DIFFERING HAEMODYNAMIC STABILITY DUE TO DIFFERING SYMPATHETIC RESPONSE: COMPARISON OF ULTRAFILTRATION, HAEMODIALYSIS AND HAEMOFLTRATION

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Summary

In 12 RDT patients the volume removal related haemodynamic changes were correlated with concomitant changes in sympathetic activity during pure ultrafiltration (UF), post dilution haemofiltration (HF) and haemodialysis using either acetate (HDA) or bicarbonate (HDB) as buffer substitute. Total peripheral resistance (TPR) and plasma noradrenaline concentrations (PNA) increased during UF indicating a qualitatively adequate reaction of ESRD patients to volume removal. This physiological response is maintained during HF, resulting in intratreatment haemodynamic stability. In contrast no increase of PNA and insignificant changes of TPR were seen in HDA and HDB. As small molecule clearances were matched to those in HF, the behaviour of PNA indicates that not PNA removal but an impaired sympathetic response during HDA and HDB is responsible for the inadequate rise of TPR.

Introduction

Symptomatic hypotension and shock as volume removal related haemodynamic complications are very common (20–30%) in routine haemodialysis treatment [1]. A variety of factors possibly interfering with tolerance to volume removal and haemodynamic stability have been discussed [2,3]: intercompartmental fluid shifts, dialysis-induced hypoxaemia, acid base changes, direct effect of acetate on the cardiovascular system, middle molecule toxicity and impaired sympathetic response. The first aim of this study was to correlate volume removal induced haemodynamic changes with the concomitant sympathetic response in chronic ESRD patients. In this basic part of the study, volume removal was achieved by pure ultrafiltration.

The second aim of this study was to investigate how this correlation is altered, when physically different modalities of solute transport are added to volume removal. Here HF was compared with HDA. The third purpose was to investigate the possibility of modifying the treatment-specific correlation between haemo-
dynamic and sympathetic changes. This was tested by replacing acetate (HDA) as dialysate buffer by bicarbonate (HDB)

Patients and methods

Treatment modalities were UF, HF, HDA and HDB. For UF, HDA and HDB the CF 1500 (Travenol) capillary dialyser was used. For HDA dialysate contained: Na+ 140, K+ 4.0, Ca++ 2.8, Mg++ 1.5, Acetate 35mEq/L and glucose 8mmol/L. For HDB acetate was replaced in equimolar concentration by bicarbonate. The fourth treatment, HF, was performed with the Amicon TM 40 haemofilter and with a replacement fluid containing: Na+ 140, K+ 4.0, Ca++ 3.5, Mg++ 1.5, acetate 35mEq/L and glucose 8mmol/L.

The basic experimental condition for all treatments was a linear weight loss of 3000g/240min, which was achieved by automatic balancing equipment. The other basic condition for HF, HDA and HDB was a solute transport, matched for small molecules using urea as a marker (mean urea clearance: 122 ± 23ml/min). The following parameters were measured: mean arterial blood pressure (MAP) using the Arteriosonde (Roche), cardiac output (CO) by thermodilution and plasma noradrenaline concentration applying the method of Da Prada [4]. Total peripheral vascular resistance (TPR) was calculated from MAP and cardiac index (CI).

The trial treatment started with insertion of needles and catheters. This was followed by an extracorporeal circulation of 30min without volume withdrawal or solute transport. Then 240min of specific treatment began. MAP was measured every 15min, CI and PNA at 0, 30, 60, 120, 180, 240min. Twelve patients, 6 males and 6 females of mean age 47 years, ranging from 31 to 63 years were studied. They were on RDT for a mean of 53 months ranging from 6 to 132 months. Four of these patients underwent all four treatment regimes. Together with four others, who were submitted to UF, HF and HDA they formed group I. Together with four additional patients who underwent HF, HDA and HDB they formed group II. This resulted in measurements of three treatment modalities, all three performed in 8 patients. In group I UF, HF and HDA was performed in each patient, in group II HF, HDA and HDB.

