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EDITORIAL REVIEW

Determinants of low clearances of small solutes during peritoneal dialysis

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Peritoneal dialysis plasma clearances of large molecular weight solutes such as inulin (5,200 daltons) usually equal or exceed plasma clearances of such solutes seen with extracorporeal dialyzers, [1–4]. Clearances of smaller solutes such as urea (60 daltons), however, are usually 15% or less of urea clearances with extracorporeal dialysis systems. In Table 1, typical values for clearances of urea and inulin, dialysis solution flow rate (Q_D), blood flow rate (Q_B), and surface area are compared for peritoneal and extracorporeal (hemodialysis) techniques. Effective peritoneal capillary blood flow rate is unknown. Gross total anatomical peritoneal surface area is estimated to be approximately equal to body surface area [2, 4].

Table 1. Comparison of typical peritoneal and hemodialysis values[a]

	C_{urea} *ml/min*	C_{inulin} *ml/min*	Q_B *ml/min*	Q_D *ml/min*	Total area m^2
Hemodialysis	150	5	200	350	1–2
Peritoneal dialysis	20	5	unknown	30	1–2

[a] Abbreviations used are: C, clearance; Q_B, blood flow rate; Q_D, dialysis solution flow rate.

Differences in small solute clearances between peritoneal and extracorporeal dialysis can be attributed in part to marked differences in Q_D [3]. Small solute clearances are dependent on blood flow and/or dialysate flow and become independent of flows (membrane limited) only at relatively high flow rates. Larger solute clearances, however, are flow-dependent only at relatively low flow rates. At peritoneal dialysis solution flow rates of 2.1 liters per 70 min (or 30 ml/min), urea clearances cannot exceed 30 ml/min and are obviously limited by Q_D. Inulin clearances, however, are well below Q_D, typically 5 ml/min, and increasing dialysis solution flow rates during peritoneal dialysis has minimal effects on inulin clearances.

With the recent renewed interest in peritoneal dialysis for the treatment of chronic renal failure, there is a parallel interest in optimizing the efficiency of small and large solute removal rates. Various techniques to increase dialysis solution flow rate in hopes of increasing small solute clearances are under study. In addition to obvious Q_D limitations on small solute clearances in peritoneal dialysis, however, small solute clearances may be limited by factors other than Q_D [1–4].

The purpose of this discussion is to review evidence suggesting limitations on small solute clearances independent of Q_D and perhaps related to total membrane resistance (for small solutes membrane resistance should represent primarily the number of functional "pores," mean pore area, rather than mean pore size, and the resistance to diffusion offered by adjacent fluid films) and/or limited peritoneal capillary blood flow.

Limitations on small solute clearances related to dialysis solution flow rate

Figure 1 relates reported peritoneal clearances of urea as measured or predicted at various dialysis solution flow rates. The clearance value at $Q_D = 30$ is the typical value reported from many series using 1.5% dextrose dialysis solutions and typical drainage volumes of 2,100 ml/70 min exchange [5]. The value at $Q_D = 200$ represents work by Tenckhoff, Ward, and Bowen with automated cycling equipment and urea clearances of 40 ml/min at $Q_D = 12$ liters/hr (200 ml/min) [6]. The values at $Q_D = 170$ and 250 represent studies by Stephen, Atkin-Thor, and Kolff using continuous dialysis solution flow through a double lumen catheter device [7]. The value at Q_D = infinity represents predictions of maximum clearances at

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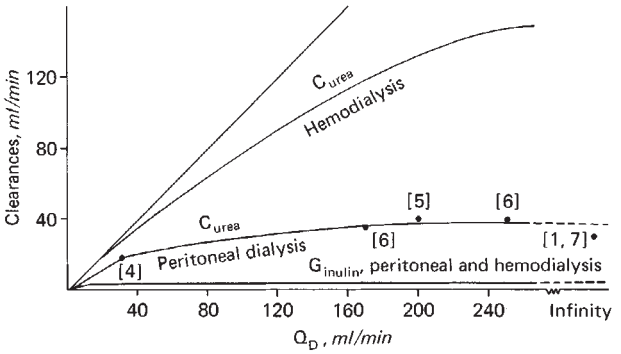

Fig. 1. *Clearances of urea and inulin related to dialysate flow (Q_D) during peritoneal dialysis.* Numbers in brackets indicate references. For hemodialysis, typical findings for many extracorporeal dialyzers when blood flow rate (Q_B) ≅ 200 ml/min are shown.

infinite Q_D (termed dialysance by Henderson and Nolph [1] and overall mass transfer coefficients by Nolph et al, and also representing the product of membrane permeability times effective membrane area [8]).

