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Validity of low-efficacy continuous renal replacement therapy in critically ill patients

Hiroo Kawarazaki[1, 2], Shigehiko Uchino[3]

[1]*Department of Nephrology, Inagi Municipal Hospital, Tokyo, Japan*
[2]*Department of Nephrology and Hypertension, St. Marianna University School of Medicine, Kanagawa, Japan*
[3]*Intensive Care Unit, Department of Anesthesiology, Jikei University School of Medicine, Tokyo, Japan*

Abstract

The 1980s saw the use of continuous arteriovenous hemofiltration whose intensity hemofiltration rate was only 3 or 4 mL kg^{-1} h^{-1}. With the installation of a blood pump, this dose went up to 8 or 10 mL kg^{-1} h^{-1}, and continued to increase, reaching about 20 mL kg^{-1} h^{-1} by the year 2000. Some studies found that a higher dose could be beneficial, and the world rapidly followed the trend, increasing the dose up to 35 mL kg^{-1} h^{-1}. Then, two randomized control trials, namely the VA/NIH Acute Renal Failure Trial Network study and the RENAL study, came along in succession which changed the Kidney Disease: Improving Global Outcomes (KDIGO) recommendation to 20 to 25 mL kg^{-1} h^{-1}. However, no good evidence exists to support this. Our recent multicenter retrospective studies from the JSEPTIC CRRT database show that the Japanese continuous renal replacement therapy dose of (14.3 mL kg^{-1} h^{-1}) does not seem to have worse outcomes when compared with a higher dose.

Key words: acute kidney injury, critically ill, CRRT intensity

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Numerous studies conducted over recent decades have demonstrated that acute kidney injury (AKI) is an independent risk factor for mortality [1, 2]. This has led to the idea that high performance renal replacement therapy (RRT) may overcome the harm of severe AKI often seen in critically ill patients. Continuous RRT (CRRT), which has become a widespread strategy in the ICU, is favored for critically ill patients who are hemodynamically unstable. There have been many discussions in the past about the most appropriate form of CRRT regarding modality, hemofiltration rate, anticoagulants, timing, etc. In this review, we will discuss the history and current trends in CRRT hemofiltration rates, a subject which has become one of the hot topics concerning CRRT in the last decade.

THE HISTORY OF CRRT

The first study on the hemofiltration rate of CRRT was published in 1991 [3]. Until 1980s, continuous arteriovenous hemofiltration (CAVH) in which blood flow is obtained by the pressure difference between the artery and vein, was used for CRRT. Later, a blood pump was introduced into the circuit which enabled stable blood flow from vein back to vein, leading to the development of continuous venovenous hemofiltration (CVVH). As blood flow was increased, the ultrafiltrate volume also grew, from 7 L per day to 15.7 L per day, while survival rates also increased, from 12.5% to 29.4% [3]. Nowadays, "mL kg^{-1} h^{-1}" is used to describe the hemofiltration rate of CRRT, meaning that 15.7 L per day for a body weight of 75 kg is approximately 8.7 mL kg^{-1} h^{-1} while 7 L per day for a body mass of 75 kg is 3.9 mL kg^{-1} h^{-1}. The Beginning and Ending Supportive Therapy for the kidney (BEST) study was a multinational observational study on acute renal failure which included 1700 patients in 54 ICUs in 23 countries [4]. In a subgroup analysis of 1000 CRRT patients, the median treatment dose was 2000 mL h^{-1}, which when corrected for body weight, was 20.4 mL kg^{-1} h^{-1} [5]. This was common practice worldwide in 2001, when this study was conducted.

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MOVEMENT TO HIGHER CRRT

HEMOFILTRATION RATE

In 2000, a single center randomized control trial (RCT) was conducted which compared CRRT intensity dosesof 20, 35, and 45 mL kg^{-1} h^{-1}. Although it found that dose of 35 had better outcome compared to 20 mL kg^{-1} h^{-1}, no difference was found between 35 and 45 mL kg^{-1} h^{-1} [6].

