Chronic peritoneal dialysis in a patient with diabetes mellitus and heart disease

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The Nephrology Forum is designed to relate the principles of basic science to clinical problems in nephrology.

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Case presentation

A 62-year-old woman was admitted to New England Medical Center Hospital (NEMCH) for evaluation of chronic renal failure. The patient’s history included rheumatic fever at age 13, two myocardial infarctions 5 and 3 years earlier, hypertension for 20 years, congestive heart failure for 2 to 3 years, and adult-onset diabetes mellitus. Ten years prior to admission, she presented with blurred vision and a blood sugar concentration of 640 mg/100 ml. She was treated with insulin but developed hives. The diabetes was well controlled, however, through oral hypoglycemic agents and a diet of 1,400 calories per day. She had no history of diabetic retinopathy, neuropathy, or peripheral vascular disease. At age 42, a heart murmur was first noted, and the patient began a regimen of digitalis. She had one urinary tract infection approximately 10 years prior to admission. The blood urea nitrogen (BUN) concentration was 40 mg/100 ml 2 years prior to admission.

During the few months prior to admission, the patient described numerous episodes of chest pain radiating to the right arm and relieved by nitroglycerin. Two weeks prior to admission, she was admitted to another hospital for lethargy and anorexia. Examination revealed a BUN concentration of 160 mg/100 ml. She was transferred to NEMCH.

On admission, the physical examination revealed the following: blood pressure, 190/90 mm Hg; pulse, 70/min and regular; respirations, 16/min; temperature, 37°C; weight, 50.6 kg; no hemorrhages, exudates, or diabetic microaneurysms of the optic fundi; the chest was clear to percussion and auscultation. Cardiovascular examination revealed the following: regular rhythm; a Grade II/VI systolic ejection murmur at the upper left sternal border radiating to both carotid arteries; peripheral edema, +1; no pericardial friction rub. The remainder of the examination was unremarkable.

Laboratory findings revealed the following data: hematocrit, 23%; hemoglobin, 7 g/100 ml; white blood cell count, 10,700/mm³ with a normal differential; serum sodium, 123 mEq; serum potassium, 4.3 mEq; serum chloride, 90 mEq; total serum carbon dioxide, 17 mEq/liter; BUN, 99 mg; serum creatinine, 10.3 mg; serum calcium, 7.4 mg; serum phosphorus, 8.5 mg; serum albumin, 3.2 g/100 ml. Results of urinalysis revealed: pH, 6; specific gravity, 1.012; 0 to 3 white blood cells and 0 to 1 red blood cells per high power field; protein, 1 +. Twenty-four-hour urine protein excretion was 2.7 g. Several urine cultures were sterile. A chest radiogram revealed cardiomegaly with engorged pulmonary vasculature. An electrocardiogram revealed calcification of the mitral valve and evidence of mitral stenosis. An electrocardiogram (EKG) revealed a sinus rhythm of 80 beats per minute, inverted T waves in leads 1, 2, V5 and V6, and voltage criteria for left ventricular hypertrophy. An i.v. urogram revealed bilaterally small kidneys. An echogram of the kidney, ureters, and bladder revealed no evidence of post-void residual or obstruction.

The patient’s uremia and congestive heart failure responded to treatment with diuretics and dietary protein and sodium restriction. An arteriovenous fistula was created for future use. Five months after the first hospitalization, hemodialysis was attempted to relieve recurring nausea and vomiting. Either a 1.0 or 0.6 m² coil dialyzer was used with an average blood flow of 140 cc/min. Four of five dialyses, however, were complicated by severe hypotension, chest pain, nausea, and vomiting thought to be attributable to poor myocardial function. Typically, the blood pressure fell as low as 50/0 mm Hg either at the beginning or within 1 hour of the beginning of dialysis. The patient frequently converted to atrial fibrillation (pulse, 100 to 110/min) during the periods of hypotension. Acetate was used as the source of acetate and no pericardial friction rub. The remainder of the examination was unremarkable.
The patient responded to conservative management with dietary manipulation alone until uremia recurred 6 months later (BUN, 150 mg; serum creatinine, 11 mg/100 ml). Hemodialysis was again attempted. Over the next 10 months, the patient was hemodialyzed three times per week, for 3.5 to 4 hours each time, with a 1.3 m² hollow fiber dialyzer. The patient had to be hospitalized on several occasions because of chest pain, hypotension, atrial fibrillation, and ischemic changes noted on EKG during hemodialysis. Attempts to remove excess fluid during dialysis resulted in hypotension.

After 10 months of hemodialysis, the patient was transferred to another hospital for peritoneal dialysis. A permanent peritoneal catheter was placed in the left lower quadrant. Peritoneal dialysis, using a conventional “bottle-hanging” system, was performed three times per week, for 10 hours each time, over the next 6 months. A 1.5% glucose dialysate supplemented by 4.25% hypertonic dialysate was used for each dialysis. Although the patient had one episode of chest pain lasting 2 hours with no elevation of cardiac enzymes, the chest pain and hypotension did not recur in subsequent dialyses. Urine volume was less than 300 cc/day. Medications included nitroglycerin, propranolol (40 mg, four times daily), furosemide (800 mg/day), and digoxin (0.125 mg/day, 5 days per week).