There are several reasons why predictions at infinitely high Q_D may fall below actual measurements at $Q_D > 200$. Predictions are based on data collected at low Q_D or during equilibration curves. Such calculations are based on the assumption that the overall mass transfer characteristics of the peritoneal membrane will remain fixed as Q_D increases. Rapid Q_D, however, influences the distribution of dialysate, leads to better mixing, and diminishes that portion of "membrane resistance" due to stagnant dialysate layers. Predictions also have assumed well mixed pools and have neglected possible blood flow limitations on clearances. Rapid movement of dialysis solution into and from the peritoneal cavity may, by mechanical irritation or other means, increase peritoneal effective capillary blood flow. Goldschmidt et al have shown that intraperitoneal fluid volume-membrane surface area relationships affect trans-peritoneal urea diffusion; different cycling techniques may alter these relationships [9]. Finally, clearances may include contributions of convective transport which are not included in predictions of diffusive transport at infinite Q_D.

Nevertheless, the important point to be taken from Figure 1 is that in peritoneal dialysis even at very high Q_D, measurements and predictions of clearances are well below those seen with extracorporeal dialyzers of comparable or less total surface area at comparable values of Q_D. In fact, in extracorporeal systems at Q_B = 200 ml/min, clearances of urea may reach values three or more times higher than possible in peritoneal dialysis as shown in Figure 1.

Thus, these studies to date suggest that increases in Q_D alone do not produce urea clearances comparable to those in extracorporeal systems. Although a Q_D of 30 is somewhat limiting, further increases in Q_D yield only modest increases in clearances. Other possible limiting factors that must be considered are total membrane resistance and effective peritoneal blood flow.

Possible limitations on small solute clearances secondary to total membrane resistance

Solutes diffusing from blood in peritoneal capillaries[a] into dialysis solution in the peritoneal cavity must move through three separate and distinct tissue portions of the peritoneal membrane. Solutes must traverse the endothelial layer of the capillary wall, the capillary basement membrane, and the mesothelium. The solutes must also traverse the fluid films adjacent to the endothelial and mesothelial surfaces.

The route utilized by solutes in traversing the peritoneal membrane is not clearly established. Recent studies suggest that solutes up to a mol wt of 30,000 daltons diffuse across the membranes primarily through intercellular channels [10–12]. Transport studies in isolated mesentery from animals are not in agreement as to whether the intercellular channels of endothelium or mesothelium are most limiting to solute diffusion [13, 14]. The basic membrane itself seems to offer little resistance to solute diffusion for solutes of mol wt less than 30,000 daltons [10–12, 14]. The permeability of the peritoneal membrane does not appear to be uniform. There are studies to suggest that the visceral mesentery is more permeable than the parietal peritoneum [11]. Some agents have been proposed to directly influence peritoneal permeability characteristics. For example, agents which interfere with metabolic processes in endothelial or mesothelial cells appear to influence peritoneal permeability, suggesting that cellular integrity is of importance [15, 16]. In isolated dog mesentery, the fraction of endothelium representing effective pore area approximates 4%, with a mean equivalent pore radius of 0.575 microns [14]. In rabbit mesentery, effective mesothelial pore area appears to occupy 0.6% of the surface area of the mesentery and 0.2% of parietal peritoneal surface area [16].

Since peritoneal clearances of larger solutes such as inulin and proteins are equal or greater than clearances with hemodialysis, and since peritoneal urea clearances are relatively low, Henderson argues that mean pore size may be greater for the peritoneum, but the number of pores per unit area are much less

[a] Some unknown portion of small solutes may move from peritoneal lymphatics, but for purposes of this discussion peritoneal lymphatic flow will not be distinguished from peritoneal capillary flow.

than in cellulosic membranes [2, 4]. For larger solutes, the increase in mean pore size outweighs the negative effects of a reduced number of pores, and large solute clearances are comparable to those in hemodialysis. The concept of a small number of pores with a relatively large mean pore radius is compatible with the number and size of intercellular channels in peritoneal endothelium and mesothelium, based on the morphological and functional studies in isolated mesentery mentioned above.

Thus, urea clearance could be limited by a small number of effective "pores" and, thus, low total pore area. A large mean pore radius could explain a high ratio of inulin to urea clearance.