Since then, several RCTs comparing different CRRT doses have been published. One compared doses of 19 and 48 mL kg^{-1} h^{-1} [7], 25 and 42 mL kg^{-1} h^{-1} [8], as well as 20 and 35 mL kg^{-1} h^{-1} [9]. These studies were all conducted in the first decade of the 21st century, with some of them finding improved outcomes [6, 8, 10].

Suggesting higher doses to be superior inspired many physicians to enforce even higher doses of ultrafiltrate volume. For example, in the DOREMI study, a multicenter observational study conducted mainly in Italy from 2005 to 2007, the median CRRT dose was 34.3 mL kg^{-1} h^{-1} [11]. Another survey conducted in the UK in 2009 and 2010 revealed that the most common standard dose of CVVH prescribed in ICUs was 35 mL kg^{-1} h^{-1} [12]. In an international survey for RRT in the ICU, in which 80% of respondents were from Europe, the average ultrafiltration dose was 35 mL kg^{-1} h^{-1}, while for septic patients it was also 35 mL kg^{-1} h^{-1} [13].

SKEPTICISM REGARDING HIGHER CRRT DOSES

The ICU community seemed to embrace and positively accommodate high CRRT doses. However, two significant papers changed the world again. One was an American study, published in 2008, which included 1124 patients and compared doses of 20 and 35 mL kg^{-1} h^{-1}, finding no difference in mortality [14]. The other was an Australian study, published in 2009, which included 1508 patients and compared doses of 25 and 40 mL kg^{-1} h^{-1}, again finding no difference in mortality [15].

Since then, multiple meta-analyses regarding hemofiltration rates have been published [16–19]. These included RCTs, as well as some observational studies, and found essentially the same result, namely that higher intensity does not improve outcome. Based on these findings, the KDIGO guidelines, the only international guidelines for AKI, recommends dose of 20 to 25 mL kg^{-1} h^{-1} for CRRT, with the recommendation grade of 1A [20].

Obviously these guidelines changed practice in the ICU yet again. A single center study in UK published last year, showed that based on the KDIGO guidelines, they switched the CRRT dose from 35 to 20 mL kg^{-1} h^{-1}, but did not find any differences in patient outcomes [21]. They also reported that costs were reduced by over £27,000 per year.

Summarizing the history of CRRT doses of, the 1980s saw the use of CAVH whose hemofiltration rate was only 3 or 4 mL kg^{-1} h^{-1}. With the installation of a blood pump, this dose went up to 8 or 10 mL kg^{-1} h^{-1}, and continued to increase, reaching about 20 mL kg^{-1} h^{-1} by the year 2000. Ronco *et al.* found that a higher dose could be beneficial, and the world rapidly followed the trend, increasing the dose up to 35 mL kg^{-1} h^{-1}. Then, two RCTs [14, 15] came along in quick succession which changed the recommended KDIGO dose to 20 to 25 mL kg^{-1} h^{-1} (Fig. 1).

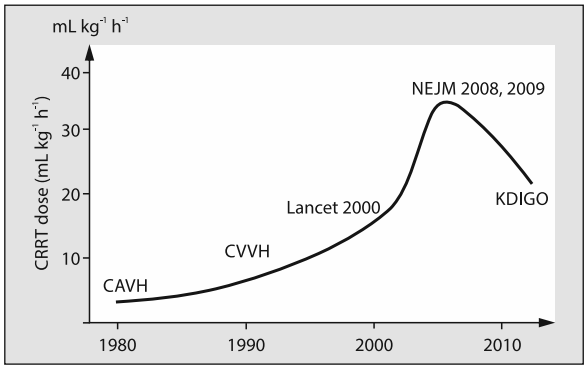

Figure 1. Dynamic change of trend in continuous renal replacement therapy (CRRT) doses [6, 14, 15]

WHY DOES HIGH INTENSITY CRRT NOT IMPROVE OUTCOMES?