During her first month of peritoneal dialysis as an out-patient, episodes of abdominal pain and signs of a peritoneal inflammatory reaction were present, but cultures were negative. A new Tenckhoff catheter was placed in the right lower quadrant, and it functioned well for the next 2 months. Blood pressures were in the range of 120 to 130/70 to 80 mm Hg both before and after dialysis. During this period, the patient’s coronary artery disease stabilized, and she was symptom-free and ambulatory at home.

At the beginning of the fourth month of peritoneal dialysis, the patient developed tenderness over the catheter site, and cephalixin in a dosage of 250 mg, four times daily, was given for 7 days. Pain persisted, however, in the lower quadrant and back; abdominal plain film and echogram were unrevealing. The symptoms subsided briefly but then recur with severe lower abdominal pain, right lower quadrant tenderness, diarrhea, and cramps. A radiogram revealed the catheter to be in the pelvic area. Because the catheter was thought to be responsible for the pain, it was retracted. Seven days later, diffuse abdominal pain and signs of peritoneal inflammation recurred, and a cloudy dialysate solution was noted. The patient was examined for possible bowel perforation associated with surgical manipulation of the catheter. Dialysate cultures grew E. coli and diphtheroids that were sensitive to cephalosporins, and cefazolin was prescribed in a dosage of 0.5 g, three times daily. The patient continued to have lower abdominal pain, and findings were consistent with peritoneal irritation in the right lower quadrant. Pelvic and rectal examinations revealed pelvic inflammatory disease near the right adnexae. An abdominal echogram was consistent with an abscess in the area of the peritoneal catheter. The catheter was removed surgically, and the patient was given a 2 week course of antibiotics, which resulted in marked improvement.

With the onset of peritonitis, peritoneal dialysis was discontinued, and hemodialysis was resumed through an existing left forearm fistula. The patient tolerated hemodialysis (1.3 m² hollow fiber dialyzer) well for several months with no significant hypertensive episodes. Laboratory findings before and after 6 months of peritoneal dialysis were the following: hematocrit, 30% and 26%; serum albumin, 5.7 g and 3.2 g; BUN, 120 mg and 50 mg; serum creatinine, 10 mg and 13 mg/100 ml. After 6 months of peritoneal dialysis, an echocardiogram revealed that the patient’s cardiac ejection fraction had increased from 40 to 60%.

Discussion

Dr. Karl D. Nolph (Director, Division of Nephrology, University of Missouri Medical Center): This 62-year-old woman with diabetes mellitus and two previous myocardial infarctions was transferred to NEMCH with angina, lethargy, malaise, anorexia, and a BUN concentration of 160 mg/100 ml. These findings coupled with physical and laboratory findings obtained on admission indicated uremia perhaps secondary to end-stage diabetic nephropathy and congestive heart failure secondary to atherosclerotic coronary artery disease. There was evidence for rheumatic heart disease as well. Following a transiently successful trial of conservative medical management, recurring nausea and vomiting were noted. Extracorporeal hemodialysis was initiated, but four of the first five hemodialyses were complicated by severe hypotension associated with angina. It is of interest that these episodes usually occurred within the first hour of dialysis. Conservative management was attempted again, but chronic hemodialysis had to be restarted when uremic symptoms, such as fluid retention, weight gain, and dyspnea, recurred between dialysis treatments. Attempts to remove excess fluid during hemodialysis frequently resulted in hypotension and related symptoms. After 10 months of this unsatisfactory therapy, chronic peritoneal dialysis was started. With easier fluid control, the patient did well for several months, but then developed an intraperitoneal abscess that was refractory to antibiotic therapy until the catheter was removed. Hemodialysis therapy was again started and this time she tolerated it much better.

This patient’s course will serve as the focal point for our discussion today of chronic peritoneal dialysis. The sequence of events in this patient highlights very nicely some of the relative advantages and disadvantages of chronic peritoneal dialysis as compared to chronic extracorporeal hemodialysis.

Chronic peritoneal dialysis and the problem patient. Chronic peritoneal dialysis is the treatment often considered for patients who have unusual problems with extracorporeal dialysis. In 1974, Tenckhoff listed the following primary indications for chronic peritoneal dialysis: (1) patients awaiting transplantation and fistula maturation; (2) small children; (3) older patients (60 years or older); (4) patients with advanced cardiovascular disease; (5) patients in whom reliable vascular access for hemodialysis cannot be maintained; (6) patients for whom hemodialysis is considered to be hazardous; (7) patients who desire home dialysis but live alone; (8) and patients who refuse blood transfusions [1]. More recently, particularly in Canada, chronic peritoneal dialysis has been advocated as a reasonable
alternative to extracorporeal dialysis in most patients [2]. Hopefully, the new cooperative study originated by the Veterans Administration will allow fair, well-controlled comparisons of peritoneal dialysis and hemodialysis in large numbers of patients [3, 4]. This individual patient’s problems, however, offer the clinician insights into some circumstances in which chronic peritoneal dialysis offers certain advantages. Let me review these specifically as they relate to this patient.

