STRUCTURAL AND ULTRASTRUCTURAL PERITONEAL MEMBRANE CHANGES AND PERMEABILITY ALTERATIONS DURING CONTINUOUS AMBULATORY PERITONEAL DIALYSIS

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Summary

Normal and abnormal structure of the peritoneum is described in biopsies obtained from 15 cadavers and 13 patients on continuous ambulatory peritoneal dialysis (CAPD) at the onset of their treatment and after several months. In a few patients a loss of ultrafiltration due to a higher permeability of the peritoneum for glucose was observed. This hyperpermeability seems to be due to a patchy or total destruction of the mesothelium; it seems also to be dependent upon the thickness of the fibrous band separating capillaries from the peritoneal cavity. The endothelium of capillaries was normal in all the specimens examined.

Introduction

Continuous ambulatory peritoneal dialysis (CAPD) is now recognised as an efficient treatment of chronic renal failure. However modifications of permeability are sometimes observed and their mechanisms remain unclear. We performed peritoneal biopsies to correlate alterations of the peritoneal membrane structure with its permeability.

Materials and methods

Forty-five samples were taken from parietal, mesenteric and intestinal peritoneum of 15 cadavers during autopsies.

Thirteen patients who had been fully informed and consented underwent 17 peritoneal biopsies: 5 patients only at the onset of CAPD, 3 patients at the onset and one year later, one patient at 17 months during appendicectomy and at 23 months during catheter removal, 4 patients after one year of treatment.

All these specimens were examined on light microscopy and five by electron microscopy. The thickness of the submesothelial fibrous band separating capillaries from mesothelium and the peritoneal cavity was measured: on each sample 10
random areas were measured with a scaled Leitz ocular and an average value calculated.

In 10 patients, during a 6 hour dwell exchange, 100ml dialysate were withdrawn and reinstilled every half hour; each time 10ml were sampled from this volume and analysed for sodium, urea and glucose concentrations. Plastic bags were weighed before and after dwell time. Dialysate/plasma (D/P) ratio was calculated for urea every 30 minutes. Blood urea concentration was taken as a mean of values obtained at the beginning and at the end of the study period. Glucose uptake from dialysate was calculated as the difference between the total amount of glucose infused and the total amount of glucose withdrawn.

Results

Membrane permeability evaluation

Among the 13 patients studied 3 had a low filtration rate or even a massive reabsorption of dialysate (case G) which we called ‘negative filtration rate’.

Glucose uptake from dialysate was much higher (70mg ± 2.7 with 3.86% Dianeeal solution) in patients with a low filtration rate than in patients with a high filtration rate (53.2g ± 8.7). The concentration of sodium in dialysate decreased to a very low value (118mEq ± 5) in the high filtering patients; this was due to free water removal and was not observed in the other patients (Table I).

Highest dialysate plasma ratio was more quickly reached with more hypertonic solutions; but in the patient with a ‘negative’ filtration rate this ratio was reached even earlier. In this last patient dialysate protein losses were 6g per day, that is to say, in the same range as our other patients.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Sodium</th>
<th>Dextrose</th>
<th>Patient with low filtration rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>132.8 ± 1</td>
<td>211 ± 12</td>
<td>132</td>
</tr>
<tr>
<td>30</td>
<td>124 ± 5</td>
<td>168 ± 47</td>
<td>130</td>
</tr>
<tr>
<td>60</td>
<td>119.5 ± 4</td>
<td>136.7 ± 31</td>
<td>131</td>
</tr>
<tr>
<td>90</td>
<td>119 ± 7</td>
<td>117 ± 29</td>
<td>132</td>
</tr>
<tr>
<td>120</td>
<td>118 ± 5</td>
<td>109.8 ± 33</td>
<td>133</td>
</tr>
<tr>
<td>150</td>
<td>118.5 ± 5</td>
<td>97.1 ± 29</td>
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<td>87.8 ± 26</td>
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<tr>
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<td>118.7 ± 3</td>
<td>73.4 ± 27</td>
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</tr>
<tr>
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</tr>
<tr>
<td>300</td>
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<td>64.5 ± 21</td>
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<tr>
<td>330</td>
<td>121 ± 4</td>
<td>59.5 ± 21</td>
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</tr>
<tr>
<td>360</td>
<td>122.5 ± 5</td>
<td>54.9 ± 18</td>
<td>139</td>
</tr>
</tbody>
</table>

