Summary  Effects of hemodialysis on extracellular fluid volume distribution, left ventricular volumes, and cardiac output were determined in patients with end-stage renal disease (n = 19). Distribution of extracellular fluid loss from hemodialysis differed widely among patients, so that weight change correlated weakly with contraction of total blood volume (index of determination 29%, p < 0.05). End-diastolic volume (EDV) decreased from 150 ± 49 ml (mean ± SD) to 118 ± 42 ml, p < 0.001; stroke volume (SV) decreased from 108 ± 36 to 86 ± 33 ml (p < 0.001) without change in ejection fraction (from 0.73 ± 0.09 to 0.74 ± 0.11).

A significant correlation was found between total blood volume (TBV) and EDV before (r = 0.66, p < 0.005) and after dialysis (r = 0.61, p < 0.01). The correlation between TBV and SV was highly significant before (r = 0.78, p < 0.001) and after dialysis (r = 0.66, p < 0.005), but there was no correlation between change in TBV and change in EDV or in SV. The ratio of EDV to TBV (EDV/TBV X 100) was reduced significantly from 3.49 ± 0.92 to 3.06 ± 0.97, p < 0.001. These results suggest that, although intravascular volume was the major determinant of cardiac output in dialyzed patients, the postdialysis reduction in cardiac output might be related more to the relocation of blood volume than to the absolute degree of blood volume contraction. (Hypertension 3: 327-332, 1981)

Key Words  • hemodialysis • blood volume distribution • cardiac output • renal disease, end-stage • extracellular fluid volume • end-diastolic volume • stroke volume

The relationship of changes in body weight (wt) and extracellular fluid volume (ECF) with alteration of cardiac output (CO) and blood pressure (BP) in dialyzed patients have been investigated extensively. However, all reported studies have dealt with the effects of extracellular fluid changes on cardiac output and blood pressure without analyzing the intermediate steps linking fluid change with cardiac performance. These include determination of the relative participation from both intravascular and interstitial compartments to the total ECF loss during hemodialysis as well as the effect of hypovolemia on cardiac filling and possible influence of changed preload on cardiac output.

In a previous communication, we reported that the ejection fraction (EF) was not reduced by hemodialysis despite decreased preload; in fact, cardiac performance, as judged from ejection-phase indices, was improved in most patients. Any reduction in output following hemodialysis cannot therefore be attributed to reduced cardiac contractility; its relationship to fluid loss and the relative importance of intravascular versus interstitial fluid volumes were investigated in a prospective study of patients on regular hemodialysis.

Methods

Patients

Patients with chronic renal failure treated with repetitive maintenance hemodialysis were asked to participate in this study. Care was taken to study only those without clinical or radiological signs of cardiac decompensation or evidence of coronary artery disease. The 15 patients studied were selected from a larger group (48 patients) solely on a technical basis, namely, the possibility of recording a clearly defined echocardiogram, especially with regard to septum, left ventricular posterior wall, and precise repeatable localization. Further, patients with markedly increased left ventricular end-diastolic diameter
(EDD > 6 cm) were rejected, to avoid the inaccuracy inherent in calculations of left ventricular volume in these cases.7 Septal and posterior excursions were normal in all cases, neither nuclear nor angiographic evaluations were performed since there was no evidence of coronary disease in any patient and, therefore, no ethical justification for these procedures. In four patients, the study was repeated twice at different levels of hydration or fluid retention during dialysis, so that a total of 19 studies were performed.

All patients were studied on an outpatient basis before and immediately after a 5-hour dialysis performed with an EXr-23 dialyzer cartridge. All forms of antihypertensive medications (usually alphamethyldopa, hydralazine, or propranolol) were discontinued 1 week before the study. A predialysis isotonic saline solution (about 300 ml) was infused for priming the extracorporeal circulation of the artificial kidney; but no patient received blood transfusions, saline, or colloid solutions during dialysis. At the end of the procedure, blood was restored from the extracorporeal circulation without addition of any solution.

