB were run on Synchron, CX5CE Autoanalyzer (Beckman, Inc., Brea, CA,

U.S.A.), HPT concentrations were determined on Array 360 Analyzer (Beckman), HGB concentrations were measured on Coulter Hemoglobinometer (Coulter, Inc., Hialeah, FL, U.S.A.), and HCT was measured manually using a Microhematocrit Centrifuge (International Equipment, Parsippany, NJ, U.S.A.).

Statistics

Paired, unpaired *t*-tests, linear regressions, and nonparametric statistics, where appropriate, were performed using the SIGMA STAT program (SPSS Inc., Chicago, IL, U.S.A.).

Results

Pump speeds, pressures in lines, and flow rates

The average values at the beginning of dialysis were as follows: pump speed 510 mL/min, real blood flow 422 mL/min, arterial chamber (prepump) pressure –350 mm Hg, and venous chamber pressure 279 mm Hg. Table I shows the means and ranges of pump speeds, arterial and venous chamber pressures, and blood flow rates in relation to needle size and catheter type at the start of dialysis. Figure 1 shows the relationship between prepump negative pressure and blood flow at the start of dialysis. The number of observations was sufficient to calculate linear regressions for 15 G and 16 G needles and PermCath catheters. Regressions for Tesio, VasCath, and AccessCath were not calculated because of the small number of observations; however, these catheters showed generally an inferior flow/pressure relationship compared to needle and PermCath dialysis (Table I, Fig. 1).

At the end of dialysis the average pump speed was 506 mL/min, true blood flow 400 mL/min, and venous chamber pressure 266 mm Hg; the arterial chamber pressure remained essentially unchanged at –348 mm Hg.

HPT concentrations in patients with catheters and AV access

The mean ± SEM haptoglobin concentrations were 140 ± 6.84 mg/dL (range 17.4 – 367 mg/dL) and 144 ± 7.68 mg/dL (range 7.31 – 347 mg/dL) predialysis and postdialysis, respectively. Patients with AV accesses had lower concentrations than patients with IV accesses both predialysis (131 ± 7.42 mg/dL vs 163 ± 13.8 mg/dL; $p = 0.0306$) and after dialysis (133 ± 8.48 mg/dL vs 169 ± 15.1 mg/dL; $p = 0.0270$). Weekly erythropoietin requirements were significantly higher in patients with catheters than those with AV access (median 19 800 vs 13 200; $p = 0.0483$ by Mann–Whitney rank sum test).

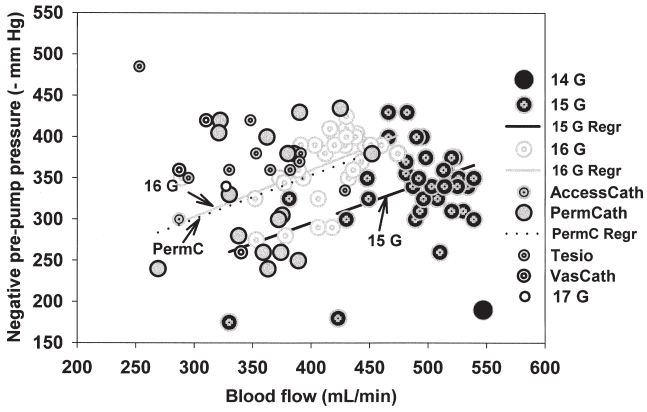

FIGURE 1 Blood flow versus negative prepump pressure at start of dialysis ($n = 100$). Linear regressions for 15 (black line) and 16 (gray solid line) gauge needles and PermCath (black dotted line) are shown. Linear regressions for Tesio, AccessCath, and VasCath catheters were not calculated because of the small number of catheters; however, the pressure/flow relationship is generally inferior to that of PermCath in this study.

ALB concentrations

Predialysis serum ALB concentration was significantly lower ($p = 0.0478$ by Mann–Whitney rank sum test) in patients with catheters (mean = 3.19; SEM = 0.098; median 3.30 g/dL) than with AV access (mean = 3.41; SEM = 0.053; median = 3.50 g/dL).