TABLE I. Dialysate sodium and dextrose concentration in peritoneum (in mmoles/L) every 30 minutes using 3.86% Dianeeal solution

200
Microscopic structure of peritoneum in normal subjects

The peritoneal structure was similar in cadavers and in patients at the onset of CAPD: it is made up of a single bed of mesothelial cells separated from the underlying capillaries by a thin fibrous band. This submesothelial fibrous band is only clearly visualised on the mesenteric peritoneum where it is well differentiated from the underlying fat tissue. The average thickness of this superficial fibrous tissue (SFT) was 21 ± 8 microns. The distance from the most external capillary to the peritoneal cavity was 24 ± 6 microns.

Microscopic structure of peritoneum in patients on CAPD

In most patients there was no inflammation: hypervascularisation was frequently observed. Capillaries, as opposed to what one observes in normal subjects, were inside the submesothelial fibrous band, but their structure was normal on both optic and electron microscopy.

Signs of peritonitis were observed in only one patient who was suffering from appendicitis. A biopsy of parietal peritoneum showed absence of mesothelium, exudative lesions and hypervascularisation. Nine months later a second biopsy was performed during catheter removal for inadequate ultrafiltration and the degree of hypervascularisation was less but again no mesothelium could be seen.

Quantitative study

Measurement of superficial fibrous tissue thickness (SFT) was only possible on mesenteric peritoneum.

Six patients dialysed for more than one year had normal or patchy mesothelium on parietal and mesenteric peritoneum; mesenteric SFT was 60 ± 14 microns. Their filtration rate was normal.

One patient who had been dialysed for 3 days had parietal mesothelium but no mesenteric mesothelium. Mesenteric SFT was 40 microns and his filtration capability was normal.

One patient who had had peritonitis at the onset of dialysis had a peritoneal biopsy one week later. He had parietal but no mesenteric mesothelium. Mesenteric SFT was 24 microns. His filtration rate was low.

One patient had no mesothelium on parietal, mesenteric and intestinal peritoneum. Mesenteric SFT was less than 10 microns. He had lost his filtration capability; he also had massive reabsorption of dialysate throughout the dwell exchange (Case GR).

One patient had no parietal, mesenteric and intestinal mesothelium and her mesenteric SFT was 96 microns. Her filtration rate was low, but filtration was maintained.

In all the patients, the distance from the most external capillary to the surface of peritoneum was about 45 microns. In the only patient who had 'negative' filtration rate the distance was only 8 microns and there was no mesothelium.
Discussion

Loss of peritoneal ultrafiltration capability has already been described by several authors for both intermittent peritoneal dialysis [5] and CAPD [2]; it seems more frequent in children.

Our results, according to previous observations [1] show a strong increase in peritoneal permeability for glucose in patients with a very low filtration rate: at this point glucose is no longer able to play its osmotic role whatever its concentration. The fact that the highest D/P ratio was more quickly reached for urea in low filtering patients could be due to an increased permeability for small molecules. Because CAPD works 'at equilibrium' small solute clearances measured during 24 hours could appear lower due to a decreased volume drained; but the solute mass transfer coefficient measured in such patients has been shown to be normal or increased [4].

Peritoneal biopsies performed in our patients might offer an explanation for this 'opened peritoneum appearance'.

Figure 1 summarises the appearances observed in mesenteric peritoneum. Patients on CAPD rapidly develop a thick fibrous tissue under the mesothelial cells. Hypervascularisation is frequently seen. Mesothelial destruction after peritonitis or progressive disappearance of mesothelial cells is sometimes observed with persistent superficial thick fibrous tissue. Such patients have a lower filtration rate and enhanced glucose absorption. The most marked decrease in filtration rate was seen in a patient (case GR) with total destruction of mesothelium associated with a thin stretch of tissue between the vascular wall and the surface of the peritoneal cavity.

This data suggests that mesothelium is the first barrier allowing glucose to play its osmotic role: the thickening of the submesothelial tissue with enlargement of the distance separating superficial capillaries from the peritoneal cavity is a kind

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Schematic aspects of different mesenteric peritoneum. 1: Peritoneum of normal subject, 2: 'Normal' CAPD, 3: CAPD with low filtration rate, 4: Case GR (massive dialysate reabsorption). PC = Peritoneal Cavity, CT = Distance Capillary – PC, FT = fibrous band thickness
of natural defence against hyperpermeability. The fact that case GR did not have increased protein losses is in agreement with Wayland’s observation that the endothelium of microvessels is an efficient barrier to macromolecular diffusion.

