Does Increasing Dialyzer Blood Flow Always Improve Dialysis Efficiency?

Thomas A. Depner

University of California, Davis, Sacramento, California, U.S.A.

As dialyzer blood flow is increased during hemodialysis, diminishing increments in clearance are inevitable. In addition, as clearance increases, diminishing increases in solute removal from the patient are inevitable. The causes of these equally self-defeating and additive effects are the fundamental self-limitation of the dialysis itself due to first-order kinetics, membrane-limited diffusion within the dialyzer, and disequilibrium within the patient. Access recirculation is a specialized cause of solute disequilibrium that is separately measurable and preventable. Cardiopulmonary recirculation (CPR) is a predictable form of solute disequilibrium that is found in all patients with peripheral arteriovenous shunts and is absent during vein-to-vein dialysis. Other forms of blood flow-dependent disequilibrium probably also play a role in diminishing the efficiency of hemodialysis. Sequestration of urea in muscle during hemodialysis is suggested by reduction in the magnitude of rebound when patients exercise (and increase muscle blood flow) during hemodialysis. This discussion is not intended to discourage attempts to increase solute removal by increasing blood flow, but rather to place this maneuver in a proper perspective. Other maneuvers such as increasing dialysis frequency may be more effective as a means of improving dialysis efficiency.

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Key words

Blood, dialyzer, flow, clearance, urea, membrane, disequilibrium, cardiopulmonary, access, recirculation

Definitions

To answer the question posed in the title, one must define the meaning of "efficiency." If efficiency is equated to solute removal, then the answer is almost always yes. Although solute removal is the measurement in question, the concept of efficiency almost always includes a denominator. If efficiency is defined as solute removal per unit of flow, then the answer is always no. Increasing blood flow increases solute delivery to the dialyzer, but the gains in both clearance and in solute removal diminish as flow increases. A limit is eventually reached beyond which solute removal is vanishingly increased with each increment in blood flow. "Dialyzer clearance" is the solute removal rate divided by the solute concentration in the dialyzer inlet. "Patient clearance" is the effective single-pool clearance of solute from the patient. More specifically, patient clearance is the solute removal rate divided by the average solute concentration between all the real body compartments during dialysis (1). In the ordinary practice of dialysis, as pumped blood flow through the dialyzer is increased, we see significant increases in dialyzer clearance, smaller increases in patient clearance, and even smaller increases in the continuous equivalent of clearance. The "continuous equivalent of clearance" is a recently proposed simple measure of intermittent dialysis (such as hemodialysis), expressed as the continuous steady-state clearance necessary to achieve the same average solute concentration (2–4). To calculate the continuous equivalent of an intermittent clearance, one must determine the average solute concentration as well as the overall solute removal. The recent emphasis on this new continuous expression of clearance is driven by a need to compare patients dialyzed according to different schedules. For purposes of this discussion wherein we will attempt to assess the effect of increasing blood flow, the continuous equivalent of clearance gives a more realistic measure of what is accomplished with dialysis.

Dialyzer clearance and dialyzer blood flow

Dialyzer clearance depends on dialyzer blood flow, but the relationship is not linear. How closely the curve approximates linearity depends on the dialyzer per-

Correspondence to:
Thomas A. Depner, MD, University of California, Davis, 4301 X Street, Sacramento, California 95817 U.S.A.

meability to the measured solute. For highly permeable membranes, the increase in clearance is nearly equal to the increase in blood flow. However, even for the same membrane, the clearance of poorly permeant solutes may increase very little as blood flow is increased. These two extremes have been called "flow-limited clearance" and "membrane-limited clearance." Figure 1 shows the curvilinear relationship between dialyzer flow and clearance at the two extremes. The bottom curve, where solute/membrane permeability is low, shows that a limit is reached beyond which increases in blood flow have no effect on clearance. This limit also exists for the solute/membrane permeability depicted in the top curve, but the plateau region is beyond the limits of the graph. The two curves depicted in Figure 1 may be valid for the same dialyzer and different solutes or for the same solute and different dialyzers.

