PERITONEAL DIALYSIS: PHYSIOLOGY, CURRENT APPLICATIONS AND FUTURE DIRECTIONS

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Peritoneal Dialysis – A Capillary Kidney?

The net removal of solutes during peritoneal dialysis is assumed to result primarily from the net movement of solutes from peritoneal capillaries into the peritoneal cavity [1]. Clinical findings to support this hypothesis include 1) solutions in the peritoneal cavity approach Gibbs-Donnan equilibrium with plasma [2], 2) peritoneal clearances decrease with shock [3,4], 3) peritoneal clearances can be altered with vasoactive drugs [5,6]. Contributions of solutes from mesothelial lining cells and lymphatics are unknown but are thought to be of minor importance due to the small size of the total solute pool in mesothelium and the relatively slow flow through lymphatics.

Factors Limiting Solute Transport During Peritoneal Dialysis (Figure 1)

Table I lists features of the dialysis system which may limit solute transport during peritoneal dialysis. Many additional factors which may influence transport have been reviewed elsewhere [7,8]. The net removal of solutes of large or small size may be limited by the sparsity of capillaries [9]. Arterioles and capillaries small enough to participate in exchange may be confined primarily to the reflection of mesentery over loops of bowel [10]. Visceral mesentery does not contain a dense capillary network. The work of Karnovsky suggests that solutes up to a molecular weight of 30,000 may move primarily through capillary intercellular channels [11]. According to Pappenheimer, such a pore area would represent less than 0.2% of the endothelial surface. If these are the effective pores of the peritoneal membrane, a very low pore area is likely.

Maximum clearance for any solute in the absence of ultrafiltration can be represented as total pore area over the sum of resistances. At least six anatomical resistance sites can be listed as in Table I. Large solutes may have major difficulties traversing capillary endothelial intercellular channels ($R_2$). Smaller solutes may be limited by pore area, but not so much by effective pore size. In fact, Popovich has recently predicted that for smaller solutes interstitial fluid film
resistance could be major [13]. The resistance offered by mesothelial intercellular channels (presumably the mesothelial pores) is unknown. Some animal studies suggest this is of minor importance [14]. The stagnant nature of fluid in the peritoneal cavity can offer another major fluid film resistance [13].

Solute movement may be primarily convective across R₁, R₂, and R₃ due to capillary hydrostatic physiological ultrafiltration [15]. Movement through R₄, R₅, and R₆ may be primarily diffusive. Ultrafiltration may add a convective component to movement across R₄ [16]. Certainly vigorous mixing of fluid in the peritoneal cavity may alter R₆ and add a convective component to solute.
distribution within the peritoneal fluid [13]. It is not known whether osmotic induced ultrafiltration represents mobilisation of interstitial fluid and prevention of the reabsorption of physiological capillary ultrafiltrate or, in contrast, actual increases in net ultrafiltration from peritoneal vessels.

Work in animals and man based on gas diffusion suggests that capillary blood flow offers modest, if any, limitations to solute clearances during peritoneal dialysis [1,3]. This could be important in severe shock with marked decreases in perfusion of peritoneal capillaries. Certainly very low dialysate flow rates can limit clearances [17]. At flow rates in excess of 4L/hr urea clearances begin to approach a maximum value of 30–40ml/min [17]. Ultrafiltration with hyperosmolar solutions can increase clearances due to enhancement of convective transport and possible effects of hyperosmolar solutions on the number of capillaries perfused (pore area) and on permeability [16].

**Behaviour of the Peritoneal Microcirculation as Suggested by Animal Studies (Figure 2)**

![Diagram](image)

**Figure 2.** (Published with permission of Kidney International) Hypothetical peritoneal microcirculatory changes based on rat studies are summarised diagrammatically (see text)
Recent studies of the peritoneal microcirculation have been reported elsewhere and will be summarised briefly [9,10,13]. First, all commercial solutions appear to be vasoactive when applied topically to rat tissue [10]. In the rat cremaster, they induce transient severe vasoconstriction (3–5 minutes) followed by marked vasodilatation. In the rat caecal mesentery they induce vasodilatation without vasoconstriction [18]. Secondly, a direct acting vasodilator such as nitroprusside prevents initial vasoconstriction in the rat cremaster and produces vasodilatation similar to that seen with commercial solutions once it occurs [10]. Thirdly, nitroprusside containing solutions appear to induce greater degrees of venodilatation and greater increases in the permeability of small venules than do commercial solutions [13]. Very large solutes such as protein may leave the vessels primarily through small venules [19]. Fourthly, those components which appear to account for the vasodilatory effects of commercial solutions, are hyperosmolality and the presence of a non-bicarbonate buffer anion [20]. The vasoconstrictive factor has not been identified. Fifthly, all vasodilatation whether induced by commercial solutions or nitroprusside appears to be associated with increased numbers of capillaries perfused (increased total pore area) and some degree of venodilatation [10]. According to Renkin, capillaries perfused in vasodilated states are more permeable [15]. Venodilatation also may increase permeability [19].

