Optimization of Design Factors of Hemodiafilter for Continuous Renal Replacement Therapy (CRRT) in terms of Solute Removal Performance

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論文内容の要旨および審査結果の要旨

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１．論文内容の要旨

Continuous Renal Replacement Therapy (CRRT) refers to all continuous and slow water and solute removal treatments intended to provide long-term support mainly for renal function in critically ill patients with hemodynamic instability in the intensive care unit (ICU). This dissertation consists of the following six chapters.

Chapter 1 provided an overview of the evolution, main treatment modes, and clinical importance of CRRT. Since Kramer *et al.* proposed continuous arterio-venous hemofiltration (CAVH) in 1977 and implemented it in clinical practice, CRRT has gained broad usage in critical care medicine. This usage has arisen from treatment mode diversification, as well as progress in the design of related consumables and blood purification devices. CRRT has become the recommended treatment approach for acute kidney injury because of its capacity to remove multiple uremic toxins while maintaining hemodynamic stability. Advances in technology have facilitated the use of CRRT in the treatment of critical illnesses such as sepsis and multiple-organ dysfunction syndrome; it has expanded from supporting renal function to supporting the functions of organs such as the heart, liver, and lung. Therefore, further improvement in the blood purification treatment effect of CRRT has become a key research focus.

Chapter 2 provided an overview of the main factors and performance indicators that affect CRRT filter performance. CRRT filters have hollow fiber structures developed from dialyzers for conventional hemodialysis (HD) therapy. For each filter, the effectiveness and safety profile are determined by the performance of the internal hollow fiber membrane and the external housing design. Thus far, there have been few *in vitro* studies regarding CRRT filters; most previous studies focused on improvements in membrane performance to satisfy the clinical need for continuous treatment lasting more than 24 hours. There has been minimal in-depth exploration of the effects of various design factors on filter performance. Furthermore, dialyzer

performance indicators are frequently used to evaluate CRRT filter performance; there is no comprehensive system for evaluating the effectiveness and safety profile of CRRT filters. CRRT filter effectiveness is mainly determined by the clearances for low molecular weight substances (LMs, e.g., urea, Cr, and inorganic P) and middle molecular weight substances (MMs, e.g., vitamin B_{12}, β_2-microglobulin, and myoglobin). In terms of the safety profile, CRRT filters are required to maintain transmembrane pressure (*TMP*) as low as possible during long-term treatment; this avoids the exacerbation of hemodynamic instability because of rapid changes in water and solute concentrations. Furthermore, it is possible to minimize the cumulative loss of nutrients (e.g., albumin) while maintaining overall homeostasis.

Chapters 3–5 presented a series of studies that evaluated the relationships of design factors with the effectiveness and safety profile of CRRT filters by analyzing nine different prototype models with combinations of packing density of the hollow fibers (*PD*) and housing shape (ratio of the effective length, *L*, to the diameter, *D* = *L*/*D* ratio). Relationships between design factors and CRRT filter removal performance were explored in Chapter 3. It is the first to conduct Doppler ultrasonography to measure the $Q_{IF\text{-}Max}$ of CRRT filters and then facilitated an exploration of the effects of various design factors on convection effects, further revealed the mechanisms influencing overall molecular uremic toxin removal performance. The results showed that design factors did not have a significant effect on LMs removal performance; however, optimization of *PD* and *L*/*D* ratio could improve MMs removal performance, enabling the same membrane to display greater effectiveness. In Chapter 4, the effects of *PD* and *L*/*D* ratio on hemodynamic stability and the loss of albumin were explored to characterize the relationships between design factors and the safety profile of CRRT filters. Through the construction of a comprehensive *in vitro* evaluation system that comprised continuous *TMP* monitoring, attenuation of hydraulic permeability, concentration polarization mass transfer resistance, albumin sieving coefficient over time, and amount of albumin removed, the mechanism of temporal protein filtration performance was analyzed; the impacts of design factors on the safety profile of CRRT filters were comprehensively evaluated. The results demonstrated that the optimization of design factors could effectively control the albumin filtration performance of CRRT filters; it could also improve the safety profile of CRRT filters. With the polysulfone (PSf) hollow fiber membrane (d = 0.20 mm, Δx = 0.04 mm, k_{UF} = 22 - 23 mL/(hr mmHg), mean pore size = 5 - 6 nm), the model LS-3 (*PD* = 60% and *L*/*D* ratio = 9.3 [-]) had the optimal solute removal performance and safety profile. Chapter 5 explored the impacts of various design factors on internal filtration (convection effects), as well as the mechanisms that influence MMs removal performance. Furthermore, experimental verification was conducted by constructing a multiple linear regression model of design factors and $Q_{IF\text{-}Max}$. Finally, an accurate and practical design equation was proposed to quantify the design factors, influencing CRRT filters and