Reduced efficiency caused by recirculation

The reduction in dialysis efficiency caused by recirculation depends on the magnitude and the type of recirculation. Two forms of recirculation have been identified: access recirculation and cardiopulmonary recirculation, sometimes called short-loop recirculation and long-loop recirculation, respectively. Access recirculation is less common, affecting less than 5% of dialyses according to recent studies (5,6). Cardiopulmonary recirculation is always a part of peripheral arteriovenous access flow and is absent when the access is a central vein catheter. Their effects on patient clearance are similar, but access recirculation can reduce effective clearance to zero (100% recirculation), while cardiopulmonary recirculation rarely reduces clearance by more than 10%.

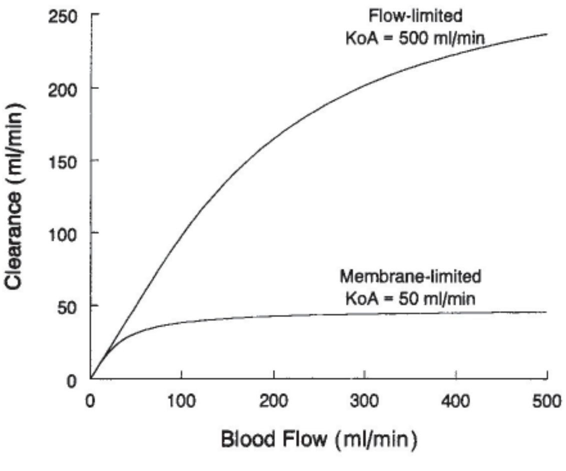

FIGURE 1 Effect of dialyzer blood flow on clearance. When solute permeability, expressed as the mass transfer coefficient (KoA), is high, clearance is highly dependent on blood flow, as shown in the upper curve. When permeability is low, as shown in the lower curve, the dependency on flow disappears. Reprinted with permission from Reference 10.

When blood flow in the access device falls below the pumped flow, local recirculation begins to appear. At this point, further increases in the pump flow have little effect on the patient urea clearance, even though dialyzer clearance continues to increase. If blood is recirculating in the access and the pump rate is increased, the concentration of urea returning to the patient decreases, but the flow returning to the patient does not change. Since the concentration of urea in returned blood is usually low anyway (fractional removal is usually greater than 70%), the increase in dialyzer clearance does little to increase urea removal from the patient. In contrast to urea, the concentration of poorly dialyzed solutes in the dialyzer outlet is only moderately or slightly reduced below the dialyzer inlet concentration. For these solutes, access recirculation has less effect on patient clearance.

Figure 2 shows the reduction in effective clearance as a function of both recirculation fraction and fractional solute clearance by the dialyzer. The lower lines represent solutes with low dialyzer clearance where recirculation has less effect on clearance.

Cardiopulmonary recirculation (CPR) results from the disadvantageous direction of blood flow in peripheral A-V (artery-vein) loops. Flow from artery to vein is caused by pressure gradients generated by the heart. If the flow could be reversed (from vein to artery) in these loops, CPR would disappear. Because this is impossible, dialysis efficiency is slightly reduced in all patients with peripheral A-V loops.

The fractional reduction in clearance due to CPR (f_{cp}) depends on the magnitude of dialyzer clearance compared to systemic blood flow (7):

$$f_{cp} = K_d Q_s / (K_d + Q_s).$$

Like the effect of access recirculation, as shown in Figure 2, the CPR effect depends as much on dialyzer

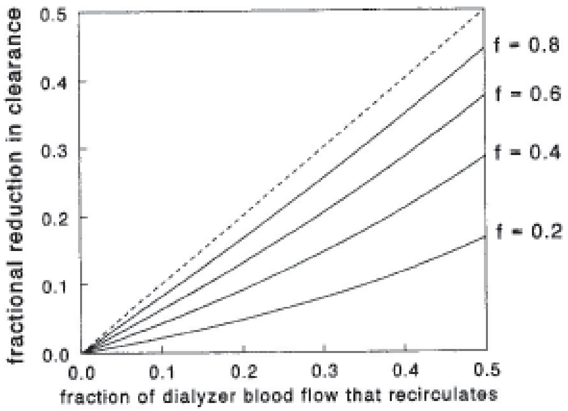

FIGURE 2 Access recirculation reduces the effective patient clearance. The reduction in clearance depends on the fractional clearance of the solute by the dialyzer (f). The dashed line is the line of identity wherein the fractional clearance is 100% and the fractional reduction in clearance is the same as the recirculation fraction. Reprinted with permission from Reference 10.