Table 1. Volume and Hemodynamic Variables Before and After Hemodialysis

<table>
<thead>
<tr>
<th></th>
<th>Weight (kg)</th>
<th>TBV (ml)</th>
<th>EDV (ml)</th>
<th>SV (ml)</th>
<th>EDV/TBV X 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>67.1 ± 11.2</td>
<td>4222 ± 1023</td>
<td>150 ± 49</td>
<td>108 ± 36</td>
<td>3.49 ± 0.92</td>
</tr>
<tr>
<td>After</td>
<td>65.0 ± 11.2</td>
<td>3755 ± 941</td>
<td>118 ± 42</td>
<td>86 ± 33</td>
<td>3.05 ± 0.97</td>
</tr>
<tr>
<td>% Decrease</td>
<td>-3.1 ± 1.0</td>
<td>-10.8 ± 7.1</td>
<td>-21.5 ± 7.5</td>
<td>-20.2 ± 8.6</td>
<td>-12.4 ± 10.5</td>
</tr>
<tr>
<td>p</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD; p = statistical significance of paired t test. TBV = total blood volume; SV = stroke volume; ECV = end-diastolic volume.

Procedure

The study was performed in the same quiet surroundings and under the same conditions before and after dialysis.

Before Dialysis

An echocardiogram was obtained with a Picker Echoview™ System 80С. The examination was performed with the patient usually supine, or occasionally in the semi-left lateral position. Care was taken to obtain the left ventricular internal dimension from a point just below the tip of the mitral leaflets at the level of the chordae tendinae (left ventricular minor axis); an excellent tracing of the septum and posterior wall endocardium was required. Echocardiogram was recorded at a paper speed of 25 or 50 mm/sec; and then an added phonocardiogram (2nd left interspace) and a carotid pulse tracing were simultaneously recorded at a paper speed of 100 mm/sec.

Plasma volume (PV) was measured after the patient had rested at least half an hour in the supine position, using 125I-human serum albumin (RISA) and a 10-minute equilibration period. Venous hematocrit was determined by micromethod from four samples of blood drawn without stasis. The total blood volume (TBV) was calculated from the plasma volume and simultaneously determined hematocrit with appropriate correction factor for the difference between total body and large vessel hematocrit.4 This correction factor is based on the individual hematocrit and approaches 1.0 at low hematocrit values.4

Blood pressure was determined by auscultation using phase I and V of Korotkoff sounds; blood samples (about 10 ml) were obtained for BUN, and serum creatinine, electrolytes, calcium, phosphorus, total proteins, and albumin.

Following Dialysis

The same protocol was followed with the exception that plasma volume was calculated rather than determined. Calculations were based on the volume measured before dialysis and changes in hematocrit following it, assuming no change in red cell mass over that short period of time in the absence of bleeding.10,11

Measurements and Calculations

Left ventricular end-diastolic diameter (EDD) was measured at the peak of the R wave of the electrocardiogram; left ventricular end-systolic diameter (ESD) was measured at the onset of the second sound. All data represent the average of 10 beats read independently by two observers.

Left ventricular volumes (end diastolic EDV and end systolic EDS) were calculated by the D4 formula,23 and stroke volume was derived as SV = EDV − ESD. Heart rate (HR) was measured from the electrocardiogram, and cardiac output (CO) calculated as the product of stroke volume times heart rate was expressed as cardiac index (CI) by correction for body surface area (BSA).

End diastolic volume/total blood volume ratio (EDV/TBV) was used as an index of distribution of blood between the left ventricle and the vascular system. This ratio is analogous to the ratio of cardiopulmonary volume to total blood volume (CPV/TBV) which has been used to study the partition of TBV between its central and peripheral compartment.15 The EDV/TBV ratio is more restricted than CPV/TBV since it does not include the right heart, the pulmonary circulation, and the left atrium. However, it can more correctly be interpreted as an index of left ventricular filling in relation to the total blood volume.
Results

Fluid Changes

Body weight decreased significantly following dialysis, from 67.1 ± 11.2 kg (mean ± SD) to 65.0 ± 11.2 kg (p < 0.001); if it is assumed that this represented ECF contraction, the mean loss of fluid during dialysis averaged, therefore, 2.1 ± 0.61 kg, or 3.1% of body weight (table 1).

