Are continuous therapies superior to intermittent haemodialysis for acute renal failure on the intensive care unit?

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Introduction

Over the last decade significant advances have been made in the techniques available for the treatment of acute renal failure (ARF) in critically ill patients. First introduced by Kramer et al. [1] as continuous arteriovenous haemofiltration (CAVH), there are now various forms of continuous therapy suggested as having major advantages relative to intermittent haemodialysis (IHD) in the treatment of critically ill patient with ARF. These may include ease of implementation, superior metabolic control, the option of being able to remove fluid at any time of day or night, the facility of aggressive nutritional support, and improved haemodynamic stability [1,2]. It is for these reasons that continuous renal replacement therapy (CRRT) is increasingly used for the treatment of ARF on the ICU as opposed to the use of IHD.

In spite of this, it is not clear whether these improvements have resulted in a decrease in mortality of these patients. In addition, while abundant data are available upon the efficiency of CRRT, comparative data is scanty. This has led to considerable controversy as to which specific form of dialytic support should be preferred in this group of patients [2,3].

Metabolic control

It is repeatedly stated that CRRT allows better control of azotaemia and electrolyte and acid–base disturbances [2]. However, few studies have directly compared metabolic control obtained during CRRT and IHD. In two studies [4,5], better control of azotaemia was observed with continuous venovenous haemofiltration (CVVH) when compared to IHD in patients with surgical or medical ARF on the ICU. However, data upon the frequency and duration of haemodialysis procedures was not provided. Mauritz et al. [6] observed better azotaemic control with continuous venovenous haemofiltration (CVVH) (ultrafiltrate volume 37 l/day, i.e. urea clearance [K] 25.9 ml/day) when compared to IHD (interdialytic interval 42±12 h; duration 4–6 h) in patients with ARF secondary to abdominal sepsis. We have noted superior control of both azotaemia and acidosis in surgical

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ARF patients treated with continuous arteriovenous haemodiafiltration (CAVHD) \( (K = 24.6 \pm 0.4 \text{ ml/min for } Q_d 16,6 \text{ ml/min}) \) when compared to patients treated with bicarbonate IHD \( (3.3 \pm 0.2 \text{ times/week} ; \text{mean duration } 4 \text{ h (range } 1-5 \text{ h); } K = 160 \text{ ml/min}) \) [3]. Using urea kinetic modelling, Clark et al. [7] recently established a methodology to make a quantitative comparison between the azotaemia control provided by CVVH and IHD for patients with ARF on the ICU. They found that intensive haemodialysis \( (5.9 \text{ times/week for } K = 160 \text{ ml/min}; \text{5.2 times/week for } K = 200 \text{ ml/min}) \) was required to achieve azotaemia control similar to that provided by CVVH \( \text{(UF volume } 941 \pm 46 \text{ ml/h, i.e. } K = 15.2 \pm 0.9 \text{ ml/min}). \)

**Haemodynamic tolerance**

Another major putative advantage of CRRT over IHD is haemodynamic stability. Many studies have reported improved haemodynamic stability and gas exchange following the institution of CRRT [2,8]. Results can at least in part be explained by gradual volume removal, thereby allowing titration of left ventricular filling pressures and reversal of any existing pulmonary oedema [2,9,10]. One other explanation may be the convective removal of middle- and large-molecular-weight inflammatory mediators with vasoactive and cardiodepressant properties from the circulation [8]. Conversely, IHD is thought to have a deleterious effect on haemodynamics and gas exchange, when used in critically ill patients. Possible explanations include the effect of dialysate bath components (i.e., buffer anion used, sodium content, presence of cytokine-inducing substances), blood–membrane interactions, and rapid volume and osmolar shifts [2].

Comparative data on the haemodynamic tolerance of both therapies is scarce. In two retrospective studies improved haemodynamic stability was reported with CVVHD [4] and CVVH [6] compared to IHD in patients with combined medical and surgical ARF. However, IHD was performed using bioincompatible (i.e. cuprophane) membranes and acetate as buffering anion, both of which may have been possible confounding variables [2,11]. In another study improved haemodynamic stability was observed with CAVHD compared to more contemporary IHD (i.e. use of modified cellulosic membranes, high-sodium dialysate, and bicarbonate as buffering anion) in patients with postoperative or traumatic ARF [3]. Haemodynamic instability, however, seems to be confined to the duration of the dialysis session itself [3,6]. In the only randomized cross-over study to date, Misset et al. compared haemodynamic tolerance of CAVH and IHD in 27 patients with septic or postoperative ARF [12]. In their study, haemodynamic parameters did not support a better tolerance of CAVH compared to IHD \( (\text{mean MAP/24 h}} 83 \pm 20 \text{ versus } 81 \pm 18 \text{ mmHg; } \Delta \text{MAP/24 h}} 46 \pm 21 \text{ versus } 48 \pm 14 \text{ mm Hg; } \% \text{drop MAP}>10 \text{ mm Hg/24 h}} 25 \text{ versus 26; NS).} \)