Stagnant fluid layers may add to the total resistance to solute diffusion. Presumably dialysate works its way between multiple folds of mesentery. The average width of a dialysate "channel" is unknown. In contrast to extracorporeal dialyzers where dialysis solution flow is countercurrent to blood flow at rapid rates in narrow channels, peritoneal dialysis solution may be quite stagnant and poorly mixed in many areas and channels relatively wide. Such inefficient distribution of dialysate and poor mixing could limit small solute clearances and add to total membrane resistance.

Thus, even at infinite Q_D and infinite Q_B, urea clearances might remain well below those possible with hemodialysis because of a limited number of "pores" and/or wide stagnant dialysate fluid layers.

Possible blood flow limitations on small solute clearances

The total abdominal splanchnic blood flow in adults usually exceeds 1,200 ml/min at rest [17]. This does not include blood flow to the parietal peritoneum. If the maximum urea clearance possible at extremely high dialysate flow rates were 30 to 60 ml/min and if this were to be explained entirely by blood flow limitations, then effective peritoneal capillary flow would presumably be less than 5% of splanchnic blood flow. To Henderson it seems unreasonable that only such small proportions of total splanchnic blood flow would be involved in peritoneal exchange [2, 4]. Such blood flow limitations must be considered, however.

Most of the splanchnic blood flow traverses arteries and arterioles which eventually divide into capillary beds in abdominal viscera. The total capillary endothelial area available for exchange in the peritoneum may represent not only a small fraction of the total peritoneal surface area, but also only a small portion of all capillary beds supplied by splanchnic blood flow. Thus, the blood flow to peritoneal capillaries that can participate in solute exchange during peritoneal dialysis could be very low. Many vessels traversing the peritoneum may be larger pre-capillary vessels on their way to capillaries of the bowel, and accordingly, contributing minimally to solute exchange. It is not known how readily urea in red cells participates in trans-peritoneal exchanges, and as with extracellular solutes such as inulin, effective flow may be less than blood flow and nearer to plasma flow.

Table 2. Evidence against major peritoneal capillary blood flow (Q_B)

Limitations on C_{urea}	
Evidence	Questions and cautions
1) C_{urea} ↓ slightly (26%) with major ↓ (62%) in splanchnic flow.	*1)* Q_B may be very low and vary slightly with splanchnic flow.
2) Vasodilators increase C_{urea} only slightly (20%).	*2)* Area increases with perfusion of additional capillaries may reduce Q_B/area to blunt effects of ↑ Q_B.
3) CO_2 gas and H_2 gas overall mass transfer coefficients 2 to 3× that of urea.	*3)* Local generation and/or absorption (cells, GI tract) may influence "equilibration curves."
4) Simulated hollow fiber dialyzer studies show C_{urea} subject to major Q_B influence only < 50 ml/min.	*4)* Low Q_D in dialyzer different than stagnant dialysate in peritoneal cavity. Entirely different membranes. Rough simulation.
5) Mathematical model of peritoneal dialysis predicts major Q_B limitation only when Q_B < 50 ml/min.	*5)* Model assumes well mixed dialysate—layers adjacent to peritoneum stagnant.

It could be possible that effective peritoneal capillary flow is only about 40 ml/min, accounting for the marked limitation on urea clearance. At the present, there is no direct evidence to exclude this possibility. Many studies, however, do inferentially suggest that effective peritoneal capillary blood flow may be at least approaching the rate at which mean clearances would be mainly "membrane" limited at infinite Q_D. We will review these studies as outlined in Table 2.

Studies of reduced splanchnic flow. Arguments in favor of such a relatively high effective peritoneal capillary flow rate with only modest limitations on urea clearances include studies showing that peritoneal urea clearances during hemorrhagic shock in dogs decreased to only 74% of control, while mean arterial pressure was reduced to 38% of control [18]. Also, studies in dogs using vasoconstrictive doses of vasopressin have demonstrated significant but small decreases in clearances of small solutes [19, 20]. In rabbits, studies have suggested that urea clearances are insensitive to peritoneal blood flow variations unless a sharp reduction occurs and the flow is reduced to about 1/5 of normal [21, 22].

Caution must be exerted, however, in extrapolating from these animal studies to man. Also, it is possible that peritoneal capillary flow remains at a low fixed value even with wide fluctuations in total splanchnic blood flow. Thus, effective peritoneal capillary flow could be relatively low at all times and perhaps reduced only slightly in severe shock. These studies can be interpreted to suggest at least marginal blood flow limitations on small solute clearances in these animals.