The reduction in blood volume averaged 447 ± 309 ml, representing a change from a mean of 4222 ± 1023 to 3775 ± 941 ml, p < 0.001; or a 10.8% ± 7.1% decrease. As we assumed that this reduction was related to a decrease in plasma volume without significant change in red cell mass, this contraction of intravascular volume accounted for 20.5% ± 11.5% of the total body fluid loss.

The relationship between change in weight (ECF) and change in total blood volume was of borderline significance (r = 0.54, p < 0.05) (fig. 1).

Hemodynamic Changes

End-diastolic volume decreased in all patients following dialysis (from 150 ± 49 to 118 ± 42 ml, p < 0.001) as well as stroke volume (from 108 ± 36 to 86 ± 33 ml, p < 0.001) (table 2). Heart rate was not significantly altered by dialysis (73.7 ± 8.2 vs 73.9 ± 9.0 bpm); cardiac index was reduced from 4363 ± 1337 to 3476 ± 1146 ml/min/m² (p < 0.001); mean blood pressure (MAP) decreased from 122 ± 19 to 107 ± 14 mm Hg (p < 0.001); a moderate increase in total peripheral resistance was observed (from 30.6 ± 11.0 to 33.9 ± 11.3 units, p < 0.01).

End-diastolic volume and stroke volume were highly correlated before (r = 0.93, p < 0.001) and after dialysis (r = 0.91, p < 0.001). There was no statistical difference between stages and intercepts; the ejection fraction (EF) did not change significantly after dialysis (from 0.73 ± 0.09 to 0.74 ± 0.11, n.s.).

A highly significant correlation was found between total blood volume (TBV) and end-diastolic volume (EDV) both before (r = 0.66, p < 0.005) and after dialysis (r = 0.61, p < 0.001). However, there was no significant correlation between the change in TBV induced by dialysis and the change in either EDV (r = 0.37, n.s.) or stroke volume (r = 0.09, n.s.). The equations describing the regression lines correlating TBV with EDV before and after dialysis showed similar slopes but different intercepts; the latter was smaller after dialysis than before (EDV = 0.029 TBV + 24.4 before dialysis, and EDV = 0.029 TBV + 6.1 after dialysis). This disproportionate reduction in end-diastolic volume by dialysis was reflected in a significant change in EDV/TBV ratio. Paired comparison of the ratio showed a highly significant reduction by dialysis from 3.49 ± 0.92 to 3.06 ± 0.97, p < 0.001.

Discussion

Results obtained suggest that reduction in cardiac output following hemodialysis is related to redistribution of blood volume away from the heart in addition to blood volume contraction. This introduces a new aspect in consideration of the hemodynamic effects of dialysis. Although changes in blood volume or in hemodynamic function during hemodialysis15-18 have been extensively studied, few studies, if any, have in-

TABLE 2. Correlations Between Changes Induced by Hemodialysis

<table>
<thead>
<tr>
<th>Correlation</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔWt and ΔTBV</td>
<td>0.54</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ΔWt and ΔEDV</td>
<td>0.29</td>
<td>na</td>
</tr>
<tr>
<td>ΔWt and ΔSV</td>
<td>0.26</td>
<td>na</td>
</tr>
<tr>
<td>ΔTBV and ΔEDV</td>
<td>0.36</td>
<td>na</td>
</tr>
<tr>
<td>ΔTBV and ΔSV</td>
<td>0.09</td>
<td>na</td>
</tr>
<tr>
<td>ΔEDV and ΔSV</td>
<td>0.80</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Wt = weight; na = not significant; other abbreviations the same as table 1.

FIGURE 1. Graph showing that the relationship between loss of weight and reduction of blood volume following dialysis was only of borderline significance, the index of determination (r²) being only 29%.

A significant correlation was found between total blood volume (TBV) and end-diastolic volume (EDV) both before (r = 0.66, p < 0.005) and after dialysis (r = 0.61, p < 0.001). However, there was no significant correlation between the change in TBV induced by dialysis and the change in either EDV (r = 0.37, n.s.) or stroke volume (r = 0.09, n.s.). The equations describing the regression lines correlating TBV with EDV before and after dialysis showed similar slopes but different intercepts; the latter was smaller after dialysis than before (EDV = 0.029 TBV + 24.4 before dialysis, and EDV = 0.029 TBV + 6.1 after dialysis). This disproportionate reduction in end-diastolic volume by dialysis was reflected in a significant change in EDV/TBV ratio. Paired comparison of the ratio showed a highly significant reduction by dialysis from 3.49 ± 0.92 to 3.06 ± 0.97, p < 0.001.

