Author's Commentary

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Intermittent hemodialysis as generally performed is a hybrid treatment, combining continuous diffusive transport of solutes (dialysis) for removal of uremic toxins with convective transport (ultrafiltration) for removal of excess fluid, accumulating during the interdialytic period. However, a major complication during hemodialysis is intradialytic hypotension associated with symptoms of discomfort, which may require temporary stop of ultrafiltration, tilting the patient head-down and injection of sodium chloride to stabilize blood pressure. This problem is especially common when the treatment time is short (3–4 h or less) and large amounts of fluid have to be removed. At the time when our study was performed (more than 17 years ago) it was generally assumed that dialysis-associated hypotension was entirely caused by hypovolemia induced by too rapid fluid removal and that solute transport had no important role.

The background of this study was a serendipity observation, which I made in 1973 when I was in charge of a small dialysis unit at St. Erik's hospital in Stockholm. After having finished one dialysis session, the nurse told me that a female patient, BS, who was fluid-overloaded and used to develop symptomatic hypotension with sighing, anxiety and nausea during each dialysis session, had this time been dialysed and ultrafiltered to reach 'dry weight' without hypotension or other symptoms of cardiovascular instability. The patient confirmed that she had been feeling perfectly fine during the whole treatment. We then looked at the dialysis monitor and found a technical fault. The machine had been in bypass position during the treatment without giving an alarm, implying that no dialysis fluid was flowing through the dialyser (no diffusive transport was taking place), while ultrafiltration by hydro-

static transmembrane pressure gradient was going on undisturbed. Hence, it appeared that in this patient some factor associated with diffusive transport rather than with ultrafiltration (hypovolemia) might be the cause of her cardiovascular instability.

After this event we made several trials in fluid-overloaded patients with cardiovascular instability in whom we separated ultrafiltration from dialysis sequentially, or, in some cases, treated them with isolated ultrafiltration on separate days. Most of these trials confirmed that ultrafiltration was better tolerated when dialysis was not going at the same time, again suggesting that diffusive transport across the dialysis membrane might be involved in dialysis-associated cardiovascular instability. I remember especially a small boy brought to the intensive care unit with nephrotic syndrome and renal failure who was severely fluid overloaded, hypotensive and intolerant to conventional hemodialysis. In his case isolated ultrafiltration was life-saving; he could later be dialysed and soon recovered.

Encouraged by these preliminary observations, we decided to do a controlled trial, for which we selected six patients with problems of hemodialysis-associated hypotension. We compared the effect on weight loss, blood pressure, pulse rate and change in blood volume (hematocrit) during (1) conventional dialysis, combining diffusive and convective transport, (2) isolated ultrafiltration with dialysate bypassing the filter and (3) dialysis against a recirculating volume of 75 l dialysate (the Rodial system), a procedure expected to give less changes in solute concentrations than conventional dialysis. Treatment time was 3 h and the ultrafiltration rate was kept as high as could be tolerated. Our results unequivocally demon-

strated that isolated ultrafiltration was superior to single-pass dialysis regarding cardiovascular stability; blood pressure and pulse rate were stable despite rapid ultrafiltration (weight loss) and a 25% fall in plasma volume. In contrast, during single pass dialysis, all patients developed symptomatic hypotension, associated with increased pulse rate, despite less fall in plasma volume and body weight, suggesting dysregulation of the peripheral vascular resistance in response to hypovolemia. Cardiovascular stability was also better during recirculation dialysis than during single pass dialysis.

Our results were presented for the first time at the EDTA congress in Hamburg in May 1976 and published in the EDTA proceedings of this year. During the following years several reports confirmed our observation that rapid ultrafiltration was far better tolerated when performed isolated from dialysis (diffusive transport). Sequential ultrafiltration and dialysis and isolated ultrafiltration became important tools for treating patients with cardiovascular instability and hypotension during standard treatment. The obvious drawback with sequential treatment was of course that the total treatment time had to be prolonged in order to compensate for the time lost during ultrafiltration.

In our paper we discussed changes in osmolality, and concentrations of urea, sodium and other ions and effects on the autonomous nervous system as factors interfering with peripheral vasoconstriction. At that time we did not know that acetate, which was the dialysate buffer source

generally used at that time, is a strong vasodilator, which might interfere with regulation of vascular tone. Intolerance of acetate in sick hemodialysis patients was first described in 1976 by Novello et al. In more recent studies we demonstrated that both low dialysate sodium and presence of acetate inhibited or minimized the vasoconstrictive response to ultrafiltration and that their effects were additive.

These observations, reported during the years 1976–1980, had a major impact on the technical development of hemodialysis. Dialysis machines were designed which enabled isolated ultrafiltration, continuous production of dialysis fluid with bicarbonate, profiling of dialysate sodium concentration and intradialytic blood volume monitoring with feed-back control. However, it took more than 10–15 years before bicarbonate more generally had replaced acetate as a dialysate buffer source and even more time before other technical innovations such as dialysate sodium and blood volume profiling were introduced. Hemodialysis-associated hypotension is still a common everyday clinical problem in most dialysis units, which contributes to reducing the patient's quality of life.

Reference

Novello A, Kelsch RC, Easterling RE: Acetate intolerance during hemodialysis. *Clin Nephrol* 1976;5:29–32.