Studies with vasodilators. There are other studies suggesting only slight blood flow rate limitations on small solute clearances. We have shown that vasodilators such as nitroprusside when added to peritoneal dialysis solution selectively increase clearances of larger solutes proportionately more than those of smaller solutes [3, 23]. This could be explained as follows. Arterioles branch into small arterioles which eventually branch into capillaries. Approximately five capillaries or more branch from given arterioles [8]. In the usual state of many tissues, it appears that less than 25% of capillaries are actually perfused [8]. Many capillaries are closed by pre-capillary sphincters and many arteriolar branches are without perfusion secondary to arteriolar tonic constriction [8, 24]. In microcirculatory studies we have shown that topically applied nitroprusside opens arterioles previously not perfused and increases the total number of capillaries perfused [3, 8]. Clearances of larger solutes would be expected to increase proportional to the increases in capillary area. Limitations of Q_D or Q_B could limit increases in small solutes. This would be particularly the case if increases in capillary endothelial area were proportionally greater than total flow increases into the splanchnic system and flow per area decreased.

We have also found that overall mass transfer coefficients (predicted clearances at infinite Q_D) may increase proportionately more for larger solutes with the addition of nitroprusside to peritoneal dialysis solutions [8]. Again, the overall mass transfer coefficients were calculated to reflect the product of permeability times area, and assume no Q_B limitation. If it is assumed that the capillary area available for solute exchange is the same for large and small solutes, then increases in endothelial area should have proportional effects on mass transfer coefficients regardless of molecular weight. Selectively greater increases for larger solutes could be explained by associated increases in permeability (which cannot be excluded) or some Q_B limitations on small solute overall mass transfer coefficients as calculated (usually assuming infinite Q_B). Until Q_B and the effects of varying it are known, measurements of overall mass transfer coefficients assuming no Q_B limitations cannot distinguish permeability changes from area changes. Nevertheless, studies described below infer that Q_B has little influence on urea mass transfer coefficients in man.

Another limitation on comparing changes in mass transfer coefficients for solutes of differing molecular weight has to do with corrections for convective transport. Larger solutes may accompany bulk water flow in amounts per volume of ultrafiltrate less than the respective plasma concentration. The ratio of amounts removed by convection per ml of ultrafiltrate to plasma concentration is the net sieving or transmittance coefficient [1, 8]. Such values for the human peritoneum are only available from a very limited number of studies [1]. We have previously shown, however, that large errors in the choice of transmittance coefficients for calculation of mass transfer coefficients could not eliminate selectively greater increases in mass transfer coefficients for larger solutes with vasodilators [8].

Thus, vasodilators increase small solute clearances only slightly. Increases in mass transfer coefficients suggest that clearance increases represent increases in area and/or permeability rather than increases in Q_B. With vasodilators, increases in total capillary area and permeability appear to be of more consequence than increases in capillary flow. Unless Q_B per area does not increase substantially, vasodilator effects imply only modest Q_B limitations on small solute clearances.

Studies of gases. Another technique to estimate peritoneal effective capillary flow has to do with determinations of overall mass transfer coefficients for solutes which diffuse even better than urea. Current techniques for calculating overall mass transfer coefficients (clearance at infinite Q_D) would truly be more indicative of Q_B (rather than true membrane resistance) if limitations of Q_B are of major importance. If Q_B is 30 to 40 ml/min, for example, overall mass transfer coefficients for solutes even more diffusible than urea (such as gases) should approach the same maximum value as for urea, near 34 ml/min [1, 8]. If Q_B is only 30 to 40 ml/min, then mass transfer coefficients for even gases as currently calculated should not exceed this value [8].

One solute which has the potential for very rapid diffusion is carbon dioxide gas. We have studied carbon dioxide diffusion during clinical peritoneal dialysis.

Figure 2 shows mean changes in pH, P_{CO_2}, and bicarbonate during six exchanges in a single patient with commercially available 1.5% dextrose dialysis solution. Dialysate was sampled frequently during dwell periods. The increase in P_{CO_2} is extremely rapid. In fact, it overshoots even the value of an

overnight equilibrated P_{CO_2}. This obviously does not represent simple diffusion of carbon dioxide into the peritoneal dialysis solution. Commercially available peritoneal dialysis solutions have hydrochloric acid added prior to sterilization to prevent carmelization of glucose. Initial pH values are very low. Bicarbonate diffusing from peritoneal capillaries to dialysis solution will be initially converted in part to carbon dioxide and water. Thus, the rapid steep rise and overshoot for P_{CO_2} reflect some local intraperitoneal carbon dioxide generation.