**Fluid balance**

The ability to remove fluid is of major importance in the management of the anuric patient, not only to treat any volume overload, which may be an independent contributor to death, but also to create space for early nutritional support and all the necessary drug and blood transfusions. CRRT provides the option of being able to remove fluid at any time of the day or night, thus allowing fine control over the intravascular volume. Indeed, an improvement of gas exchange [9] and cardiac index [10] was documented following gradual fluid removal over several days. Most studies of CRRT have demonstrated that a significant negative fluid balance may be attained (net fluid removal exceeding 5 l/day) without compromising the already precarious condition of the critically ill patient with ARF [2,8]. With IHD, the ability of fluid removal is restricted to 2-4 h, thus necessitating high ultrafiltration rates, which may in itself create haemodynamic instability [3,4,6].

In one retrospective comparative study, CRRT allowed the daily delivery of 3.8 l of hyperalimentation or medications compared to only 2.1 l with IHD [13]. Others have also shown earlier and more aggressive nutritional support in patients treated with CRRT compared with patients treated with alternate-day IHD [3,4]. However, it is not yet clear whether aggressive nutritional support improves survival and the optimal nutritional strategy is still being sought [14]. Nevertheless, allowing catabolic ARF patients to become more malnourished would seem unjustified.

**Renal recovery**

Several observations suggest that IHD may contribute to the prolongation of ARF. In biopsies of patients with ARF requiring prolonged dialytic support, fresh ischaemic lesions were found clearly remote from the initial inciting event [15]. One effect of ischaemic ARF may be to impair renal autoregulation [3,15]. It may be that recurrent episodes of hypotension, as may occur during IHD [3,6], results in a proportionate fall in renal perfusion pressure, thus inducing fresh episodes of tubular necrosis or preventing healing of established ARF.

The type of membrane may also play a role in the prolongation of ARF. Both experimental and clinical data suggest that use of cuprophane membranes in the treatment of ARF may prolong the duration of ARF when compared to the use of synthetic membranes [11]. Recently, a significant decrease was observed in residual renal function during IHD using synthetic membranes in 15 patients with non-anuric ARF on the ICU (combined average of creatinine and urea clearance [i.e., and estimate of GFR] pre-IHD \( 7.5 \pm 4.7 \text{ cm}^3/\text{min versus post-IHD } 5.4 \pm 3.2 \text{ cm}^3/\text{min; } P<0.01 \)) [16].

Few authors have compared the length of ARF in patients treated with CRRT or IHD. In one study
[17], as a significant difference was found in the duration of ARF, as defined by the length of dialytic treatment, between patients treated with CAVH combined with isovolaemic IHD compared to conventional IHD (17 (3–89) days versus 28 (8–111) days; \( P<0.05 \)). In another study [4], a trend towards a shorter duration of oliguria was found in patients treated with CVVHD compared with patients treated with IHD (13.8 days versus 22.8 days; NS). In these studies, however, differences may in part be explained by the use of acetate as buffering anion and use of cuprophane membranes in patients treated with IHD compared to the use of synthetic membranes in those treated with CRRT [2,11]. Van Bommel et al. [3] observed a significant difference in the duration of ARF, as defined by the length of dialytic support, between patients treated with CAVHD using polyacrylonitrile membranes and patients treated with bicarbonate IHD using cellulose-triacetate membranes (10.9 \( \pm \) 1.6 versus 17.6 \( \pm \) 3.4 days; \( P<0.05 \)).