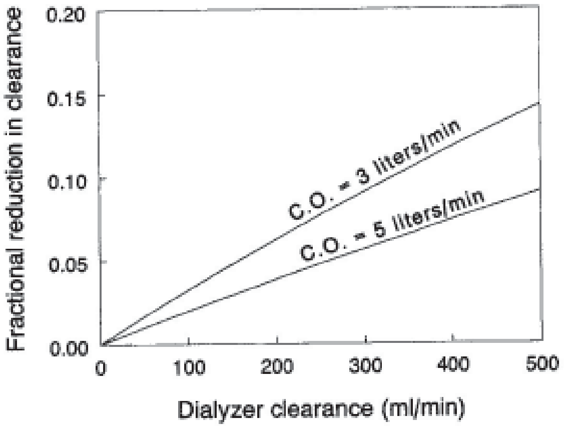

FIGURE 3 Reduction in patient clearance due to cardiopulmonary recirculation (CPR). The detrimental effect of CPR increases as dialyzer clearance increases and is enhanced in patients with low cardiac output (C.O.).

clearance (K_d) as it does on the fractional recirculation. Because systemic blood flow (Q_s) is governed by tissue oxygen requirements that are independent of shunted flow through the loop, the adverse effect of CPR on patient clearance is almost entirely a function of dialyzer clearance, with blood flow in the loop having little influence. An important clinical consequence of CPR is a larger reduction in clearance during high-efficiency dialysis. Recent advances in technology that permit higher blood flow and dialyzer clearances force the clinician to pay attention to CPR, which has become another source of frustration, limiting the success of efforts to remove more solute by increasing blood flow.

The effect of CPR is a function of dialyzer clearance and is also slightly enhanced in patients with low cardiac output. In patients with high cardiac output the converse effect, a slight improvement in clearance, occurs only if the high cardiac output is not due to shunting, that is, true systemic flow is increased. Recent studies of heavy exercise during dialysis that increases blood flow to muscle have confirmed these theoretical predictions (8,9). Figure 3 shows the relationship between dialyzer clearance and the reduction in patient clearance due to CPR for two systemic blood flow rates.

Effects of solute disequilibrium among tissues

As blood concentrations fall from the effect of dialysis, concentrations in peripheral tissue remain relatively elevated because of delayed blood flow between the tissue compartments and because of delayed movement of solute from tissue to blood. The convective effect of differential regional blood flow and the diffusive effect of delayed solute movement from tissue to blood are additive and in combination create solute gradients or disequilibrium between the patient's body compartments. In general, centrally located, well-perfused compartments tend to have lower concentrations of solute during dialysis than peripherally located, poorly perfused compartments. The diffusive effect but not the convective effect also creates larger gradients for solutes that are well dialyzed but equilibrate more slowly between body compartments (e.g., creatinine). The maximum gradient for all solutes is found in the central blood compartment, which has the lowest concentration. The reduced concentration of solute in blood entering the dialyzer from the central blood compartment further diminishes solute removal by the dialyzer, because the diffusion of solute across the dialyzer membranes is driven by the concentration gradient from blood to dialysate. Less solute is available to the dialyzer for removal when movement from tissue to blood is slowed. This effect adds to and further diminishes the effect of increasing blood flow that was discussed above.

Intermittent versus continuous dialysis

A discussion of the factors that thwart attempts to improve dialysis by increasing blood flow would not be complete without considering the effect of intermittent treatment. All the previously discussed factors that diminish dialysis efficiency, including resistance to diffusion in the dialyzer and in the patient, access recirculation, CPR, and flow-dependent disequilibrium, apply to continuous as well as intermittent hemodialysis, but all are markedly enhanced during intermittent dialysis. For access recirculation, the requirement for increased blood flow to achieve a higher clearance during intermittent dialysis can be directly blamed. For the other factors the required increase in clearance itself reduces efficiency, whether the increase in clearance is achieved by increasing blood flow, increasing dialysate flow, or increasing membrane area and permeability. As clearance increases, efficiency decreases; this is evident from the higher average clearance required to maintain the same blood urea nitrogen (BUN) when treatment is applied intermittently versus continuously. Because of the increased clearance requirement, intermittent dialysis is always less efficient than continuous dialysis when the goal is to attain the same average solute concentration. Several reasons can be invoked for this.