High intensity CRRT is not without risks. Inevitably, it could lead to electrolyte abnormalities such as hypophosphatemia and hypomagnesemia, frequent machine problems, and inadequate drug administration, especially antibiotics. Therefore, seeking a lower limit regarding CRRT doses seems clinically important. Furthermore, the advantage of lower intensity CRRT is also related to the economic issues concerning CRRT. It is reported that the cost of CRRT is higher than that of intermittent hemodialysis [22], while the cost of higher-intensity CRRT is more than that of lower-intensity CRRT because of the greater volume of replacement/dialysis fluid required [23, 24]. This high cost can have a major impact, particularly in low- or middle-income countries.

ADVERSE EFFECTS OF HIGH INTENSITY CRRT

Higher doses of RRT may be associated with an increased risk of iatrogenic complications and/or comorbidity. Maynar-Molier coined the term "dialytrauma" for overdose RRT in critically ill patients with AKI [25]. The VA/NIH Acute Renal Failure Trial Network study [4] found higher incidences of hypotension, requiring vasopressor support and electrolyte disturbances such as hypophosphatemia and hypokalemia, and a longer duration of both RRT and hospital stay in the high-intensity group compared with the less-intensive group. The Renal Replacement Therapy study [15] documented seven serious adverse events (three cases of disequilibrium syndrome despite the early initiation of RRT;

one case of cerebral edema; one case of rectal bleeding; one case of cardiac arrest; and one case of too rapid correction of hyponatremia). In the lower-intensity group, there were five serious adverse events (three cases of heparin-induced thrombocytopenia; one case of hypoxemia; and one of cardiogenic shock). Hypophosphatemia was detected in 65.1% in the higher-intensity group and in 54% in the lower-intensity group.

CRRT THE "JAPANESE WAY" COMPARED TO THE MULTINATIONAL PRACTICE

In Japan, government policy allows the use of only 15 to 24 L per day of replacement fluid. Adjusted for a body mass of 60 kg, the dose is between 11 and 16 mL kg^{-1} h^{-1}. In such a defined policy, we conducted a retrospective observational study of fourteen Japanese ICUs in 12 tertiary hospitals (Japanese Society of Education for Physicians and Trainees in Intensive Care (JSEPTIC) CRRT cohort) [26] and compared it with the previously conducted multinational prospective observational (BEST) study including 54 ICUs in 23 countries [4]. This comprised a cohort of consecutive adult patients with severe AKI requiring CRRT admitted to the participating ICUs in 2010 (Japan, n = 343) and 2001 (BEST, n = 1006).

In the Japanese cohort, the median dose was 14.3 mL kg^{-1} h^{-1}, with very few patients having been treated with a higher dose. In the BEST study, however, the median was 20.4 mL kg^{-1} h^{-1} with many patients having been treated with higher doses (Fig. 2). Patient demographics showed (Table 1) that patients in Japan were older, with higher SAPS II scores, and as anticipated, lower body weight. Although vasopressor and ventilation requirements were almost the same, in Japan lactate was higher while platelet count was lower. These data suggest that the JSEPTC CRRT cohort may be more seriously ill than that in the BEST study. CRRT was

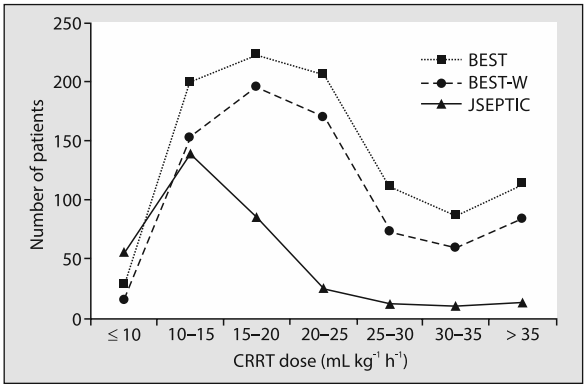

Figure 2. Distribution of CRRT doses in different cohorts. BEST — The Beginning and Ending Supportive Therapy for the kidney study cohort; BEST —W, only western countries of BEST cohort; JSEPTIC — Japanese Society of Education for Physicians and Trainees in Intensive Care cohort

Table 1. Demographics and variables of patients included in BEST cohort and JSEPTIC cohort

