From Isolated Ultrafiltration to Blood-Temperature-Controlled Feedback: An Odyssey Started by Jonas Bergström

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Exactly 30 years ago, in 1976, Bergström, Asaba, Fürst and Oulès presented their ground-breaking findings on the benefits of isolated ultrafiltration at the EDTA congress. To mark this anniversary, the present issue of *Blood Purification* contains a reprint of the first description of the beneficial effects of isolated ultrafiltration, compared to ultrafiltration combined with haemodialysis, on haemodynamic stability during dialysis. Although a more detailed haemodynamic analysis of the effect of isolated ultrafiltration was published by the same group in *Kidney International* in 1979 [1], the first description of its clinical effects, as discussed at the EDTA congress in 1976, never appeared as a Medline-listed paper. A commentary to this paper was written some years ago by Jonas Bergström (1929–2001), professor emeritus at the Karolinska Institute in Stockholm, but was also never published until now. Here, it is published together with the original paper as an acknowledgement of the reviving interest in the thermal effects of dialysis and to give credit to the initiators of this odyssey.

Bergström, however, was not the first to prescribe isolated ultrafiltration. As you can see in figure 1, Alwall [2]

already applied isolated ultrafiltration in 1952. Alwall showed that ultrafiltration resulted in far better fluid removal when compared to haemodialysis with a high dialysate glucose concentration, which was employed until that time. However, Alwall did not report haemodynamic differences between isolated ultrafiltration and ultrafiltration combined with haemodialysis.

It is tempting to read, in the commentary of Jonas Bergström himself, that the improved haemodynamic stability during isolated ultrafiltration was actually discovered in 1973 by a technical fault of the dialysis module, which had been in bypass position without alarming, meaning that no dialysate had passed during the treatment. During this faulty treatment, fluid removal was remarkably well tolerated in a patient who used to experience symptomatic hypotension during every treatment. Due to Bergström's combination of clinical and scientific interest, this single observation was translated into a structured research program. The paper published in the EDTA proceedings and now again in this issue of *Blood Purification*, confirmed the initial observations in 6 hypotension-prone patients. As you also can read in the addendum to the EDTA proceedings paper, this road was further followed by Stanley Shaldon, who developed the sequential ultrafiltration-haemodialysis concept.

Prof. Jonas Bergström (1929–2001) was a honorary member of the International Society of Blood Purification.

Fig. 1. Original description of isolated ultrafiltration by Alwall. Illustration modified from Alwall [2; p. 8] and reproduced with permission.

In clinical practice, the name of Jonas Bergström was linked to the technique. One of the authors (J.K.) remembers, when starting his career in dialysis in 1990, hearing the term 'bergströmen' for the first time when performing research in the Kuratorium für Heimdialyse in Aachen. After some semantic misunderstandings due to differences between Dutch and German, it took only a short while before the meaning of this expression and its implications became clear to him. Not long after, a paper on the differences in arteriolar and venous reactivity between bicarbonate dialysis and isolated ultrafiltration was published [3].

The pathophysiological mechanisms behind the improved haemodynamic stability became clear during the years following the initial observations. Jonas Bergström showed that the discrepant effects of isolated ultrafiltration and haemodialysis on intra-dialytic blood pressure control were primarily due to an increase in peripheral vascular resistance during isolated ultrafiltration and a decrease during haemodialysis [1]. Initially, this increase was attributed to the absence of diffusive influx from acetate to the patient. However, peripheral vasodilation also turned out to be present, albeit to a lesser degree, during bicarbonate dialysis [4].

Already in the early eighties, the group of Quirino Maggiore pointed towards the importance of thermal factors in the pathogenesis of intra-dialytic hypotension during haemodialysis. During standard haemodialysis with a dialysate temperature of 37–37.5°C, core temperature increases, which leads to cutaneous vasodilation and interferes with the normal homeostatic response to hypovolaemia [5, 6]. It was already shown by Maggiore et al. [7], and later confirmed [8] that core temperature increases during dialysis even if no passive heat is transferred from the extracorporeal circuit to the patient. The pathophysiological mechanisms behind this phenomenon are still not completely elucidated. The increase in core temperature cannot be solely explained by circadian changes, and also occurs with sterile dialysate and biocompatible membranes [7, 9]. Moreover, endogenous pyrogen production is less likely to play an important role, because of the fact that core temperature also increases after administration of acetylsalicylic acid infusion [7] (fig. 2). Increased energy expenditure does also not appear to play a role [9]. It has been suggested that reduced heat dissipation from the skin, due to initial cutaneous vasoconstriction in response to a decline in blood volume could be responsible [10, 11], although also this hypothesis could

Fig. 2. First description of the hyperthermic effects of haemodialysis by Maggiore et al. [7]. Core temperature increases during dialysis in the absence of an arteriovenous temperature gradient and despite the infusion of acetylsalicylic acid. Reproduced with permission.

not be disproved in a later study [9]. Thus the cause behind the increase in core temperature during dialysis remains to be determined and is the scope of ongoing investigations. It would be of interest to study the thermal effects of seasonal and environmental factors and the effects of uraemic toxin removal.

Whatever the cause, with increased extracorporeal blood cooling, part of the fall in blood pressure during haemodialysis can be prevented [5]. This led to the emergence of so-called 'cool dialysis' as a manoeuvre to prevent intra-dialytic hypotension [12, 13]. It was also initially observed by the Maggiore group [14, 15] that thermal factors were largely responsible for differences in haemodynamic stability between haemodialysis on the one hand and isolated ultrafiltration and haemofiltration on the other. With more detailed thermal and/or haemodynamic analyses, these initial observations were in a later stage fully confirmed by other groups [16–18].

Although cooling of the dialysate to 35 or 35.5°C results in a reduction in symptomatic hypotension in sus-

ceptible patients [12–14], it is not an individualised treatment. The efficacy may depend upon the pre-dialytic body temperature of the patient [19]. Moreover, also depending on the pre-dialytic temperature of the patients, body temperature may decline during cool dialysis, which can result in shivering and uncomfortable feelings for the patient, but may even still increase in others [8]. By feedback technologies, a more sophisticated way of controlling core temperature has become available. By very frequent on-line measurements of core temperature during dialysis, followed by adjustment of dialysate temperature, the increase in core temperature during dialysis can be prevented without side-effects. It was again shown by Maggiore et al. [20] in a multi-centre trial that preventing the increase in core temperature by temperature-controlled feedback resulted in a greatly reduced incidence of intra-dialytic hypotension in susceptible patients.

Thus, in 25 years, a single observation which arose from a fault in dialysis treatment was followed by increased pathophysiological understanding of the haemodynamic response during dialysis, which in turn resulted in the emergence of sophisticated technological tools. Prevention of intra-dialytic hypotension not only has the opportunity to improve the quality of life of our patients [21], but might even have beneficial effects on the outcome of our patients [22].

In this time of evidence-based medicine and large randomised trials, an important lesson to be learnt from this paper is that skilful clinical observations, even in a single patient, can have important therapeutic implications. In this case, such an observation has translated into important clinical benefits to our patients and has greatly increased our understanding of the pathophysiological effects of dialysis treatment. However, it is no coincidence that such an observation was made by Jonas Bergström, one of the most eminent clinical scientists in the history of dialysis therapy.

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