Figure 3 shows the similar measurements if sodium hydroxide is first added to the peritoneal dialysis solution to bring the pH above 7. P_{CO_2} now rises less rapidly, and neglecting any local generation of carbon dioxide in solution or by peritoneal walls, as well as losses of carbon dioxide gas that dissolves in solution (some of which is converted to carbonic acid), the results represent more nearly the diffusion of carbon dioxide gas into peritoneal dialysis solution. Determinations of mass transfer coefficients for carbon dioxide gas from such data in three studies yielded mass transfer coefficients ranging from 68 to 82 ml/min. These are substantially above respective values for urea overall mass transfer coefficients and clearances and suggest that effective peritoneal capillary flow, Q_B, is well above the clearance of urea.

These results in man analyzing carbon dioxide diffusion are similar to the findings of Aune measuring hydrogen gas clearance from (rather than into) peritoneal dialysis solution in rabbits [21]. Hydrogen clearances during circulatory arrest (4.0 to 9.2 ml/min), presumably representing mainly hydrogen diffusion into fat, intestinal contents, and other nonvascular compartments were subtracted from the total clearance (14.8 to 33 ml/min) with the cardiovascular system intact. The mean difference of 17.04 ml/min (termed blood flow clearance) was compared to a mean plasma urea clearance of 2.75 ml/min and a mean urea "permeability coefficient" of 2.96 ml/min.

Both the carbon dioxide studies in man and the hydrogen studies in rabbits are subject to many questions. Gas movement may be transcellular through endothelium and mesothelium and across arteriolar walls as well as capillaries—thus, more total membrane area may be available. Tissue generation or

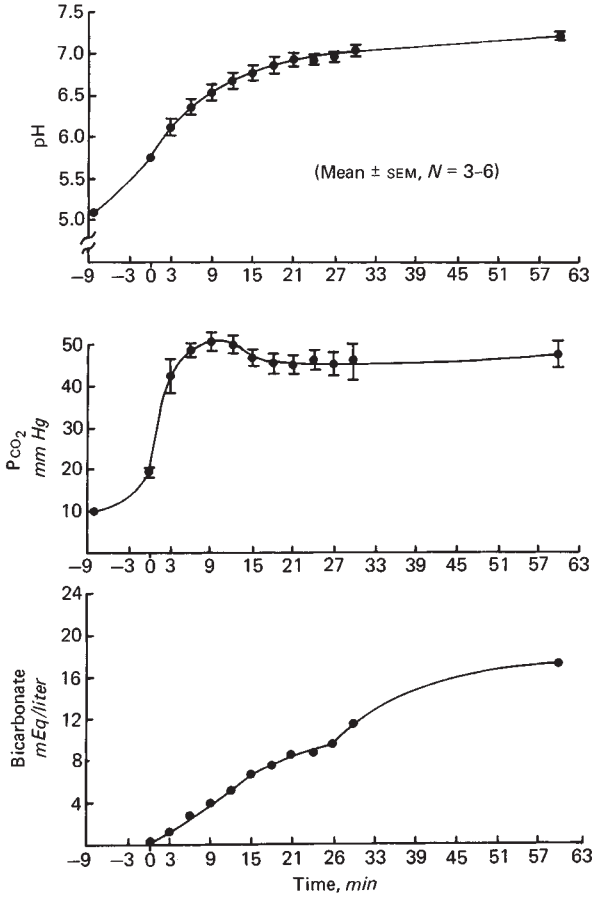

Fig. 2. *Mean dialysate pH, P_{CO_2}, and calculated bicarbonate related to time from completion of instillation during six exchanges in one patient.*