Demographics	BEST	JSEPTIC	*P*-value
Age, years	66 (51–74)	69 (59–77)	< 0.001
Gender, male	65.80%	65.90%	> 0.99
Body mass, kg	75 (65–85)	59 (50–68)	< 0.001
Chronic kidney disease	33.70%	28.90%	0.12
SAPS II score	48 (39–62)	53 (40–68)	< 0.001
Postoperative admission	45.30%	30.90%	< 0.001
Septic shock	50.20%	48.70%	0.66
Variables at CRRT initiation			
Vasopressor	78.80%	73.20%	0.036
Mechanical ventilation	84.10%	82.50%	0.5
PaO_2/FiO_2 ratio, Torr	210 (142–302)	205 (132–301)	0.68
Lactate, mmol L^{-1}	2.3 (1.2–5.2)	2.8 (1.5–6.2)	0.008
Glasgow Coma Scale	14 (10–15)	14 (9–15)	0.4
Platelet count, G L^{-1}	119 (63–196)	87 (54–152)	< 0.001
Bilirubin, mmol L^{-1}	20 (12–49)	19 (10–41)	0.017
Urine output, mL h^{-1}	17 (4–47)	19 (8–43)	0.15
Creatinine, µmol L^{-1}	292 (192–427)	240 (164–334)	< 0.001
Urea, mmol L^{-1}	23 (15–34)	17 (12–26)	< 0.001
ICU to start of CRRT, day	1.2 (0.4–4.1)	0.8 (0.2–1.9)	< 0.001

BEST — The Beginning and Ending Supportive Therapy for the kidney study cohort; JSEPTIC — Japanese Society of Education for Physicians and Trainees in Intensive Care cohort; SAPS — simplified acute physiology score

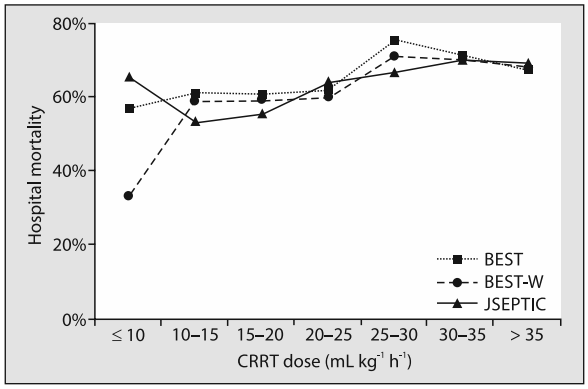

Figure 3. Hospital mortality among different CRRT doses in different cohorts. BEST — The Beginning and Ending Supportive Therapy for the kidney study cohort; BEST —W, only western countries of BEST cohort; JSEPTIC — Japanese Society of Education for Physicians and Trainees in Intensive Care cohort

started slightly earlier, 0.4 days or 10 hours as a median in Japan. As it turned out, there seemed to be no difference between the two cohorts, and no improvement with increasing intensity of treatment (Fig. 3). The result of a multivariable analysis of hospital mortality showed that the JSEPTIC CRRT cohort had a very low odds ratio compared with that in the BEST study (Table 2A). This may be because there is nine-year difference between the two studies. More importantly, compared to 20–25 mL kg^{-1} h^{-1} as a reference, lower and higher doses did not have significantly different odds ratios.

As septic patients may require higher doses, a subgroup analysis for this group was performed (Table 2B). Moreover, since the BEST study included lower-income countries which may affect the significance of doses, another subgroup analysis including only patients from Western countries was carried out. However, compared to 20–25 mL kg^{-1} h^{-1} as a reference, lower and higher doses still did not show significantly different odds ratios (Table 2B).