**Advantages of chronic peritoneal dialysis in diabetes (see Table 1).** Chronic peritoneal dialysis has been suggested in diabetes mellitus for several reasons [5]. In patients with widespread vascular disease, vascular access may be difficult to maintain, although this did not seem to be a problem in our patient. Problems are also evident with intermittent extracorporeal dialysis in the repeated use of heparin and the retinal ischemia associated with fluctuations in blood pressure; both may accelerate diabetic retinopathy and increase the risks of retinal hemorrhages [5, 6]. In contrast, stabilization of diabetic retinopathy with chronic peritoneal dialysis has been described [2, 5, 6]. Unfortunately, there are no prospectively controlled studies to substantiate these reports. It is an important question, however, and needs to be addressed. It is noteworthy that this patient had no evidence of diabetic retinopathy. Since end-stage diabetic nephropathy is so often associated with diabetic retinopathy, the absence of characteristic fundoscopic changes raises a question about the cause of her end-stage renal disease.

Diabetes is frequently complicated by cardiovascular disease: hypotension is less likely with peritoneal dialysis than with hemodialysis in such patients. A most important problem in the management of this patient was the repeated hypertensive episodes during hemodialysis. Let us explore those factors that can contribute to hypotension during hemodialysis and then consider how peritoneal dialysis may avoid many of these precipitating mechanisms.

**Factors predisposing to hypotension during hemodialysis (see Table 2).** In hemodialysis, patients must tolerate a blood volume shift into the artificial kidney. Even though dialysis machines are primed with saline, the initial shift of blood to the dialyzer may cause hypotension. The coil dialyzer initially tried in this patient has a somewhat larger priming volume than the hollow fiber dialyzers used later [7]. Hypotension occurs less frequently with these smaller volume dialyzers. During this patient’s first treatments hypotension occurred very early in dialysis and may have been related to these initial blood volume shifts.

Ultrafiltration takes place throughout dialysis at a rate depending on transmembrane hydrostatic pressure. With modern dialyzers, ultrafiltration rates can be achieved that will precipitate hypotension in almost any patient because plasma volume is contracted more rapidly than extracellular fluid can be mobilized to replace the ultrafiltrate. Prior to the mobilization of extracellular fluid, reflex increases in heart rate and increases in peripheral resistance can help to prevent significant decreases in blood pressure. In patients with autonomic insufficiency—due to diabetes, for example—or underlying cardiovascular disease, cardiovascular responses may be inadequate and result in an increased sensitivity to even low rates of ultrafiltration [8].

Recent evidence suggests that rapid decreases in extracellular fluid osmolality with efficient large surface dialyzers may increase the likelihood of hypotension [9]. This complication may be due to fluid shifts into the intracellular space and central nervous system where osmolality decreases more slowly. Bergstrom has recently reviewed evidence obtained during isolated ultrafiltration—that is, ultrafiltration in the absence of flowing dialysate. Under these circumstances many patients tolerate more rapid rates of fluid removal without developing hypotension [9]. Simultaneous ultrafiltration and dialysis seems to predispose patients to hypotension. Tolerance to ultrafiltration during dialysis can be improved with the administration of solutes such as mannitol, which prevent rapid decreases in extracellular fluid osmolality [10].

The rapid absorption of acetate during extracorporeal dialysis and the consequent increase in serum acetate concentration may contribute to the development of hypotension; bicarbonate loss may also play a role [11]. This patient was dialyzed against a solution containing acetate. With efficient

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<th>Table 1. Advantages and disadvantages of peritoneal dialysis in diabetes</th>
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<td><strong>Advantages</strong></td>
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<td>No vascular access needed</td>
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dialyzers, acetate absorption rates exceed acetate metabolic rates, and measurable increases in serum acetate are common. It is hypothesized that acetate may contribute to a patient’s intolerance to rapid ultrafiltration by affecting the cardiovascular response. Some preliminary studies indeed suggest that patients tolerate ultrafiltration better when a bicarbonate containing bath is used [11]. Isolated ultrafiltration has the advantage of eliminating acetate absorption during the process, which may explain some of the beneficial effects.

Factors minimizing hypotension during peritoneal dialysis (see Table 2). Because the “blood-path” of peritoneal dialysis is the peritoneal capillary bed, there are no blood volume shifts during peritoneal dialysis [12]. Unlike hemodialysis, ultrafiltration occurs at a relatively slow rate. Even with hypertonic 4.25% dextrose dialysis solutions, ultrafiltration rates in excess of 10 ml/min are unusual [13]. Still, hypotension can be induced during peritoneal dialysis, particularly with repeated use of hypertonic exchanges, but it is generally easy to avoid this complication by using the 4.25% dextrose solutions only intermittently. With 1.5% dextrose solutions net ultrafiltration rates are very low, usually less than 3 ml/min. In contrast, many of the extracorporeal dialyzers have much higher ultrafiltration rates, even at low transmembrane pressures.