Data are given as mean values ± SD, significances of inter- or intratreatment differences were calculated applying the paired t-test.

Results

The results for groups I and II are given in Table I as pre and post treatment values.

MAP stayed constant during UF and HF but fell significantly (p < 0.05) during HDA. Post treatment, significant differences existed only between UF and HDA (p < 0.01) and between HF and HDB (p < 0.05). CI fell significantly during UF (p < 0.01), HF (p < 0.01) and HDB (p < 0.05) but only insignificantly during HDA. Post treatment differences were significant between UF and HDA (p < 0.01) HF and HDA (p < 0.01) and between HF and HDB (p < 0.05). TPR
TABLE I. Results. Mean pre and post treatment values for MAP, CI, TPR and PNA of groups I (UF, HF, HDA) and group II (HF, HDA and HDB). Significant differences between pre and post values are given as *(p < 0.05) or †(p < 0.01)

<table>
<thead>
<tr>
<th></th>
<th>MAP (mmHg)</th>
<th>CI (L/min · m²)</th>
<th>TPR (dyn sec · cm⁵ · m²)</th>
<th>PNA (ng/L)</th>
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<tbody>
<tr>
<td><strong>Group I n = 8</strong></td>
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<td>UF</td>
<td></td>
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<tr>
<td>ECC</td>
<td>94 ± 17</td>
<td>4.3 ± 0.9</td>
<td>1.82 ± 0.51†</td>
<td>356 ± 78</td>
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<tr>
<td>240 min</td>
<td>87 ± 15</td>
<td>3.1 ± 0.7†</td>
<td>2.29 ± 0.55†</td>
<td>547 ± 143†</td>
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<td>HDA</td>
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<tr>
<td>ECC</td>
<td>94 ± 17</td>
<td>4.2 ± 0.8</td>
<td>1.79 ± 0.49</td>
<td>419 ± 149</td>
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<tr>
<td>240 min</td>
<td>73 ± 17†</td>
<td>3.9 ± 0.9</td>
<td>1.52 ± 0.28</td>
<td>424 ± 205</td>
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<tr>
<td>HF</td>
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<tr>
<td>ECC</td>
<td>92 ± 13</td>
<td>4.5 ± 0.9</td>
<td>1.69 ± 0.43</td>
<td>384 ± 84</td>
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<tr>
<td>240 min</td>
<td>89 ± 18</td>
<td>3.2 ± 0.7†</td>
<td>2.29 ± 0.51†</td>
<td>492 ± 182*</td>
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<td><strong>Group II n = 8</strong></td>
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<tr>
<td>HF</td>
<td></td>
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<tr>
<td>ECC</td>
<td>87 ± 15</td>
<td>4.1 ± 1.1</td>
<td>1.76 ± 0.47</td>
<td>359 ± 157</td>
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<tr>
<td>240 min</td>
<td>86 ± 17</td>
<td>3.1 ± 1.0†</td>
<td>2.37 ± 0.67†</td>
<td>558 ± 183†</td>
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<tr>
<td>HDA</td>
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<tr>
<td>ECC</td>
<td>88 ± 22</td>
<td>3.9 ± 1.1</td>
<td>1.95 ± 0.71</td>
<td>364 ± 154</td>
</tr>
<tr>
<td>240 min</td>
<td>73 ± 14*</td>
<td>3.7 ± 1.3</td>
<td>1.64 ± 0.44</td>
<td>366 ± 151</td>
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<tr>
<td>HDB</td>
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<tr>
<td>ECC</td>
<td>88 ± 17</td>
<td>4.0 ± 1.1</td>
<td>1.93 ± 0.66</td>
<td>315 ± 141</td>
</tr>
<tr>
<td>240 min</td>
<td>79 ± 12*</td>
<td>3.6 ± 1.5*</td>
<td>2.07 ± 1.00</td>
<td>319 ± 139</td>
</tr>
</tbody>
</table>

increased significantly during UF (p < 0.01) and HF (p < 0.01). There was an insignificant rise during HDB and an insignificant decrease during HDA. At the end of treatment the difference between UF and HDA (p < 0.01) and between HF and HDA (p < 0.01) became significant. This was not the case between HDB and HF or HDB and HDA.