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Fluctuations in the extracellular fluid (ECF) and reduction in cardiac output. Thus, for many, a change in weight was taken as equivalent to a change in blood volume, assuming there was no alteration in the PV/IF ratio with dialysis; yet it has been repeatedly shown that partition of ECF is not immutable and assumptions regarding it are not always warranted.19

Assessment of our results depends in large part on the methods used; for ethical reasons, these were chosen to be minimally invasive. Use of serial hematocrit measurements has been shown to be a valid method for short-term follow-up of plasma volume changes; it correlates well with estimates based on RISA and plasma protein concentration;19 this method assumes only minimal alterations of red cell mass during the procedure. During hemodialysis, blood is usually trapped in the extracorporeal circulation despite all precautions to reinfuse the whole volume in the tubes at the end of dialysis. However, the amount of blood loss was shown to be minimal, usually not exceeding 50 ml.20

The accuracy of echocardiography in determining left ventricular volume has been extensively discussed; the consensus now is that determination of stroke volume by echocardiography correlates closely with values obtained by angiography, Fick principle, or dye dilution methods.21–24 provided two conditions are present. The first is a perfect delineation of echocardiographic tracing to allow left ventricular measurement; in this work this was a condition for the selection of patients investigated. Out of 48 patients screened, only 15 were enrolled in the study. As reported, quantitative echocardiography is most useful for following the clinical course of individual patients.25 The second is the exclusion, as was done in this work, of patients with signs of coronary artery disease and possible asynergic ventricular contraction.

Fluid Changes During Hemodialysis

Removal of fluid is one of the goals of hemodialysis; the fluid loss occurs through the intravascular compartment but it is naturally derived from both the intravascular and interstitial fluid volume.4 This implies a continuous shift of fluid between the two compartments involving simultaneous loss of plasma and its refilling. The net refilling rate has been defined as the difference between total fluid loss and plasma volume loss per unit time. In our study, the plasma refilling rate averaged 330 ml per hour, a value close to that reported by Kim et al.4 This refilling rate is markedly higher than the rate calculated in healthy subjects after hemorrhage;28 the increased rate in dialyzed patients could be due to either or both of the following reasons. Hemodialysis leads to only minimal loss of protein;27 in our patients, plasma protein concentration increased significantly from 6.7 ± 0.6 to 7.3 ± 0.9 mg% (p < 0.001). The rise in oncotic pressure secondary to fluid loss should enhance plasma refilling from the interstitial compartment. Further, venous pressure decreases during hemodialysis whereas it did not change significantly in normal subjects after hemorrhage.29

Continuous fluid exchange between the two compartments of the extracellular space (ECF) implies that different partition ratios can occur among patients. This was evident in the correlation of weight loss among our patients with the degree of plasma volume contraction. Correlation between the two was barely significant (p < 0.05) (table 2); the resultant low coefficient of determination (r² = 29.2%) indicated, therefore, the great variability in partition of fluid loss between intravascular and interstitial (IF) compartments of ECF and the difficulty in calculating or predicting changes in one from the other.

To the extent that weight loss after dialysis is due to loss of ECF,4 one could trace the fluid lost mainly to
the interstitial compartment in some patients with small alteration of intravascular volume, whereas in others, blood volume decreased more than expected. This variation could be analyzed using the ΔTBV/ΔWt ratio; this varied widely from 0.05 up to 0.40. Similar differences in partition of extracellular fluid loss after acute diuresis were noted by Greene et al. with chlorothiazide and by Tarazi and Dustan with furosemide. The distribution of fluid between the intravascular and interstitial compartment is regulated by complex mechanisms that include neural factors regulating the ratio between pre- and postcapillary resistance and possibly humoral influences from the kidney. Whatever the mechanism involved in different patients, the result of this variability in PV/IF ratio helps explain the very low correlation between changes in weight and changes in stroke volume following dialysis (r = 0.25, p > 0.05) (table 2).