convection effects: $Q_{\mathrm{IF-Max}} = -34.775 + 4.749 \times \frac{N}{D^2} + 2.293 \times \frac{L}{D}$, where the impacts of N/D^2 and L/D ratio on $Q_{\mathrm{IF\text{-}Max}}$ are 15.0% and 85.0%, respectively. With the range of parameters evaluated in this study (continuous veno-venous HD mode, Q_{BI} = 100 mL/min, Q_{D} = 16.7 mL/min (= 1000 mL/hr); PSf hollow fiber membrane (d = 0.20 mm, Δx = 0.04 mm, k_{UF} = 22 - 23 mL/hr/mmHg, mean pore size = 5 - 6 nm); PD, 50 - 60%; L/D ratio, 2.9 - 9.3), the design equation is generalizable. Through simple substitution of design factor parameters without the requirement for filter sample production or experimental investigation, the proposed design equation was able to effectively quantify the convection effects of CRRT filters with different design factors, thereby predicting MMs removal performance.

Chapter 6 summarizes three previous chapters (Chapters 3–5) to have comprehensive discussions of the measured internal filtration rate, design factors (PD and L/D ratio) of a diafilter, and the design equation to predict and/or to design diafilters with better solute removal performance.

Considering the widespread application of CRRT in critical care medicine and nephrology, improvements in CRRT diafilter performance are expected to have major impacts on clinical treatment effectiveness. This study conducted a series of analyses concerning the impacts of design factors on CRRT diafilter performance and established a complete evaluation system, which has significant implications for the development of new CRRT filters.

２．審査結果の要旨

Although diafilters used in CRRT are similar to dialyzers used in conventional HD therapy, since the therapeutic conditions, including blood flow rate, dialysate flow rate, ultrafiltration flow rate, and substitution flow rate, are totally different each other, a design procedure specifically prepared for CRRT must be preferred. In this study, it was the first in this field to measure the rate of internal filtration, the forward ultrafiltration from the blood to the dialysate compartment and its reverse filtration from the dialysate to the blood compartment occurring in one dialyzer at the same time, for the nine prototype diafilters in CRRT by using the Doppler ultrasonography; moreover, it was reported that measured values were surprisingly high in one of nine models (model LS-3, shown below). Also, the decision was made to move towards to increase the rate of internal filtration in order to maximize performance (clearance) for removing middle molecules that are known to have higher toxicity.

The applicant measured clearances for low and middle molecular weight substances and found that higher clearances were associated with higher packing density of the hollow fiber and higher L/D ratio (model LS-3 with PD = 60% and L/D ratio = 9.3). The applicant also developed

a design equation of diafilters for CRRT, introducing a multiple linear regression analysis technique. By using this equation, one can predict the solute removal performance of a specific model with the same membrane without performing any experiments. Although a trial-and-error method is still an important procedure in the design process of dialyzers, it is crucial to decrease the number of trial-and-errors in order to reduce the development budget and to shorten the development time. Although the design equation may be valid only for the model with the same PSf membrane, it is yet simple and is easy to use for predicting the performance just by input necessary design factors without performing cumbersome experiments. A series of these findings obviously contribute to the development of new diafilter models with better performance for CRRT that contributes for the treatment of patients with acute and critically ill.

The oral examination results on this dissertation and other related scholarly fields including three peer-reviewed articles indicated that the applicant has sufficient academic knowledge both in chemical engineering and in critical care medicine. Based on all of these facts, this examination committee is unanimous that the submitted doctoral thesis is fully qualified as a Doctor of Philosophy (Science).