Predialysis HPT versus ALB

Figure 2 shows the relationship between predialysis HPT and ALB. There was a significant, negative correlation between serum HPT and ALB concentrations in all 100 patients (HPT = 281 – 42 ALB, $R = 0.299$, $p = 0.002$). The correlation passed both normality and homoscedasticity tests.

TABLE I Pump speed, pressures in arterial and venous chambers, and blood flow in relation to needle size and hemodialysis catheter type

	Pump speed (mL/min)	*Arterial chamber pressure (mm Hg)*	*Venous chamber pressure (mm Hg)*	*Blood flow (mL/min)*
Needle 14 G	590	–190	270	547
Needles 15 G	546 (460–600)	–340 (–175; –430)	280 (170–370)	487 (330–539)
Needles 16 G	506 (350–590)	–367 (–275; –425)	304 (130–390)	412 (289–474)
Needle 17 G	400	–340	330	327
AccessCath	350	–300	150	287
Tesio	460 (400–500)	–380 (–335; –485)	288 (180–420)	354 (253–429)
PermCath	438 (310–590)	–335 (–240; –435)	246 (180–340)	365 (269–452)
VasCath	393 (350–430)	–347 (–260; –420)	203 (180–240)	312 (287–340)

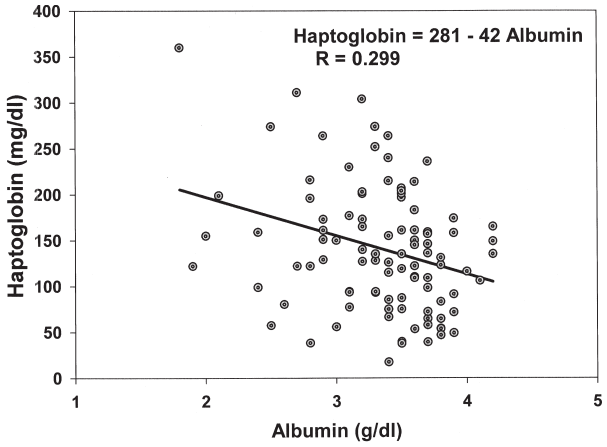

FIGURE 2 Predialysis haptoglobin versus albumin (n = 100).

Weight loss and blood chemistry

Mean ± SD weight loss during dialysis was 3.74% ± 1.74% body weight (range –0.31% to 9.23%). Table II presents mean ± SEM percent increases of HPT, LDH, ALB, HGB, and HCT at the end of dialysis. Statistical significance of differences between magnitudes of increases is also shown. The highest increase was noted for LDH (18.2%), then ALB (11.3%), HGB (9.17%), and HCT (5.52%). The smallest increase was noted for HPT (2.27%).

HGB, ALB, and LDH in relation to arterial chamber pressures

Table III shows percent increase of HGB and ALB in dialyses with arterial chamber pressures below –350 mm Hg and arterial chamber pressures above –350 mm Hg. In dialyses with arterial chamber pressures less negative than –350 there was no difference in concentration changes of ALB and HGB. In fact, the median concentration of HGB increased more than ALB but not significantly. Erythropoietin dose was not significantly different in patients dialyzed with more and less negative arterial chamber pressures (17 645 ± 1226 U/week vs 16 308 ± 1506 U/week).

In dialyses with arterial chamber pressures more negative than –350 the median concentration of ALB increased significantly more than the median concentration of HGB. This indicates significantly more hemolysis in dialyses with more negative pressures compared to those with less negative arterial chamber pressures. LDH increased more in dialyses with more negative prepump chamber pressures, but not significantly; however, LDH increases were significantly higher than either HGB or ALB.

Discussion

The average pump speed at the beginning of dialysis was 510 mL/min and real blood flow 422 mL/min. To achieve such blood flows, the average negative arterial chamber (prepump) pressure was –350 mm Hg and venous chamber pressure 279 mm Hg. At the end of dialysis the average arterial chamber pressure remained essentially unchanged at –348 mm Hg, but the average pump speed dropped to 506 mL/min, true blood flow to 400 mL/min, and venous chamber pressure to 266 mm Hg. The lower blood flow at the end of dialysis with essentially unchanged negative arterial (prepump) pressure is clearly related to the increased blood viscosity due to hemoconcentration.