Hemodynamic Consequences of Fluid Loss

Besides differences in PV/IF ratio, other factors appeared to play an important role in determining the effect of dialysis in cardiac output. For the group as a whole, there was a decrease in end-diastolic volume, stroke volume, and cardiac output by about 20% for each index; these results are in agreement with previous hemodynamic studies during hemodialysis. The decrease in cardiac output was not explained by a decrease in cardiac performance; we have found that the ejection fraction was not altered by dialysis. In fact, other ejection phase indices of cardiac function, such as rate of circumferential fiber shortening (Vcf) or mean systolic ejection rate (MSER), were even increased. The maintenance of unaltered EF despite lower preload could be attributed in part to the concomitant reduction in arterial pressure by dialysis; this, however, was not the only factor since EF was maintained in some patients who did not show any reduction in pressure. One could postulate than an unchanged EF in such patients might be due to the beneficial effects of dialysis on myocardial contractility; this, however, must remain speculative until more direct data are obtained.

Thus, reduction in stroke volume and cardiac output was basically the result of fluid loss. However, calculations of averages can often hide significant differences, and the final hemodynamic alterations associated with fluid loss varied among our patients. A more complete analysis of the relationship between blood volume and cardiac output had to involve a study of the relationship between blood volume and the degree of ventricular filling (LVEDV).

Blood Volume and Left Ventricular Volume Relationship

The high correlation found between TBV and left ventricular volume suggests that intravascular volume was the major determinant of cardiac output before and after dialysis in our patients. The decrease in cardiac output after dialysis was, therefore, due in good measure to the blood volume contraction. However, the relationship between ΔTBV and ΔSV did not hold to the same degree in all patients nor was the ΔEDV quantitatively correlated to ΔTBV (table 2). Therefore, another factor in addition to the fluid loss must have influenced the degree of filling of the heart (EDV) and thus, the level of systemic flow (CO). We suggest that relocation of blood might play a significant role in cardiac output decrease after dialysis.

The reduction in end-diastolic volume of the left ventricle (20%) induced by hemodialysis was found to be greater than expected from the contraction of blood volume (10%). The TBV-EDV regression lines before and after dialysis showed the same slope but a lower intercept after dialysis. This could be expressed in a different way such as by the ratio EDV/TBV, which allows paired analysis of data, and thus revealed a highly significant reduction (p < 0.001) following dialysis. These results suggest that the blood volume, in addition to being reduced by water loss, must have also been pooled away from the heart (or the left ventricle, at least). Whether the pooling of blood volume away from the left heart was predominantly in the systemic or pulmonary vasculature, or was divided proportionately between the two, cannot be decided on the basis of our observations. Studies comparing pulmonary blood volume with total blood volume variations would help clarify the extent and site of vascular responses to hemodialysis.

The suggestion of peripheral relocation of blood with dialysis contrasts with the usual response to simple hypovolemia; hypovolemia alone would have been expected to provoke venoconstriction. The paradoxical response following hemodialysis could be related to the metabolic changes associated with the procedure. Metabolic acidosis, a common feature in patients before hemodialysis, is temporarily or partially corrected by it. We did not measure the blood pH in this study, but blood CO₂ concentration increases significantly with hemodialysis (from 20.8 ± 2.6 to 23.2 ± 2.3 mEq/liter, p < 0.001). Correction of acidosis has been shown to reduce pulmonary vascular resistance and correct systemic venoconstriction due to reduced pH.

In summary, the hemodynamic changes induced by hemodialysis are not a simple reflection of volume loss but also depend on a complex of factors. Cardiac performance was found to improve irrespective of reduction in preload, and this has been related to electrolyte changes (unpublished observations). Loss of plasma volume could not account alone for the fall in cardiac output associated with hemodialysis. Our results suggest that alterations in vascular tone also play an important role. As regards to the latter, the final result will vary among individual patients since it depends on many competitive mechanisms. To cite only two, activation of the nervous system by hypovolemia will favor venoconstriction as opposed to the venodilation provoked by correction of acidosis. Differences in autonomic neural function among dialysis patients could add to the complexity of the picture. Other mechanisms might include the reduction in tissue pressure with loss of interstitial fluid and its possible effect on compliance of systemic veins.
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