### Outcome

Data available on outcomes in patients treated with CRRT are varied with mortality ranging from 40 to 80%, probably reflecting differences in underlying diseases or differences in the severity of disease that led to the development of ARF [2,8]. Because today renal failure is often but one of several failing organ systems, arising from complicated surgery or sepsis, these outcomes are often considered favourable compared to results of (earlier) reports of ARF patients treated with IHD [2]. However, lack of adequate description of the severity of disease in most studies precludes a meaningful comparison. The same holds true for some retrospective comparative studies in which enhanced survival was suggested of patients treated by CRRT compared to patients treated by IHD [6,18]. In few retrospective studies the APACHE II scoring system was used to describe disease severity to allow a meaningful comparison of both groups (Table 1). Enhanced survival of patients treated with CRRT was suggested by the finding of similar survival rates in patients treated with CRRT and IHD despite greater illness severity in those treated with CRRT [3,13]. In addition a significant survival advantage was found in patients with intermediate degree of illness (APACHE II 24–29), when treated with CRRT [4]. In the only prospective randomized study to date [19], no significant survival advantage was found in patients treated with CRRT compared to patients treated with bicarbonate IHD (29% versus 17%; NS). In addition other differences in dialysis delivery between CRRT and IHD, particularly the use of cellulosic membranes in patients treated with IHD as opposed to the use of synthetic membranes in patients treated with CRRT, may in part explain observed differences in favour of CRRT [4,6,13]. Indeed, recent data suggest that decreased mortality of ARF patients may in part represent a membrane effect (i.e. increased biocompatibility) [11,20].

Outcome and recovery from ARF may also relate to the ultrafiltration volume, which is attributed to the enhanced clearance of inflammatory mediators involved in the pathogenesis of septic shock and multiple organ systems failure (MOSF) [2,8,21]. Indeed, several authors have extended their indications for CRRT to various shock states, irrespective of the presence of ARF [2,8]. However, such potential beneficial effect in the treatment of septic shock/(non-renal) MOSF has not yet been evaluated in a formal prospective, controlled clinical trial. In addition, combined data from 32 published reports showed similar outcome in ARF patients (\( n=1614 \)) treated with different forms of CRRT [2].

### Conclusion

Final proof that continuous blood purification techniques improve outcome in ARF on the ICU has still to be provided. It may be that renal failure as such does not contribute sufficiently important to death in MOSF for there to be a demonstrable difference in outcome between patients treated with CRRT and IHD. However, ease of implementation, the facility of full nutritional support, superior metabolic control, improved haemodynamic stability, and perhaps a shorter duration of oliguria afforded by CRRT would appear to justify its use as the treatment of choice in the ICU setting. Recently pump-driven forms have been advocated as the preferred continuous treatment modality as it eliminates the need for arterial cannulation and its inherent complications [2,4], and

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<th>First author [ref]</th>
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For abbreviations see text. \# \( P<0.05 \) versus IHD; \# no statistical analysis performed. IHD was performed using cuprophane [4,13] or cellulose-triacetate [3] membranes as opposed to the use of synthetic membranes in CRRT [3,4,13].
because of the possible enhanced convective clearance of inflammatory mediators from the circulation [2,8]. However, no particular form of CRRT has yet been shown to be superior in terms of survival and patient outcome continuous to depend on the underlying disease process [2].

Further studies are needed to assess long-term effects of CRRT on morbidity and mortality and to establish the preferred continuous treatment modality unequivocally. In addition, research is warranted to provide a rational for the use of CRRT in the absence of conventional indications for dialytic support.

References


Hyperlipidaemia of the nephrotic syndrome—the search for a nephrotic factor

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Nephrotic syndrome, a controversial syndrome

Although nephrotic syndrome has been recognized for centuries, and considerable effort has been devoted to understanding the mechanisms underlying this condition, the pathophysiological processes involved are a source of continuing controversy. More specifically, the exact pattern of the hyperlipidaemia is still under discussion [1], mainly because: (a) the influence of a number of possible variables is difficult to surmount in controlled studies, e.g. diabetes mellitus, medication, renal failure, histological diagnosis, differences in age, sex or body weight, the wide range in proteinuria and hypoalbuminaemia, hypertension, etc.; (b) the existence of different causative factors in the primitive glomerular lesion; and (c) the lack of simple, reliable and safe technologies to study the human nephrotic syndrome in vivo. Therefore, the mechanisms of hyperlipidaemia in the nephrotic syndrome remain obscure, and no single mechanism so far proposed explains the different rearrangements observed in triglyceride- and/or cholesterol-rich lipoproteins. The reported increase in serum lipoprotein (a) levels, which are genetically determined, has added more confusion, suggesting a possible role of the kidney in lipoprotein metabolism [2]. The importance of clarifying this