Thus we can begin to understand why intraperitoneal nitroprusside in humans mainly increases large solute clearances and protein losses with only modest increases in small solute clearances [9]. By the mechanisms listed above, nitroprusside may increase area and permeability. Flow per capillary may increase only modestly or actually decrease with vasodilatation and have modest to no effects on solute clearances at any time.

Ways to Increase Peritoneal Dialysis Efficiency

Numerous investigators are exploring the potential for using systemic or intraperitoneal vasodilators. Vasodilators may increase the number of capillaries perfused and, thus, increase pore area. By opening more permeable capillaries or increasing venular permeability, vasodilators may decrease $R_1$ and $R_2$ which are probably of major importance in terms of resistance to the net removal of large solutes. Vasodilatation may increase capillary blood flow, but this will probably have little impact on clearances.

The highest small solute clearances possible will be achieved only with rapid cycling (greater than 4L/hr). Rapid cycling and better mixing may also decrease $R_6$. Nevertheless, small solute clearances will probably always be quite limited due to some minimal unalterable $R_4$ resistance. Hypertonic exchanges may cause both vasodilatory effects and convective enhancement of solute transport. Recent studies with alternating hyperosmolar and hypo-osmolar solutions show that clearances are increased during both hyperosmolar and hypo-osmolar exchanges [21]. Mechanisms for sustained clearance increases with hypotonic exchanges are not clear.

In summary, it is likely that small solute clearances during peritoneal dialysis
will always be relatively low compared with what can be accomplished by haemodialysis or haemofiltration. Larger solute clearances and protein losses may be proportionately much more susceptible to manipulation.

A New Approach — Continuous Ambulatory Peritoneal Dialysis (CAPD) — A Trade Off of Efficiency for Time

Continuous ambulatory peritoneal dialysis (CAPD) utilises continuous peritoneal dialysis 24 hours a day, 7 days a week [22–24]. Patients usually do 4 exchanges per day. Exchanges are 4–6 hours in duration during daytime hours and near 8 hours overnight. Dialysis solutions containing 4.25% dextrose may be used as required to control sodium and water balance. Detailed descriptions of the CAPD technique have been described elsewhere [22–24].

At the University of Missouri we have now had over 2½ years experience with the CAPD programme. For the first two years our experience was based on the experience with dialysis solution in bottles. The technique with bottles is much more cumbersome and risky than with solutions in plastic bags. For the last six months we have begun to accumulate experience with plastic bags. We have trained a total of 24 patients to carry out CAPD. Six of these patients have now been on CAPD for over 1 year and 3 of these for over 2 years. I will herein list those questions initially raised by CAPD for which I think there are at least preliminary answers. I will also list those questions which will demand our future attention (Table II).

<table>
<thead>
<tr>
<th>Impressions</th>
<th>Questions</th>
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<tr>
<td>1 Steady state control of BUN, Cr, Ca, P, Hct, electrolytes</td>
<td>1 Minimum incidence of peritonitis? Best Connector?</td>
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<tr>
<td>2 Clinical status of patients seems good</td>
<td>2 Intraperitoneal protein supplementation when necessary?</td>
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<tr>
<td>3 Nerve conduction stable</td>
<td>3 Non absorbable osmotic agent? Ways to decrease carbohydrate absorption?</td>
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<tr>
<td>4 Peritonitis 2–3 episodes per year; with bags probably can be reduced</td>
<td>4 Control of hypertriglyceridaemia?</td>
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<td>5 BP usually easily controlled</td>
<td>5 Safe antiseptic solutions?</td>
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<td>6 Residual renal function can be minimal</td>
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<td>7 Protein losses tolerable</td>
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<td>8 No immunoglobulin depletion</td>
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<td>9 Minimal cardiovascular stress</td>
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<td>10 Reasonable control of glucose in diabetics possible</td>
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Some of my impressions to date can be summarised as follows:
1 CAPD has provided control of BUN, creatinine, electrolytes, and other
routinely monitored parameters in ranges most would consider acceptable. BUN's usually run 50–70mg%, creatinine 10–12mg%, and haematocrit 28–30 without androgens. The control of calcium and phosphorus has been excellent and in many patients serum PTH values have decreased.

2 From the standpoint of clinical well being, most patients seem to feel well most of the time.

3 Nerve conduction velocities so far remain stable.

4 With bags, the incidence of peritonitis can be reduced to 2–3 per year per patient in contrast to 6 or more per year per patient with bottles. With recent innovations such as changing connecting tubing only during clinic visits and with the anticipated arrival of new connectors, I think the infection problem can be reduced even more.

5 In most patients blood pressure control on CAPD is easily accomplished, often without medication.

6 All but one of our patients have had residual creatinine clearances less than 1ml/min and 19 less than 0.5ml/min. Adequate therapy with CAPD appears possible at very low levels of residual renal function.

7 Mean protein losses with 4 exchanges per day based on 79 twenty-four hour collections in 16 patients were 12.2 ± 0.4 (SEM) grams/day (range 3.6–20). On a protein intake of 1g/kg patients maintain weight, total body potassium, serum total proteins and serum albumin in the acceptable range and thus appear adequately to replace losses.