Urea is removed less rapidly during peritoneal dialysis than during hemodialysis and thus extracellular osmotic changes occur more slowly [13]. Decreases in BUN concentration are coupled with glucose absorption—often approximately 15 and 40 g/hr, respectively, when using hourly 1.5% and 4.25% dextrose exchanges [14]. As a result, serum glucose concentration increases, thereby blunting the decrease in extracellular osmolality. Also, the electrolyte concentration of the net ultrafiltrate formed during peritoneal dialysis is lower than the electrolyte concentration of the extracellular fluid [15–17].

Finally, if changes in serum acetate and bicarbonate concentrations play a role in hypotension, it is noteworthy that acetate absorption rates and bicarbonate removal rates are relatively slow in peritoneal dialysis compared to extracorporeal dialysis [12], and that many peritoneal dialysis solutions contain lactate rather than acetate.

Thus, there are many possible but mostly unproven explanations for why hypotension is less likely to develop during peritoneal dialysis compared to hemodialysis. Most reports of these advantages remain anecdotal or hypothetical. Nevertheless, it is widely accepted that hypotension can usually be avoided in peritoneal dialysis. In this particular patient, hypotension might have been avoided during hemodialysis by using isolated ultrafiltration, bicarbonate dialysate, or smaller dialyzers with less surface area and lower priming volumes.

Disadvantages of chronic peritoneal dialysis in diabetes (see Table 1). In intermittent peritoneal dialysis, the serum concentrations of urea and creatinine are usually less well controlled. In this patient, BUN and creatinine concentrations were higher during the period of peritoneal dialysis treatments. She was treated, however, with only three 10-hour sessions per week. Many centers now recommend four 10-hour sessions per week and achieve slightly better control of the blood chemistries [2, 13]. This recommendation remains empirical because acceptable definitions of the adequacy of dialysis remain elusive. If it is true that the major uremic toxins are large molecular weight solutes, then 30 hours of peritoneal dialysis per week should achieve “middle molecule” removal rates comparable to or greater than most extracorporeal techniques [18].

A possible problem with peritoneal dialysis in some patients with diabetes mellitus and far-advanced vascular disease may be relatively low peritoneal clearances [19]. This is certainly not the case in all patients with diabetes mellitus [5, 6]. We do not know what the peritoneal clearances were in this patient. Such measurements are helpful in deciding the total weekly peritoneal dialysis requirement. Low clearances are not an absolute contraindication to chronic peritoneal dialysis in patients with diabetes. Even with very low clearances, continuous ambulatory peritoneal dialysis (CAPD) may be considered [20, 21]. There is now a good clue to why clearances might be low in

| Table 2. Comparison of hypotensive mechanisms in hemodialysis and peritoneal dialysis |
|---------------------------------|---------------------------------|
| **Hemodialysis**                | **Peritoneal dialysis**         |
| Extracorporeal blood volume     | No extracorporeal blood         |
| not tolerated                   | distribution                     |
| Ultrafiltration rate often      | Ultrafiltration rates relatively |
| very high                       | low                             |
| Rapid decreases in extracellular| Low urea clearances, glucose    |
| osmolality with high urea       | absorption, and hyponic         |
| clearances                      | ultrafiltrates slow osmolality   |
| Acetate absorption and          | Low bicarbonate clearances       |
| bicarbonate loss at rapid rates | and slow acetate absorption      |

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diabetes mellitus and other diseases involving small vessels. Accumulating evidence suggests that the status of the peritoneal microcirculation may be a major determinant of both the effective peritoneal area and peritoneal permeability [12, 22, 23]. Small vessel disease of the peritoneum may decrease both and explain the selective decreases that have been reported in larger molecular weight solute clearances [19].

Protein losses are a problem with chronic peritoneal dialysis, especially during episodes of peritonitis [2, 13]. As exemplified by this patient, serum albumin concentration often is decreased. In the absence of infection, however, most patients can be maintained in an acceptable state of nitrogen balance with an adequate protein intake [24, 25].

Another disadvantage of peritoneal dialysis in this patient, as mentioned earlier, was the increase in dialysis time to 30—and perhaps more appropriately 40—hours per week. This is one of the main drawbacks to chronic peritoneal dialysis. I am hopeful that this disadvantage may be overcome in the future with the use of CAPD; using the Oreopoulos bag, this technique may require only brief interruptions of normal activities four times per day [26]. I will say more about this in a moment. Nevertheless, in this patient, increased dialysis time was required.

Since ultrafiltration during peritoneal dialysis is dependent on the osmotic gradient created by glucose in the dialysate, the patient with diabetes must deal with the increased problems of glucose absorption. The problem can usually be controlled by increasing insulin through the usual route or by using intraperitoneal insulin, as reported by Rubin et al [27].