CRRT DOSES AND SMALL SOLUTE REMOVAL

From the JSEPTIC CRRT cohort, the daily delivered dose and average delivered dose was calculated to reveal a relationship with small solute changes in the blood [27]. The daily dose was defined as the mean dose over each 24-h period (from 6:00 AM to 6:00 AM next day). For example, if CRRT was performed at 15 mL kg^{-1} h^{-1} for 4 h and also at 10 mL kg^{-1} h^{-1} for 10 h in one day (with a period of 10 h with no CRRT), the daily dose was calculated as: (15 mL kg^{-1} h^{-1} × 4 h + 10 mL kg^{-1} h^{-1} × 10 h) / 24 h = 6.7 mL kg^{-1} h^{-1}. The average dose was defined as the mean of the daily dose during the period during which CRRT was being performed in the ICU.

Creatinine increased by approximately 3% only in the < 10 mL kg^{-1} h^{-1} group and decreased in correspondence to

Table 2. Multivariable logistic regression analysis for hospital mortality; a) for the whole cohort and b) subgroup analysis including only septic patients or those from western countries

A

	Odds ratio (95% CI)	*P*-value
Database		
BEST	1.000 (Reference)	–
JSEPTIC	0.518 (0.363–0.739)	< 0.001
Intensity, mL kg^{-1} h^{-1}		
≤ 10	1.483 (0.740–2.972)	0.27
10–15	1.173 (0.740–1.860)	0.5
15–20	1.061 (0.668–1.686)	0.8
20–25	1.000 (Reference)	–
25–30	1.415 (0.741–2.701)	0.29
30–35	1.283 (0.648–2.539)	0.47
> 35	1.166 (0.619–2.197)	0.63

B

	All patients with sepsis		BEST-W & Japan	
	Odds ratio	*P*-value	Odds ratio	*P*-value
Database				
BEST	1.000 (Ref)	–	1.000 (Ref)	–
JSEPTIC	0.409	0.001	0.571	0.0033
Dose, mL kg^{-1} h^{-1}				
≤ 10	1.039	0.94	1.144	0.59
10–15	1.274	0.49	1.556	0.22
15–20	0.857	0.65	1.019	0.94
20–25	1.000 (Ref)	0.78	1.000 (Ref)	–
25–30	1.387	0.47	1.147	0.69
30–35	1.314	0.56	1.187	0.65
> 35	0.786	0.6	1.316	0.42

BEST — The Beginning and Ending Supportive Therapy for the kidney study cohort; JSEPTIC — Japanese Society of Education for Physicians and Trainees in Intensive Care cohort; SAPS — simplified acute physiology score

the increasing daily dose in the other groups (10–15, 15–20, > 20 mL kg^{-1} h^{-1}). Urea decreased and creatinine increased as the average dose increased. The relative changes of serum creatinine and urea levels remained at the same level over the 7 days in the < 10 mL kg^{-1} h^{-1}group [27].

WHERE DO WE STAND? IF LESS IS MORE, HOW MUCH LESS?

As mentioned in a recent editorial entitled "'Less is more" in critically ill patients; not too intensive', in a "group of highly vulnerable patients, more intensive treatment may promote the chances of unwanted adverse effects and hence, iatrogenic damage" [28]. If the lower limit of CRRT intensity was to be defined by the limit of solute control, this would seem to be somewhere around 10 mL kg^{-1} h^{-1}.

Adequate treatment for AKI probably does not merely mean that small solutes such as urea should be intensively removed. The kidney is a very complex organ sustaining homeostasis with many vital roles which are often mentioned in the chronic kidney disease literature; e.g. solute removal, correcting electrolyte disorder, blood pressure control, anemia correction, inflammation reduction, glycometabolism, nutrition etc. However, not much is known about its multi-functional role in the AKI setting. Perhaps a greater knowledge of the role of the kidneys in the critically ill may further advance progress in intensive care.

CONCLUSION

Although KDIGO guidelines recommend the lower limit of CRRT intensity as 20–25 mL kg^{-1} h^{-1}, no good evidence exists to support this. The current Japanese CRRT dose (14.3 mL kg^{-1} h^{-1}) does not seem to have worse outcomes when compared with higher doses .

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Adres do korespondencji:
Prof. Hiroo Kawarazaki
Department of Nephrology, Inagi Municipal Hospital
1171 Ohmaru, Inagi City, Tokyo, Japan
e-mail: hirookawarazaki@yahoo.co.jp

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