According to the Poiselle equation, the flow through the tubing is directly proportional to the pressure difference and fourth power of tubing radius, and is inversely proportional to the tubing length and viscosity of the fluid. The viscosity of blood depends mostly on HCT. The length of needles was the same regardless of gauge; thus, in general, the flows were higher with the lower needle gauge, but the scatter was substantial, most likely due to difference in HCT but also could depend on the needle position in the access. All needles were provided with a back eye; thus, if the main bore was

TABLE II Mean ± SEM percent increase of concentrations of HPT, LDH, ALB, HGB, and HCT during dialysis. Comparisons of percent change. Significance by Wilcoxon signed rank test is also shown.

HPT	*LDH*	*ALB*	*HGB*	*HCT*
2.27±3.37%	18.2±2.66%	11.3±1.58%	9.17±1.20%	5.52±0.84%
HPT vs LDH $p < 0.0001$	LDH vs ALB $p = 0.0015$	ALB vs HGB $p = 0.0714$	HGB vs HCT $p < 0.0001$	
HPT vs ALB $p < 0.0001$	LDH vs HGB $p = 0.0001$	ALB vs HCT $p < 0.0001$		
HPT vs HGB $p < 0.0001$	LDH vs HCT $p < 0.0001$			
HPT vs HCT $p = 0.0656$				

HPT = haptoglobin; LDH = lactate dehydrogenase; ALB = albumin; HGB = hemoglobin; HCT = hematocrit.

TABLE III Percent increase of ALB, HGB, and LDH in dialyses with prepump chamber pressure less negative than –350 mm Hg and more negative than –350 mm Hg.

Prepump pressure	*ALB increase (%) during dialysis*	*HGB increase (%) during dialysis*	*LDH increase (%) during dialysis*	*Paired test*
>–350	mean 9.93	mean 10.29	mean 17.21	ALB vs HGB $p = 0.760$[a]
$n = 48$	SEM 2.04	SEM 1.68	SEM 3.31	ALB vs LDH $p = 0.019$[b]
	median 4.79	median 9.15	median 13.78	HGB vs LDH $p = 0.031$[b]
<–350	mean 12.62	mean 8.12	mean 19.10	ALB vs HGB $p = 0.030$[a]
$n = 52$	SEM 2.37	SEM 1.69	SEM 4.09	ALB vs LDH $p = 0.053$[a]
	median 8.70	median 7.99	median 16.19	HGB vs LDH $p = 0.004$[a]

ALB = albumin; HGB = hemoglobin; LDH = lactate dehydrogenase.
[a] Wilcoxon signed rank test.
[b] *t*-test.

occluded by sucking against the vessel wall, the flow was provided through the back eye, which has a smaller diameter than the main bore. The relationship between blood flow and negative prepump pressure in PermCath catheters was almost identical to that of 16 G needles, but the scatter was also substantial. This scatter depends not only on the differences in HCT, but also on the catheter length, its position in the superior vena cava or the right atrium, and the eventual presence of a fibrin sheath at the tip of the catheter. The high scatter of values in Tesio catheters also depended on the different length of the external part of the catheters.

The average weight loss was almost 4% and caused substantial hemoconcentration. This was reflected by increases in blood or serum concentrations of all measured non-dialyzable substances. If all these substances could not escape from the intravascular space and were not produced or changed during dialysis, the percent of their increase would be identical. However, HGB should rise proportionately more than ALB because HGB trapped in red blood cells cannot escape from the intravascular space, whereas ALB can. Instead of rising more than ALB, HGB tended to increase less than ALB (9.17% and 11.3%, respectively; $p = 0.07$), thus supporting a presence of hemolysis during dialysis. Hematocrit did not increase to the same degree as HGB. This may be explained by shrinking of red blood cells because of increased plasma oncotic pressure.