The greatest problem with peritoneal dialysis, again well exemplified by our patient, is infection. Using automated closed systems, the incidence of peritonitis in chronic peritoneal dialysis has been reduced to very low levels in most centers; it should be possible to keep the infection rate to less than 1% of catheter connection-disconnection procedures [2, 28]. Some patients who have problems with recurring infections develop intraperitoneal abscesses. Gram-negative organisms are not the usual cause of peritonitis, and when these organisms are found it must raise, as in this patient, questions about an intra-abdominal source. This patient was appropriately examined for possible bowel perforation but none was found; she improved after the catheter was removed. Some patients simply cannot clear recurring or persistent peritonitis without removal of the catheter; resistance to therapy in such instances may be due to the presence of infected debris within the catheter or along the exit site. In our center, gram-positive organisms account for 77% of infections. Gram-negative infections do occur in the absence of intra-abdominal disasters but are infrequent—about 9% of all infections. Aseptic peritonitis has also been relatively unusual—about 14% in our experience.

Contrary to common belief, there is evidence that the incidence of peritonitis is not increased in patients with diabetes [27]. Thus, one might have considered returning this patient to chronic peritoneal dialysis with a new catheter after a reasonable period of time.

There are many other potential complications of peritoneal dialysis [13], but I have touched on those particularly germane to this woman. Other concerns include an increase in central venous pressure [29], an increase in pulmonary pressure [30], bradyarrhythmias [31], and a decrease in arterial oxygen tension [32] with fluid instillation. These seem minor, however, compared to the adverse hemodynamic effects of hemodialysis. No long-term differences in the degree of hyperlipidemia encountered during hemodialysis versus peritoneal dialysis have been reported.

The return to hemodialysis. On returning to hemodialysis, this patient seemed much improved and tolerated the required degree of ultrafiltration without hypotension. Her improved tolerance for hemodialysis may have resulted from the several months on peritoneal dialysis during which time better control of extracellular fluid volume could have permitted her cardiac function to improve. An alternative explanation is that the smaller priming volumes required by hollow fiber dialyzers were less stressful to her circulation. Another possibility is that autonomic neuropathy may have improved. This patient's course demonstrates very well the difficulties in comparing peritoneal dialysis and extracorporeal dialysis even in the same patient. The apparently better stability of her blood pressure during peritoneal dialysis compared with the first experience with extracorporeal dialysis is not a consistent advantage if compared with the later treatments with hollow fiber dialyzers. Clinical comparisons are fraught with problems of changes in patient status and modifications of extracorporeal techniques, which may influence markedly the comparisons. The Veterans Administration cooperative study hopes to establish more legitimate comparisons of peritoneal and extracorporeal dialysis.
by randomizing the techniques in good dialysis candidates [3]. There are many variables, however, and interpretation of comparative data will be a challenge.

I have discussed the possible advantages of switching to chronic peritoneal dialysis in this patient; most are hypothetical or anecdotal. Peritoneal dialysis was carried out in this patient with less hypotension. Persistent peritoneal infection led to a return to extracorporeal dialysis; this time, hemodialysis was better tolerated than previously. In many patients, peritoneal dialysis offers a reasonable alternative to circumvent problems with hemodialysis. Peritoneal dialysis, however, has its own disadvantages. The choice of technique in problem patients at this time must be individualized and often determined by the circumstances of the moment.

Questions and Answers

DR. J. T. HARRINGTON: Dr. Nolph, you indicated that an increased acetate concentration could present a problem by affecting cardiac output or cardiac function during dialysis. It has been our experience that significantly increased serum concentrations of acetate are more common in patients who have been dialyzed using a 2.5 m² hollow fiber artificial kidney. Although we don’t have serum acetate values for this patient, it seems unlikely that she had very high concentrations during the time she was using the 1.0 or 0.6 m² coil dialyzer. We did measure serum bicarbonate concentrations prior to some of the hypertensive episodes and they were not reduced significantly. Thus, I am not convinced that hyperacetatemia was responsible for the hypertensive episodes in this patient.

DR. K. D. NOLPH: I think your points are well taken. Most of the studies that have shown significant increases in serum acetate concentrations, decreases in serum bicarbonate concentrations, and increases in the anion gap during dialysis have involved the use of large surface area dialyzers. Whether the serum acetate concentrations reached are toxic to the cardiovascular system is not clear. In some of the initial studies in dogs, the acetate injected was shown to cause cardiovascular problems, but the doses used were enormous [33]. A more recent study demonstrated that hypotension could be induced in dogs by acetate infusion rates comparable to those achieved during hemodialysis [34]. I think increased serum acetate concentrations are a problem with large surface area dialyzers and serum concentrations should be monitored carefully in any patient who has unusual sensitivity to small increases in the serum concentration of acetate. I mentioned acetate for the sake of completeness in listing all of the mechanisms that have been proposed to explain hypotension during hemodialysis. Hyperacetatemia is probably unlikely in the patient we are discussing today.

