INDOXYL SULFATE CLEARANCE RISES WITH TEMPERATURE: BUT IS THERE A HYSTERESIS EFFECT?

João Brás (1), Fokko Wieringa (1,2), Emma Sünnen (1), Jeroen Vollenbroek (1,2,3), Karin Gerritsen (1)

1. Department of Nephrology and Hypertension, University Medical Centre Utrecht, Utrecht, The Netherlands; 2. IMEC, Holst Centre, 5656 AE Eindhoven, The Netherlands; 3. BIOS Lab on a Chip Group, MESA + Institute, University of Twente, Hallenweg 15, 7522 NH Enschede, The Netherlands

Introduction

Current hemodialysis methods inefficiently remove protein-bound uremic toxins (PBUTs, which are strongly bound to plasma proteins like albumin) leading to complications such as cardiovascular disease and uremic syndrome. Several PBUT removal strategies are currently explored, such as the use of chemical displacers, adsorbents, increased ionic strength or pH variations [1], but still require more research before reaching clinical use. In this work, we investigated whether increased albumin temperature (up to 42°C) may improve Indoxyl Sulfate (IS) removal, as albumin-IS binding is known to be temperature dependent (higher temperatures lead to lower bound fractions) [2].

Methods

Fig. 1 shows the used setup, where caprylate-stabilized, isotonic infusible albumin solution (40g/L) was spiked with IS (60µM) and dialyzed (Polyflux 2H) against fresh bicarbonate dialysate (Dirinco BV). Both dialysate and albumin solutions were recirculated throughout the test. Real-time dialysate IS concentration was measured with an in-line fluorescence sensor (OptoFluid Tech., Estonia). After 30 mins stabilization, dialysate IS levels reached equilibrium, after which temperature was stepwise increased and then decreased (Fig. 2).

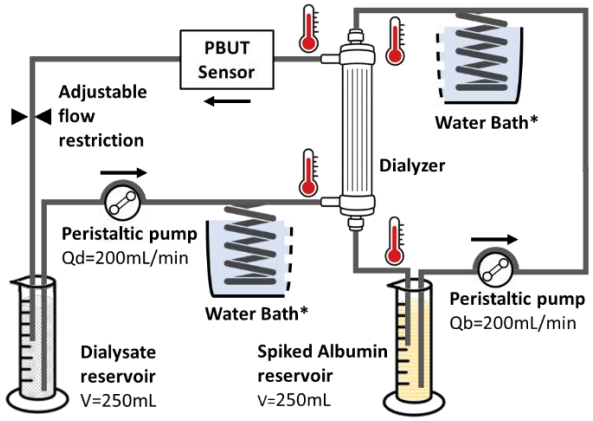

*Figure 1: Experimental setup. Qd = dialysate flow; Qb = albumin flow. *One water bath held both coils. We drew both coils separately for circuit clarity.*

Both solutions were heated by coiled tubing sections in the *same* water bath. Thermocouples monitored all 4 dialyzer connectors. Free IS fractions were derived from the PBUT sensor readings using Eq. 1:

$$\text{Free Fraction}_{IS} = \frac{C_{IS,free}}{C_{IS,total}} \qquad (1)$$

Where: $C_{IS,free}$ is 2x the sensor reading with the system in equilibrium, and $C_{IS,total}$ was determined with HPLC.

Results

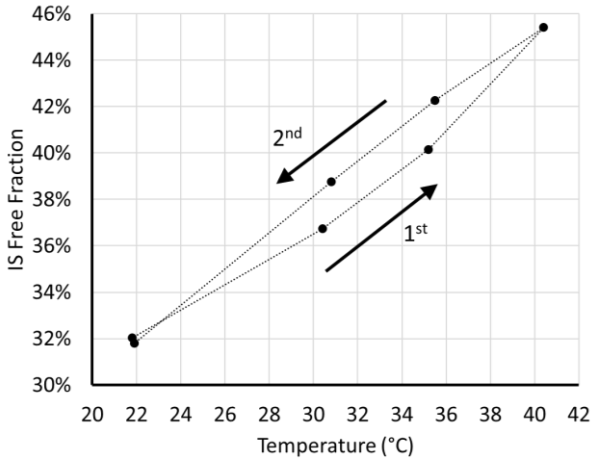

Figure 2: Effect of increasing (1st) and decreasing (2nd) temperature on Indoxyl Sulfate free fraction.

Discussion

Temperature-enhanced PBUT removal works and might be desirable because it doesn't break circuit sterility, is reversible and looks technically combinable with current HD machines. However, our results reveal a peculiar hysteresis-like behavior with a convex/concave shape which we'd like to discuss during the ESAO ALBUNET session. Existing literature is scarce and suggests a linear behavior (but based at just 3 temperatures) [2]. We present work-in-progress. More research, with repetitive temperature cycles, seems needed regarding the - here observed - "hysteresis-like" effect, as well as regarding long-term blood integrity, maximum safe blood temperature and other possible side effects.

References

1. Sánchez-Ospina D. et al, J. Clin. Med, 13:1428, 2024.
2. Deltombe O. et al, Anal. Methods, 9:1935-1940, 2017.

Acknowledgements

We thank the ALBUNET group for their advice regarding the use of albumin in this work.
This project was funded by a KidneyX Artificial Kidney Prize (project name: MI-TRAM).