8 In our studies there has been no evidence for depletion of immunoglobulins.

9 Patients who have had severe problems with hypotension during haemodialysis usually tolerate CAPD. In general, the slow continuous nature of CAPD may have advantages for all patients especially those with cardiovascular instability.

10 The control of blood sugar in patients with diabetes mellitus has not been difficult with subcutaneous insulin in diabetic patients on CAPD.

Challenges in CAPD that deserve our future attention can be listed in part as follows:

1 There are some patients (6 in our programme) who have never had peritonitis with bags on CAPD. This suggests that peritonitis is almost invariably secondary to breaks in technique. The development of human-proof connectors could make peritonitis a rare event in CAPD.

2 Patients with alcoholism, denture problems, or other problems preventing adequate protein intake cannot be maintained on CAPD. The possibility of administering adequate protein through the peritoneum needs further exploration.

3 In our experience, patients using four 1.5% dextrose exchanges per day will absorb approximately enough glucose to generate 350 calories. Patients using four 4.25% dextrose solutions (a rare requirement) could absorb the equivalent of 850 calories per day. Patients who tend to eat excessive amounts of carbohydrate often also consume the greatest amounts of sodium and water. These patients then often elect to use more 4.25% dextrose solutions. Combined excessive consumption and peritoneal absorption of carbohydrate in some patients may result in undesirable weight gain and obesity. A non-absorbable osmotic
agent would offer many advantages for some patients. The potential of using electrolytes trapped in dialysis solution by large polymers needs further exploration [25].

4 Serum triglyceride is elevated in most patients; markedly so in some. This problem could possibly be helped by the use of a non-glucose osmotic agent, better attention to oral carbohydrate intake, and the initiation of exercise programme. Better understanding of the pathophysiology of the hypertriglyceridaemia and its treatment are needed.

5 Some centres are experimenting with irrigants containing low iodine concentrations (2 parts/million) [26]. The use of a non-antibiotic sterilising non-toxic solution following obvious contamination has appeal. Antibiotic prophylaxis always raises the possibility of the development of infections due to resistant organisms. Safe, effective antiseptic prophylaxis might be of value.

**Summary**

The peritoneal dialysis system is a sophisticated dialyser. It probably represents a capillary kidney regulating the number of capillaries perfused, the nature of capillaries perfused, and the overall permeability of its membranes. Its sophistication far exceeds that available with extracorporeal man-made haemodialysis systems. However, because of limited pore area and inaccessible fluid film resistances, it will never be an efficient dialyser for small solute removal. One way to overcome this intrinsic inefficiency is to utilise CAPD which trades efficiency for time. Our first two years of experience with CAPD have answered many initial questions, at least in a preliminary fashion. The future of CAPD has exciting potential, but many questions remain.

**References**

12 Pappenheimer, JR (1953) *Physiol. Rev.*, 33, 387

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Open Discussion

COLOMBI (Luzern) When we changed from home haemodialysis to CAPD we found it rather difficult to teach the patients to regulate their state of hydration. We felt that some patients within a few weeks get dehydrated and other patients overhydrated. On your ultrafiltration graph we can see that you have negative fluid balance over 8 hours even with the solution having 1.5% glucose. We do not have this and I know other investigators have less ultrafiltration. Can we hear something about this difference?

NOLPH The studies with intraperitoneal dextran by Drs Popovich and Moncrief suggest that ultrafiltration continues at low rates over many hours. Actual drainage suggests a peak intraperitoneal volume at 2 hours and then a steady decrease in volume at 40ml/hour. The drainage volumes are probably more truly an indication of net ultrafiltration to the patient. Differences may be explained by incomplete drainage and/or some dextran absorption. Net ultrafiltration is obtained up to 6 or 7 hours even with 1.5% solution. Now there are certain patients that certainly do not have typical drainage volumes. First, there can be mechanical problems in draining intra-peritoneal fluid pools and dilution of dialysate osmolality by mixing of fresh instillate with such pools.

Secondly if you have a diffuse decrease in permeability such as in a diabetic with widespread severe changes in capillaries, you may find more ultrafiltration. As permeability decreases the glucose becomes a more effective osmotic agent as the absorption rate of glucose is decreased.

Thirdly you may find less ultrafiltration if total area decreases because of poor fluid distribution or fibrosis and loss of membrane surface. Dr Oreopoulos describes several patients who after a successful period on CAPD later developed small drainage volumes. It is not clear which mechanisms are involved.

GAHL (Berlin) According to yours as well as our results there is a tremendous variation in protein loss in patients treated with intermittent peritoneal dialysis as compared to CAPD. Could you comment on this phenomenon?

NOLPH The number of exchanges per day appears to be important. There is almost a linear increase in protein concentration during early exchange hours but the rate of increase does slow after six hours. If you use a series of more
rapid short exchanges you might be working in the area of steeper slope and get
greater protein loss per hour. That is why protein losses increase with more ex-
changes per day. Also, with intermittent peritoneal dialysis there are higher con-
centrations of protein in early exchanges of each treatment session.