DR. ELBERT TUTTLE (Professor of Medicine, Emory University School of Medicine): This patient’s difficulty with acute volume changes may have been aggravated by autonomic nervous system insufficiency. How do you assess autonomic function in your patients?

DR. K. D. NOLPH: One can often get a clue at the bedside about the presence of autonomic insufficiency. If there is a substantial decrease in systolic blood pressure unaccompanied by a rapid pulse rate, there is likely to be a problem in the cardiovascular reflexes. A variety of maneuvers, such as the Valsalva and the cold pressor test, can document further the autonomic problems. It is a common problem not only in diabetes but in patients with uremia from other causes [8].

DR. PAUL TESCHAN (Associate Professor of Medicine, Vanderbilt University School of Medicine): In addition to the fact that patients acutely bleed blood into the extracorporeal circuit, which is usually replaced only by saline during the first pass through the dialyzer, do you think that the so-called “dynamic volume” of certain of the dialyzers—especially coils and loosely connected plate dialyzers—can also play an important role in causing hypotension?

DR. K. D. NOLPH: The priming volume given for most dialyzers is that associated with a fairly low pressure. Yet, as the transmembrane pressure is increased to achieve ultrafiltration, coil dialyzers in particular expand enormously, volume becoming a linear function of the pressure within the dialyzer. The parallel plate and hollow fiber dialyzers, on the other hand, have relatively fixed volumes. The hollow fiber dialyzers are especially noncompliant, their fiber dimensions remaining almost unchanged as the positive pressure within the fiber or the negative pressure outside the fiber is increased. In those dialyzers that do expand as the transmembrane pressure is increased, a deterioration in clearance characteristics is evident; this is probably due to membrane-masking, which occurs when the membrane is pushed up against mesh supports. Although extracorporeal volume can increase enormously in certain coil dialyzers as transmembrane pressure is
increased, hypotension occurred so soon after starting the dialysis procedure in this patient that I assume maximum transmembrane pressure had not been approached and that hypotension occurred at a fairly low pressure.

DR. J. T. HARRINGTON: It did.

DR. J. J. COHEN: Dr. Nolph, you mentioned loss of protein as one of the potential disadvantages of intermittent peritoneal dialysis. The range for protein loss has been estimated to be about 10 to 15 g per dialysis session [25]. This rate of protein loss is similar to that seen in patients with moderately severe nephrotic syndrome accompanied by hypoalbuminemia. Yet, hypoalbuminemia does not seem to be an issue in most patients undergoing chronic peritoneal dialysis. Is there an explanation for this differing response to protein loss?

DR. K. D. NOLPH: In the nephrotic syndrome the decrease in serum albumin concentration as a function of urinary protein loss is greater than with similar degrees of protein loss by other routes [35]. In nephrosis the whole body catabolic rate for albumin is increased [35]. Patients undergoing peritoneal dialysis seem able to keep up with the protein loss by ingesting adequate amounts of protein.

DR. J. J. COHEN: Is hypoalbuminemia during chronic peritoneal dialysis more common in patients who had the nephrotic syndrome before progressing to end-stage renal disease.

DR. K. D. NOLPH: Not to my knowledge. As renal disease progresses, urinary protein losses decrease with reductions in glomerular filtration rate (GFR). Also, since the nephrotic kidney itself may be the site of enhanced albumin catabolism [36]—that is to say that filtered albumin is catabolized by the tubules so that urinary protein losses are only a fraction of the total albumin filtered—progressive reductions in GFR and nephron mass also decrease albumin catabolism.

DR. E. TUTTLE: Katz, Rosenfeld, and Sellers [37], studied the filtration and catabolic reabsorption of albumin in the nephrotic syndrome. They clearly showed that the filtered load of albumin in this condition greatly exceeds the amount excreted, the remainder being catabolized during passage through the tubules.

DR. K. D. NOLPH: That is why in animal models of the nephrotic syndrome, the high catabolic rate for albumin decreases following nephrectomy [36]. We have no documentation, however, that this patient ever had the nephrotic syndrome, and, in fact, I am doubtful that she had diabetic nephropathy. I think there is considerable evidence to the contrary, such as kidney size and absence of retinopathy.

DR. VICTOR POLLAK (Professor of Medicine, University of Cincinnati Medical Center): What do we know about the character of the protein losses in patients undergoing chronic peritoneal dialysis? How much of the loss is albumin, and what is the molecular weight of the proteins being lost?

DR. K. D. NOLPH: Some high molecular weight proteins are lost, but the predominant protein lost in these patients is albumin. Very interesting studies in patients with multiple myeloma have shown that peritoneal dialysis can be used to remove myeloma proteins, including high molecular weight myeloma proteins [38]. Still, the major loss is albumin.

DR. J. J. COHEN: In view of the lesser efficiency of peritoneal dialysis, at least for the removal of some substances, do you want to comment on recent techniques developed to increase blood flow to the peritoneal microcirculation and consequently to improve the efficiency of the technique?