Figure 4 shows the decrease in efficiency expressed as the ratio (log mean BUN)/(mean BUN) during dialysis as the dose of dialysis (Kt/V) increases. Because dialysis is a first-order process, if solute concentration falls during dialysis, it falls in a logarithmic pattern, and the true mean BUN is the log mean concentration. The true mean BUN during the treatment reflects the driving force for solute removal within the dialyzer, whereas the arithmetic mean reflects the mean weekly concentration and the mean for continuous dialysis. As the dose of dialysis increases, the log mean and arithmetic mean diverge, the log mean falling below the arithmetic mean, thus reducing dialysis efficiency. This effect accounts in part for the increased efficiency of more frequent dialysis, which allows the same average solute concentration to be maintained with a lower time-averaged clearance.

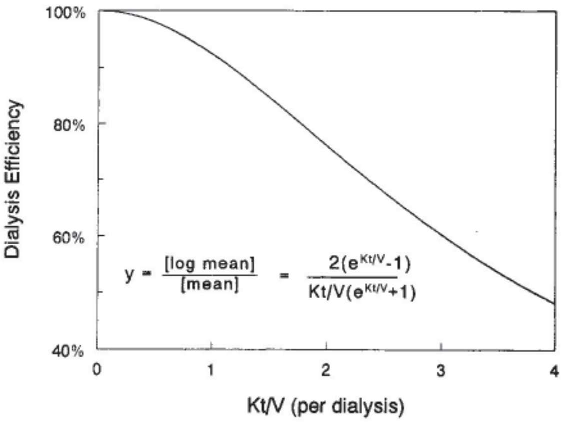

FIGURE 4 The efficiency of single-pool dialysis falls as the dose of dialysis (Kt/V) increases. Efficiency is expressed as the ratio of the log mean concentration to the arithmetic mean concentration during dialysis. No generation or volume change is assumed. Reprinted with permission from Reference 11.

Figure 5 shows the benefit of more frequent dialysis expressed in terms of the weekly Kt/V required to achieve the same time-averaged BUN. Also shown is the effect of solute disequilibrium within the patient which increases the requirement for a higher clearance when dialysis is prescribed less frequently. This effect of dialysis frequency is significant for urea, a compound that diffuses relatively easily between body compartments. An even greater dependency on frequency is shown for another theoretical compound that dialyzes well across the dialyzer but diffuses less readily and consequently exhibits more disequilibrium within the patient (open triangles in Figure 5). Creatinine is an example of the latter compound.

The asymptotic value of Kt/V shown in Figure 5, representing the required dose as dialysis frequency is extrapolated to infinity, is the continuous equivalent of the intermittent dialysis dose (see above). For any patient who is dialyzed regularly and is in a steady weekly state with respect to urea kinetics, the continuous equivalent of urea clearance can be calculated

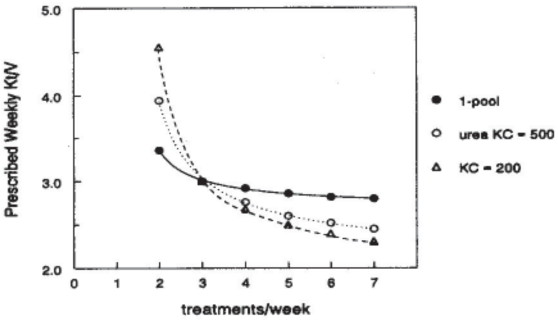

FIGURE 5 Effect of dialysis frequency on efficiency. Dialysis efficiency is enhanced by more frequent treatments. Efficiency here is expressed as the weekly dose (Kt/V) required to maintain the same time-averaged BUN (TAC) achieved with thrice-weekly treatments. KC is the intercompartment mass-transfer coefficient. TACs differ for each curve but are constant within each curve. The middle line (open circles) represents urea. See text for details. Reprinted with permission from Reference 11.

from the average urea generation rate (G) and the weekly time-averaged BUN (TAC) (2,3):

$$eKR = G/TAC.$$

Although this approach does not lend itself to simplified techniques (calculation of G and TAC requires formal iterative modeling of solute kinetics), it provides a method for comparing the effective dose of dialysis in patients dialyzed according to different weekly schedules and to some extent a comparison of different modalities of treatment (3).

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