PNA increased significantly during UF (p < 0.01) and HF (p < 0.05), but stayed constant during HDA and HDB. At the end of treatment the differences between UF and HDA (p < 0.05), HF and HDA (p < 0.05) and HF and HDB (p < 0.05) became significant.

The mean intratreatment changes of TPR and PNA for group I and group II are given in Figure 1.

Discussion

Reduction of intravascular volume is normally sensed by the baroceptors. In compensation, both an increase in cardiac output and an increase in total peripheral
Figure 1. Change of TPR and PNA during treatment in group I (UF, HF, HDA) and group II (HF, HDA, HDB). Intratreatment significant change is given as *(p < 0.05) or **(p < 0.01)
resistance occur in an effort to maintain a stable blood pressure. This regulatory mechanism is mediated by the autonomic nervous system which is reported to be defective in uraemic patients [5]. From results obtained in this study we would conclude that the entire arc of autonomic nervous circulatory regulation is qualitatively intact in ESRD patients on RDT. In regard to the adequacy of quantity of response no conclusion can be drawn from this study. The qualitatively adequate response to volume removal with increase of TPR and PNA was found in UF and HF. During haemodialysis, regardless of whether HDA or HDB was performed, this autonomic nervous regulatory mechanism is impaired, resulting in a lack of increase in PNA and an inadequate rise in TPR. Clinically this is noticed as a tendency to hypotensive episodes and shock.

The site and mechanism of interference of haemodialysis with the autonomic nervous system cannot be clarified by our experiments. Membrane dependence [6] seems to be unlikely, because in experiments in which identical membranes were used (UF and HDA), the discrepancy in sympathetic response was rather evident.

The importance of catecholamine loss, which was suggested as a possible cause for the impaired sympathetic response during haemodialysis [7], can be excluded, because small molecule removal rate (urea) was matched between HF, HDA and HDB.

Acetate as a cardiodepressant and vasodilating agent [8] can also be excluded as the main causative factor for impaired sympathetic response during haemodialysis, because acetate was used in dialysate during HDA as well as in infusate during HF.

One possible explanation why patients on HF show the physiological response to volume removal whereas the same patients on HDA or HDB lack this reaction, might be related to the physical differences in solute transport [9], removal of the higher molecular substances during HF but not during HDA and HDB. However this argument is not supported by the UF experiments, where an adequate sympathetic response was observed in spite of rather insignificant solute removal of higher molecular weight substances.

The clinically observed improved tolerance to volume removal during HDB [10,11] could also be verified by our results. MAP did not fall to the same degree as observed during HDA. This might be explained by the opposite change of TPR in spite of an identical lack in sympathetic response, a slight increase during HDB and a decrease during HDA. Although both changes per se were not significant, the additive effect of both might be the reason for the better tolerance to volume removal during HDB.

The small increase in TPR during HDB without increase in PNA might be the result of an improved receptor response at the end of haemodialysis [12], whereas the decrease of TPR during HDA could possibly be explained by the vasodilating effect of acetate [8]. Studying the differences between HDA and HDB in a larger number of patients and at higher volume removal and solute exchange rates might help to clarify this problem. For clinical purposes it must be stressed that HF is the haemodynamically most stable form of ESRD treatment, it is certainly superior to HDA and also to HDB. Presently the cause for impaired sympathetic response during haemodialysis remains unknown.
Acknowledgment


References

12. Rowoff MS, Campese VM, Lane K, Massry SG. *Kidney Int* 1978; 14: 731

Open Discussion

WALLS (Leicester) We have been doing similar studies using ultrafiltration in sequential ultrafiltration diffusion experiments and measuring cardiac output with the echocardiograph. With a percentage decrease in plasma volume of 20% we get similar data to yours but I do notice in your abstract that the heart rate does not increase during ultrafiltration nor during haemofiltration. Would you like to comment on that in view of your postulate that this is increased sympathetic activity, because the corollary is that during haemodialysis when you have a fall in blood pressure and a fall in cardiac output and total peripheral resistance, you develop a tachycardia?