DR. K. D. NOLPH: A number of techniques are being evaluated but none has received widespread acceptance at this time. We do know that intraperitoneal vasodilators can increase clearances and are beneficial in those patients who have reduced clearances, although those with very destructive vascular disease may remain refractory. Increased clearances also result in increased protein losses; to date most of the maneuvers designed to increase clearances with vasodilators do so primarily for solutes in the high molecular weight range, such as protein, not in the low molecular weight range. These findings are presumably related to the small number of capillaries involved in exchange and membrane resistance due to fluid films [12]. The entire surface area of the peritoneal membrane approaches that of the skin; the total effective pore area, however, is probably less than 1%. The effective pore area is in the range of the pore area of the intercellular channels, particularly the capillary endothelial intercellular channels [12]. The peritoneal vessels that are small enough to engage in exchange—some 10 μ or less in diameter—are largely confined, at least in rats, to the visceral peritoneum just as it begins to reflect over the intestine; it is at this point that one can see a number of small branches that could participate in exchange. Elsewhere in the peritoneum one finds mainly conduit vessels of 30 μ in diameter or more leading to visceral organs. Of the small arterioles that then branch into capillaries, most probably branch into five capillaries or more [23]. Studies suggest that in
the nonvasodilated state only one of four capillaries is perfused; the others are held in reserve [23]. It appears to be the sphincter tone of the final arteriole or the so-called precapillary sphincter that controls perfusion into these reserve capillaries. Vasodilators probably increase flow into perfused arterioles but also dramatically increase the number of capillaries perfused [23]. The work of Renkin [39] also suggests that those capillaries that open later in the vasodilated state are more permeable and have a larger mean "pore" diameter than the ones that are perfused in the nondilated state. This could explain why those maneuvers that vasodilate might increase selectively the clearances of the higher molecular weight solutes, thus, increasing protein losses. Recent studies in our microcirculatory laboratory suggest that some vasodilators have selective effects on the venular side of the capillary bed, and preliminary evidence suggests that this may be the main site for protein transfer. Nitroprusside, for example, has dramatic effects on the venular side as opposed to the arteriolar side of the capillary bed.

Therefore, all of the maneuvers that increase the number of capillaries perfused may serve primarily to increase the transfer of higher molecular weight solutes by these area and permeability changes. Yet, peritoneal dialysis usually provides clearances of the larger solutes that are as high as or even higher than clearances achieved through hemodialysis techniques. One could question, therefore, whether the quest for new vasodilator techniques is really going to accomplish anything useful. Instilling intraperitoneal vasodilating agents or administering oral vasodilating agents usually increases the clearances of the higher molecular weight solutes proportionately more than the clearances of the lower molecular weight solutes. On the other hand, most peritoneal diseases as well as hypoperfusion caused by hypotension are associated with disproportionate decreases in the clearance of higher molecular weight solutes. The clearances of lower molecular weight solutes remain remarkably stable when vasoconstriction is induced and presumably the number of capillaries perfused decreases as does mean pore size. Thus, we can more easily manipulate the loss of protein and high molecular weight solutes: What we would like to do is increase the clearance of lower molecular weight solutes. I am skeptical at this point that this can be done except with very rapid dialysis solution cycling techniques to minimize dialysate flow limitations and provide better mixing. Even then urea clearances rarely exceed 30 to 40 ml/min in humans [12]. We have viewed possible reasons for limitations on urea clearances elsewhere [12]. In brief, limited total pore area—number of capillaries—, fluid films, and poor mixing may all be involved. There is little evidence to support limitations due to effective capillary blood flow [12].

With vasodilators, urea clearances generally show increases in the range of 5 to 10%—at the most 15 to 20% [23]. On the other hand, inulin clearance increases as much as 50 to 300%, as do protein losses. The question becomes, Is one willing to double protein losses for the sake of increasing small solute clearances by less than 20%?

DR. J. T. HARRINGTON: Would you comment on the efficiency of CAPD?

DR. K. D. NOLPH: Continuous ambulatory peritoneal dialysis takes an alternative approach to improving the efficiency of peritoneal dialysis—namely, operating at very low clearances but doing so continuously. In this manner, total clearances of urea per week can approach 75% of the weekly clearance of urea on the standard hemodialysis regimen [20]. Another interesting advantage of CAPD is that even if 80% of the peritoneum were destroyed, approximately the same degree of control of BUN would be possible because urea clearance would remain largely dependent on dialysate flow rate. That is, even with marked reduction in peritoneal surface area, diffusion equilibrium can be achieved for urea during the typical 4-hour dwell time used in CAPD, and the same amount of urea will be removed. Higher weight molecules such as inulin, however, would have a reduced clearance proportional to the reduction in peritoneal surface area—for example, some 20% of the clearance of the intact peritoneum. Nevertheless, because inulin clearances per week on CAPD are about six times that with hemodialysis, CAPD approaches the efficiency of hemodialysis even at 20% of normal clearance. Thus, CAPD does offer a way around the problem of low clearances of small solutes in peritoneal dialysis. Otherwise, the patient is faced with long hours of intermittent peritoneal dialysis at very high flow rates and even then the weekly urea clearances of hemodialysis are not approached.