We did not observe any statistical correlation between peritoneal membrane alterations and the frequency of peritonitis. In five patients we found birefringent material with polarised light microscopy. There was no cellular reaction around this material. This could be due to accumulation of plastic particles from the bags used to contain dialysate. Gandhi et al [3] looked for such material and did not find any in four patients treated by IPD and one on CAPD.

Conclusions

Most patients on CAPD have a thickening of their peritoneal submesothelial tissue. The loss of ultrafiltration capability observed in some patients is due to hyperpermeability to glucose. This hyperpermeability is associated with patchy or total mesothelium destruction and is dependent upon both the distance separating capillaries from peritoneal cavity and the degree of vascularisation. Endothelium of capillaries was not damaged in our patients either on optic or electron microscopy examination. Membrane hyperpermeability to proteins seems not to be seen as long as capillary endothelium is intact. The causes of peritoneal membrane alterations are still unknown; peritonitis, permanent hypertonic solution and foreign material deposits may be involved to different extents. The future of CAPD seems to depend more upon a possible loss of membrane convective capacity than a loss of diffusive possibilities.

Acknowledgment

We warmly thank our colleague Dr B Perrone for his efficient collaboration and Miss J David and Mr F Bernard for their technical assistance.

References

1 Canaud B, et al. *Néphrologie 1980; 1, 3:* 126
2 Farrell PC, Randerson DH. *Trans ASAIO 1980; XXVI:* 197
4 Randerson DH, Farrel PC. In *Seventh Australian Conference on Chemical Engineering 1979;* 36
Open Discussion

GAHL (Chairman) I think it may be difficult to obtain informed consent for this procedure, but I think this is exactly the basic work which we need for our understanding of peritoneal dialysis. Could you tell us something about the technique of the biopsy?

VERGER In all the patients the first biopsy was performed at the onset of CAPD; when we put the catheter in we had a small piece of peritoneum; the second biopsy was performed either during catheter removal or catheter changes and during the laparotomy we took a 1 sq. cm piece of mesenteric and parietal peritoneum. We took a piece of the mesenteric peritoneum because it is the only one which is easy to observe. All these peritoneal biopsies were performed either under local anaesthetic or general anaesthetic depending on the patient. We did not have any complications after these peritoneal biopsies.

ING (Hines, Illinois) You have done an excellent piece of work. We have encountered several examples of what is known as sclerotic peritonitis among patients treated with intermittent peritoneal dialysis. Our findings were similar to those of the most severe case that you have just presented, with marked thickening and hardening of the peritoneal membrane. We have also measured serial peritoneal creatinine clearances on some of our patients and have found them to be markedly decreased. Some of our results have been published in Archives of Internal Medicine 1980; 140: 1201.

VERGER Do you mean that you have observed a decrease of the peritoneal clearances for creatinine in some patients with the loss of ultrafiltration?

ING No, I did not say with loss of ultrafiltration. Histologically, we found thickening and sclerosis of the peritoneal membrane in several patients maintained with peritoneal dialysis done by the intermittent method. The pathological changes were similar to the ones that you showed in the last slide. We also performed serial measurements of creatinine clearances across the peritoneal membrane. These measurements were found to be decreased.

VERGER Yes, but did you measure exactly the amount of dialysate in and out because if you have a decrease of the dialysate volume of course the total clearance during a six or four hour exchange is decreased. What is important to check is not the peritoneal clearances for creatinine but the transfer coefficient.

ING Yes I know. I just would like to convey the fact that we have observed similar changes in terms of pathology.

LEWIS (Ulm, FRG) Do you think it would be of consequence to suggest the use of polysaccharides or some larger molecules rather than glucose in the dialysate to promote ultrafiltration, rather than glucose which seems to go through the membrane?
VERGER  To use another osmotic agent?

LEWIS  Yes, a much larger molecule. It seems a logical conclusion from what you have stated today.

GAHL  What do you feel is the best place for biopsy and does it make any difference which part of the peritoneum you biopsy? Is there any difference if you biopsy the parietal peritoneum or the visceral peritoneum? I think it is less dangerous to biopsy certain parts of the peritoneum than others.

VERGER  The most interesting answers are obtained when you biopsy the mesenteric peritoneum.