Haptoglobin is a tetrachain ($\alpha_2\beta_2$) glycoprotein (molecular weight 85 000 D) synthesized in the liver and secreted into plasma. It is similar in structure to the chymotrypsinogen family of serine protease [12]. The main function of HPT is binding to free HGB after hemolysis. After binding free HGB, the HPT–HGB complex is taken by reticuloendothelial system within minutes [13]. Acute hemolysis is always associated with a decrease in concentration of HPT; massive hemolysis causes complete consumption of HPT within minutes [7–13]. The half-life of unbound HPT is about 4 days [14]. As a large molecular weight protein, it is not removed by dialysis. Depending on the degree of ultrafiltration, it should be concentrated during dialysis to the same degree as ALB. A minimal increase of HPT, markedly lower than that of ALB, indicates that HPT is consumed during dialysis, thus supporting the notion of hemolysis during dialysis.

Lactate dehydrogenase is a tetramer containing muscle and heart subunits. It is an enzyme of the oxidoreductase class that catalyzes the reduction of pyruvate to (S)-lactate, using NADH as an electron donor. The reaction is the final step in glycolysis. Red blood cells use unoxidative glycolysis for energy delivery and contain large amounts of LDH. Red blood cell destruction releases LDH; therefore, serum LDH activity rises proportionally to the degree of hemolysis [14]. A significantly higher increase of LDH during dialysis compared to ALB may indicate that it is released from red blood cells and further support the presence of hemolysis during hemodialysis.

In dialyses with arterial chamber pressures less negative than –350 there was no difference in concentration changes of ALB and HGB. In fact, the median concentration of HGB increased more than ALB but not significantly (9.17% vs 4.79%; $p = 0.76$). Lactate dehydrogenase increased significantly more than ALB and HGB (Table III). In dialyses with arterial chamber pressures more negative than –350 the median concentration of ALB increased significantly more than the median concentration of HGB. The median rise in LDH was significantly higher than that of HGB (16.19% vs 7.99%; $p = 0.004$). This indicates significantly more hemolysis in dialyses with more negative pressures compared to those with less negative arterial chamber pressures. Erythropoietin dose was not significantly different between these two groups. The degree of hemolysis is difficult to calculate on the basis of this study, but judging by the fact that the amount of consumed HPT was low, the amount of released HGB was in the range of milligrams per deciliter, which corresponds to about 0.1% (1/1000) of red blood cells destroyed during dialysis with arterial chamber pressure more negative than –350.

Whether this slightly higher hemolysis in dialyses with more negative prepump pressures is of clinical significance is uncertain. If blood flow is to be decreased to keep prepump pressure less negative than –350 mm Hg, then to obtain the

same efficiency of dialysis with the same dialysis frequency, either blood access has to be changed (shorter and/or larger diameter of needles and larger diameter of catheters) or time of dialysis needs to be increased. Longer dialysis duration is beneficial for better control of blood pressure [15,16]. We do not see a compelling reason to recommend a change in the dialysis prescription on the basis of this study; however, a slightly higher hemolysis at higher blood flows adds another argument to prolong dialysis duration at lower blood flows.

A lower concentration of HPT in patients with AV access as compared to those with catheters may indicate that the presence of the AV anastomosis with constant turbulence causes chronic, continuous, low grade hemolysis; however, the lower erythropoietin requirement in these patients contradicts this hypothesis. Haptoglobin is an acute phase reactant, and some changes in concentrations before and after dialysis may be related more to the inflammatory process(es) than to hemolysis. Serum ALB is also an acute phase protein, but, contrary to HPT, its concentration decreases during the acute phase reaction [17]. Serum ALB concentration was significantly lower in patients with catheters than with AV access, and there was negative correlation between serum HPT and ALB concentrations in all 100 patients (Fig. 2). This suggests that higher HPT levels might be related to an acute phase reaction and not low grade hemolysis. A study is under way to determine other acute phase reactants in our hemodialysis patients.

In summary, hemodialyses with negative arterial chamber pressures greater than –350 mm Hg cause slightly higher hemolysis than dialyses with less negative arterial chamber pressures, but this increased hemolysis is not associated with an increased requirement of erythropoietin dose. Whether this increased hemolysis is of clinical significance is uncertain.

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