BALDAMUS This is a well known phenomenon that you find an increase in pulse rate in acetate dialysis which you do not see to that extent in haemofiltration. An explanation, however, is lacking. Whether there is also an increase in adrenaline which might result in an increase in pulse rate I cannot tell you.

HAMPL (Berlin) We found the same haemodynamic stability in bicarbonate dialysis as in haemofiltration and we found balanced acid-base values during bicarbonate dialysis compared with acetate dialysis, and CO₂ loss is avoided during treatment with bicarbonate. Stable arterial pCO₂ seems to be very important to keep a stable circulation, that means to have a high peripheral resistance, because there is a sensitivity to change in arterial pCO₂ in the response to catecholamines.

BALDAMUS I cannot explain the difference between your results without having analysed your data.
There was better haemodynamic tolerance to volume removal in bicarbonate dialysis when comparing it to acetate haemodialysis, resulting in differences in MAP and TPR. However there was no change in catecholamine levels indicating other factors which possibly interfere with total peripheral resistance. Whether pCO₂ is one of these I cannot tell you.

CHVATIKOVA (Prague) How many patients had heart failure in your group? We investigated 11 patients after ultrafiltration and we found different haemodynamic responses in patients with and without heart failure. In patients without heart failure our results were the same as yours but in the group of patients with severe heart failure we found after ultrafiltration an increase of cardiac output and stroke volume and decrease in total peripheral resistance. It is possible to explain it by Starling’s principle but is there any difference between these two groups of patients in the response of the sympathetic nervous system to ultrafiltration?

BALDAMUS From the clinical point of view none of those patients investigated was a cardiac insufficient patient and the group seemed to be homogenous in regard to cardiac performance. We did not investigate cardiac insufficient patients specifically, and I am unable to explain your results.

SHALDON (Montpellier) Firstly I have to disagree with Dr Hampl and support Dr Baldamus because using a different method for cardiac output we have published, quite independently, virtually identical results in haemodialysis, bicarbonate or acetate and haemofiltration, acetate and bicarbonate. The only difference was that our urea clearances were about 30% higher than yours and we saw an increase in the pulse rate during haemofiltration with acetate but not with bicarbonate, so that I think that a lot of this must depend on the type of systems that we are using and I think we should define our systems more before we say bicarbonate does this or acetate does that. I think Dr Hampl’s work bears no relationship to ours in experimental design at all. If I may be so bold, I don’t think you can talk about recirculated Redy cartridge bicarbonate dialysis when there are so many other variables occurring which are not controlled, and compare to single pass dialysis. Would you care to speculate on why this difference occurs? Do you feel that it is more something that diffusion is producing rather than something filtration is preventing?

BALDAMUS I would guess that the physical difference in solute transport between haemofiltration and dialysis in regard to molecular size seems to be very unlikely to be the only explanation. In ultrafiltration where we just removed volume but did not change the concentration of a hypothetical toxic substance we found a very good haemodynamic stability. If you want to interpret the described data as being due to removal of a high molecular weight substance then you would need to speculate that it is generated during the process of solute removal. It would be cleared then in haemofiltration but not in haemodialysis.

ZUCCHELLI (Bologna, Italy) Because in haemodialysis with acetate you have a greater decrease in blood pressure you might have a greater increase in plasma noradrenaline so why do you think that there is no difference in plasma noradrenaline removal? You might have more stimulation in sympathetic activity, so the difference in plasma noradrenaline need not be related to difference in removal.
BALDAMUS I would agree with you that the lower the blood pressure the higher one would expect the PNA to rise. However this is not the case in haemodialysis. Regarding PNA removal, the absolute amount removed can be different in both treatments, and it is dependent on the PNA concentration. So far I agree. However, I am talking about a matched removal rate of PNA for all treatments. This is the only way that a change in PNA release would be reflected by a change in PNA concentration.