DR. J. J. COHEN: On your scale of small versus large molecules, where does the "middle molecule" fall?

DR. K. D. NOLPH: The so-called middle molecule usually refers to substances with molecular weights in the range of 500 to 5,000 daltons [40]. The middle molecule hypothesis actually stemmed from observations that patients treated with chronic peritoneal
dialysis had a lower or no greater incidence of neuropathy than those treated with hemodialysis [41-45]. It seemed to follow that since the main difference between peritoneal and hemodialysis was that peritoneal dialysis removed large solutes well and small solutes poorly, neuropathy must be related to some higher molecular weight substance or substances. At what molecular weight does peritoneal dialysis become more efficient than hemodialysis? It seems to depend on the peritoneal dialysate flow rate. With the flow rates used in CAPD, the break point is at approximately 1,000 daltons on a weekly clearance basis [20].

DR. J. T. HARRINGTON: One important issue raised by this patient is the difficulty in comparing the effects of hemodialysis and peritoneal dialysis even in the same individual. A major problem is the fluctuating nature of the hemodynamic status in patients undergoing dialysis, illustrated in this woman by the change in ejection fraction that occurred over the period of observation. Does the Veterans Administration study attempt to control for changes in hemodynamic status?

DR. K. D. NOLPH: Obviously, there are many variables within the study. The hemodialysis technique, for example, is not standardized; a variety of techniques are permitted within the peritoneal dialysis regimen as well, although all techniques are intermittent rather than continuous; a variety of types of dialysis solutions and differences in approach are permitted. All of these nonpatient-related variables are important. The variables that I tried to point out in connection with this patient are patient-related variables. I tried to show how many different factors can affect a patient’s tolerance of one technique or another. In this patient, hemodialysis was very poorly tolerated at one time in her course, but tolerated well at a later time. That compounds the problem. In the Veterans Administration study, the intent is to overcome all of these variables by studying the results in a large pool of patients from a large number of centers. If there are distinct differences between hemodialysis and peritoneal dialysis regarding control of serum chemistries, symptoms, physical findings, and so on, it is felt they will emerge even though many uncontrolled variables are present. My major concern is that quantifiable differences will not emerge. I suspect that there may be more variables within the peritoneal dialysis group and within the hemodialysis group than there are between the two groups.

DR. E. TUTTLE: Do we know the size of this patient’s heart? The change of ejection fraction from 40 to 60% may be the result of a reduction in the end-diastolic volume because she was ultimately unloaded. It would be useful to know whether this improvement was the result of an improvement in the physical anatomical state of the heart or whether it reflected improved myocardial contractility. I would suspect that the major reason for the improvement was the reduction in fluid volume, which diminished her preload. I think it would be interesting to know this in assessing the change in her hemodynamic response.

DR. J. T. HARRINGTON: I think that you are right, Dr. Tuttle. Our assumption was that better volume control was responsible for the improvement in cardiac function.

DR. K. D. NOLPH: We have all seen improvement in cardiac status through good volume control, and I think that could have been a major factor in our patient. One could also question whether autonomic insufficiency due to uremic neuropathy played a role, which raises again the possibility that peritoneal dialysis, by removing middle molecules better, might have reduced her uremic autonomic insufficiency. Since we don’t have firm evidence that she had autonomic insufficiency, that is of course only a speculative possibility.

DR. J. J. COHEN: If you had the full range of dialysis techniques available to you, including CAPD, and were faced with a patient over the age of 50 with diabetes and evident vascular disease, what would your recommendation be concerning the mode of dialysis to employ?

DR. K. D. NOLPH: I have great hopes that, with the availability of peritoneal dialysis solutions in sterile bags, we will be able to reduce the infection rate in CAPD, rendering it more acceptable for use in many patients. Continuous ambulatory peritoneal dialysis has many advantages for the patient with cardiovascular instability because with it there are really no fluctuations at all in body fluid chemistries; they remain at a virtual steady state. Ultrafiltration doesn’t even have to be increased to the level of that with intermittent peritoneal dialysis; it goes on during each exchange four to five times daily. We have had several patients with diabetes who underwent CAPD using the less satisfactory glass bottle technique rather than sterile bags, and results have been relatively satisfactory aside from the infection problem. At this time, probably because I am at a center that is evaluating CAPD, I think I would be more than willing to consider a patient such as this for it. Because of the problems of vascular access and cardiovascular instability in pa-
tients with diabetes, I am often asked to accept such patients into the CAPD program.

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References


The editors should like to expand the scope of these exercises by encouraging active participation of the journal's readership in Nephrology Forum. Questions or comments pertaining to this month's discussion may be submitted to Nephrology Forum, Box 212, New England Medical Center Hospital, 171 Harrison Avenue, Boston, Massachusetts 02111. Correspondence received by July 31, 1979 will be eligible for inclusion in a forthcoming installment.