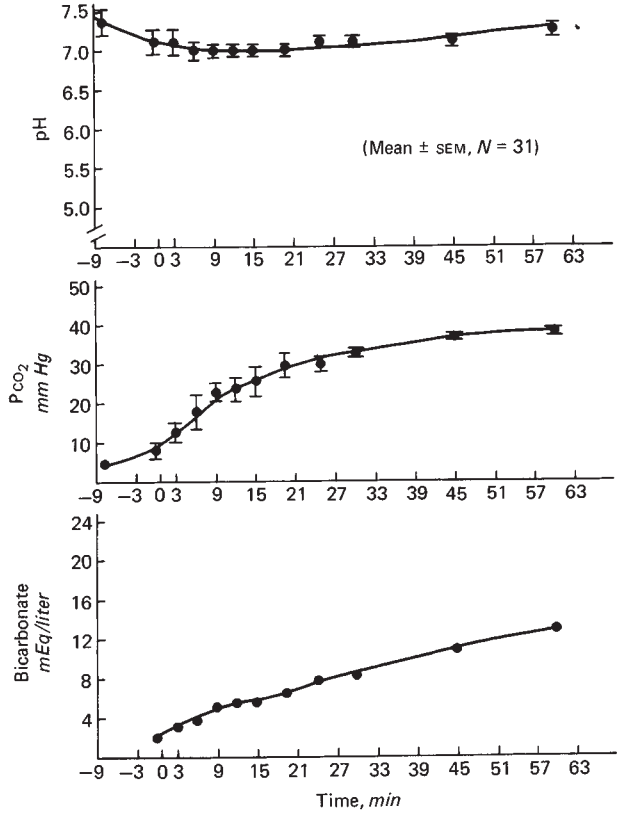

Fig. 3. *As in Figure 2 during three exchanges in one patient; however, sterile 1 M sodium hydroxide was added to the solution prior to instillation to raise pH above 7.0.*

absorption of gases has been mentioned. Gases may diffuse from red cells more readily than urea so that total delivery of solute available for rapid diffusion is greater. This emphasizes the fact that urea "plasma" clearances and mass transfer coefficients do not necessarily reflect "blood" clearances. Nevertheless, the equilibrations of the intraperitoneal dialysis solution with blood or plasma should be blood flow dependent, and gas plasma clearances or overall mass transfer coefficients may be considered crude estimates of minimum peritoneal capillary blood flow (assuming that plasma clearances are essentially the same as blood clearances for all small solutes). Mass transfer coefficients for gases several times values for urea again suggest no major Q_B limitation on urea clearance.

Low Q_D and Q_B studies in a hollow fiber dialyzer (simulated peritoneal dialysis). We have performed studies in a Cordis-Dow hollow fiber kidney (2.5 m^2), utilizing combinations of low Q_B and low Q_D, and analyzed effects on small and large solute clearances. Figure 4 shows that at a fixed Q_D of 30 ml/min, clearances of a small solute, in this case sodium, are Q_B-dependent over a large range of Q_B, but only slightly so when Q_B exceeds 50 ml/min. In these studies, Q_B and Q_D were concurrent with negligible ultrafiltration.

Even though the hollow fiber kidney presumably has markedly different permeability characteristics, and presumably less stagnant fluid layers with dialysate flow, the patterns of relationships can demonstrate principles. For example, Figure 4 also shows the effect of repeating the studies with 40% of the fibers occluded (openings to fibers covered). Small solute clearances are affected negligibly by fiber loss in the flow-dependent range. The clearances of a larger solute, B_{12}, are only Q_B-dependent at very low Q_B, and changes with fiber occlusion are proportional to area over most of the Q_B range. A major point, however, is the observation that in this low Q_D study simulating peritoneal dialysis conditions, Q_B is only modestly limiting for small solute clearances above 50 ml/min.

Computer simulations of peritoneal dialysis. Figure 5 shows hypothetical relationships of clearances (for solutes with a range of mass transfer coefficients) to Q_B at a fixed Q_D of 30 ml/min. The curves are derived from a previously described mathematical model of peritoneal dialysis, now corrected to include effects of Q_B [8]. For these calculations, ultrafiltration rate (Q_{UF}) was considered to be = 2 ml/min, peritoneal drainage = 2,100 ml, exchange time = 70 min, and transmittance coefficients = 0.8. Note that for a mass transfer coefficient (MTC) of 30 (typically reported value for urea [1, 8]), Q_B has very little influence on clearance (C) until Q_B falls below 50 ml/min. Results for MTC = 30 closely approximate C_{Na} results in Figure 4 from simulated low-flow studies in a hollow fiber dialyzer.

Using the same mathematical model, MTC values were calculated from typical urea and inulin peritoneal clearances correcting for Q_B over a hypothetical wide range of Q_B. Assumptions were as above. Results are shown in Figure 6. Note that Q_B would have little effect on calculated MTC values above 50 ml/min. Calculations of MTC at $Q_B < 50$ could markedly underestimate MTC if Q_B was assumed infinite.

Summary of blood flow studies. None of the above findings or arguments establish effective peritoneal capillary blood flow (see Table 2). The gas studies suggest that Q_B is well in excess of urea clearances and may exceed 60 ml/min. Clearances and mass transfer coefficients for urea are thus probably well below Q_B and only slightly Q_B-limited (i.e., the relationship between urea clearance and Q_B is nearing a plateau, but this has yet to be firmly established). Simulated studies in hollow fiber kidneys demonstrate such relationships at low Q_D and Q_B. Mathematical models of peritoneal dialysis predict minimal

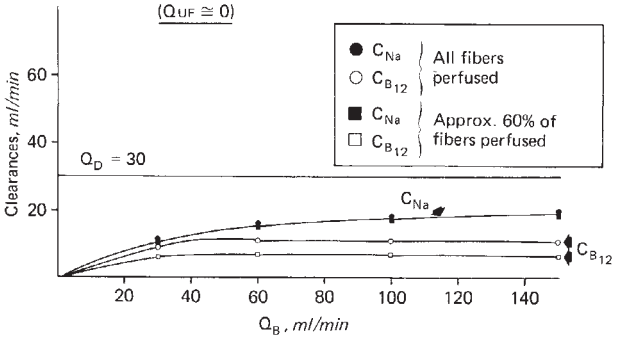

Fig. 4. *Clearances measured in a 2.5 m^2 hollow fiber dialyzer at dialysate flow (Q_D) = 30 related to blood flow rate (Q_B).* Low flows and fiber occlusion were performed to simulate peritoneal dialysis and effects of variations in peritoneal capillaries perfused.

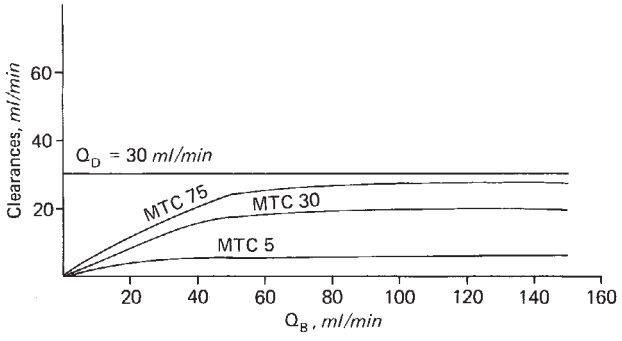

Fig. 5. *Theoretical peritoneal clearances predicted for three solutes with mass transfer coefficients of 75, 30, and 5 at dialysate flow (Q_D) = 30 and varying blood flow rate (Q_B).*

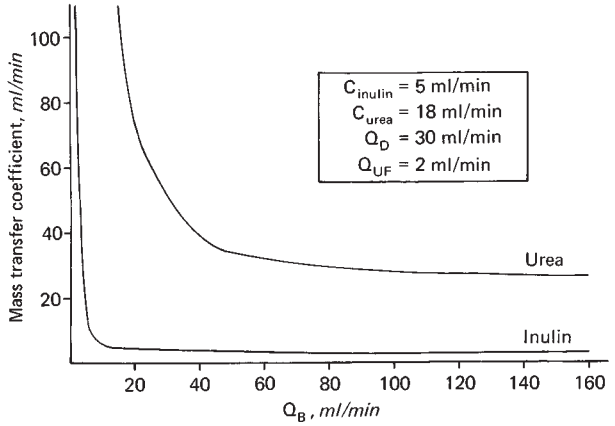

Fig. 6. *Mass transfer coefficient values predicted to yield typical peritoneal inulin and urea clearances at $Q_D = 30$ and varying Q_B.*

effects of Q_B on C_{urea} unless Q_B is less than 50 ml/min.

Conclusion

Our understanding of the limitations on peritoneal dialysis clearances and the appropriate ways to optimize efficiency will depend on better ways to determine effective peritoneal capillary blood flow and other factors affecting mass transfer. At this time, inferential evidence tends to support greater urea clearance limitations by total membrane resistance (perhaps secondary to low total pore area or stagnant fluid films) than by effective peritoneal capillary blood flow. Q_B is probably in excess of 60 ml/min in a range where blood flow limitations are minor compared to total membrane resistance.

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