Dialyzer single use versus reuse. Scientific verification of dialyzer reuse

--Evaluation of solute permeability, safety and biocompatibility of reuse dialyzer in vitro and in vivo--

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Outline

- Introduction
- In vitro experiment:
  - Blood leak & TCV
  - Risk of reuse
  - Water permeability
  - solute permeability for large middle molecule
- Clinical trial (Preliminary analysis)
- Conclusions

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Introduction

- Almost 60 years have passed since the concept of dialyzer reuse in hemodialysis patients was introduced for primarily economic reasons.
- In the United States, more than 80% of dialysis facilities reused dialyzers in 1997[1], but the practice declined steadily thereafter, and it is currently estimated to be employed by only a minority of American facilities [2].
- The practice is substantially less prevalent in Europe and prohibited in Japan [3].
- Dialyzer reuse, however, remains widespread in some developing countries [4, 5].

1. Recommended practice for reuse of hemodialyzers. Arlington, VA, AAMI 1993
2. Zumoff R: Dialysis providers shift towards single-use dialyzers. Nephrol New Issues, 2016
3. Vinhas J, et al. : Haemodialyser reuse: facts and fiction. Nephrol Dial Transplant 15:5–8, 2000
4. Cusumano A, et al. : The Latin American Dialysis and Transplantation Registry (RLDT) annual report 2004. Ethn Dis 16:S2-10–S2-13, 2006
5. Jha V: Current status of end-stage renal disease care in South Asia. Ethn Dis 19:S1-27–S1-32, 2009

What we do/don’t know about dialyzer reuse

What We Know about Dialyzer Reuse

① Risk of bacterial contamination during the reprocessing process[1)]

② Decrease in blood side volume (TCV) due to reuse

③ No decrease in small molecule removal performance [2)]

What We Don't Know about Dialyzer Reuse

① Removal performance of middle-molecule

② Biocompatibility:

“Reusing dialyzers improves biocompatibility because the proteins are coated”, ← Is this scientifically correct?

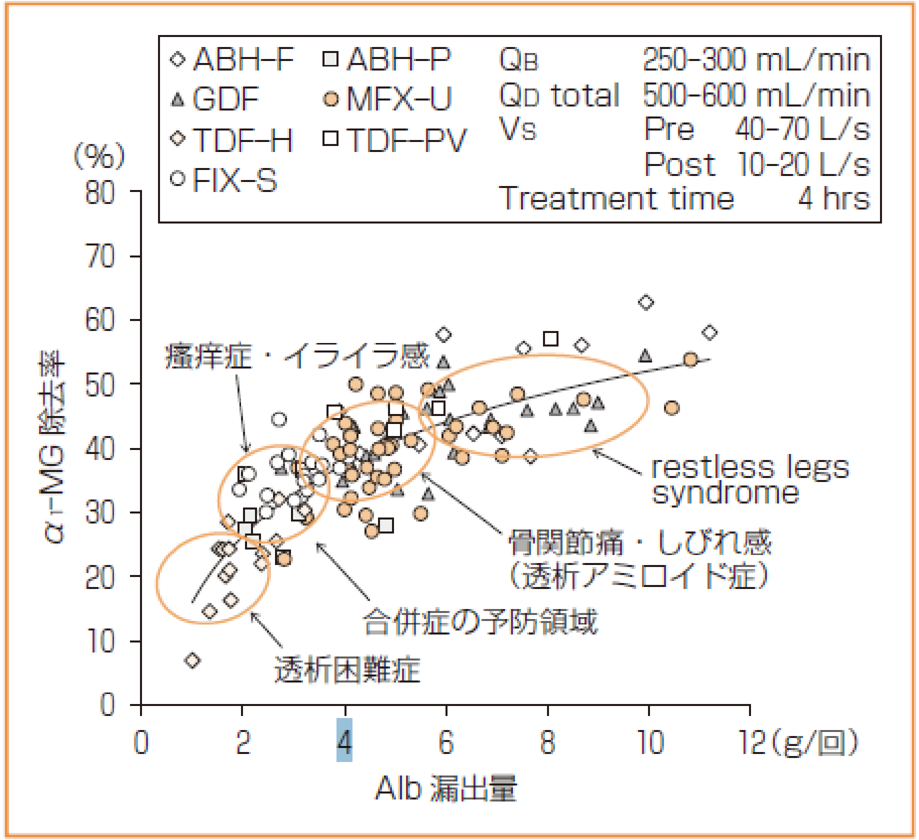
We have less data on oxidative stress, inflammation, leukocyte function when using reused dialyzer

1) Hamid A, Dhrolia MF, Imtiaz S, Qureshi R, Ahmad A. Comparison of Adequacy of Dialysis between Single-use and Reused Hemodialyzers in Patients on Maintenance Hemodialysis. J Coll Physicians Surg Pak. 2019;29(8):720-723.

2) Suprapti B, Nilamsari WP, Rachmania, Widodo, Alderman C.Medical problems in patients with chronic kidney disease undergoing hemodialysis and their therapy.J Basic Clin Physiol Pharmacol. 2019 Nov 20;30(6):jbcpp-2019-0250. doi: 10.1515/jbcpp-2019-0250

Why should we consider to remove the large-middle molecule?

Recent trends: HDF with Super high flux membrane as a treatment to remove Large-middle molecule and HDx with Super high flux membrane (MCO membrane)



- α1-microglobulinA protein with a molecular weight of 33 kD.
- Since α1MG has free thiol groups, it has a binding action with heme, as well as reducing and radical scavenging actions.
- Therefore, it is effective in reducing oxidative stress of heme and free radicals.
    - Åkerström et al.: Free Radic Biol Med. 74: 274-282, 2014
- Recently, an oxidized form of radical-trapped α1MG considered to be accumulated in dialysis patients.
    - Kawanishi： 透析会誌 55 : 509-514，2022
- Furthermore, removing that oxidized form of α1MG promotes the turnover of α1MG and increases new α1MG, thereby improving the pathological condition (antioxidant and radical trapping effects), so the more it is removed, the better.
  It is now believed that α1MG is not a surrogate marker but the substance itself to be removed.
    - Kim S. 腎と透析 92 別冊ハイパフォーマンスメンブレン 21 : 289-303, 2022

Sakurai K. Biomarkers for evaluation of clinical outcomes of hemodiafiltration. Blood Purif. 35 Suppl 1: 64-68, 2013

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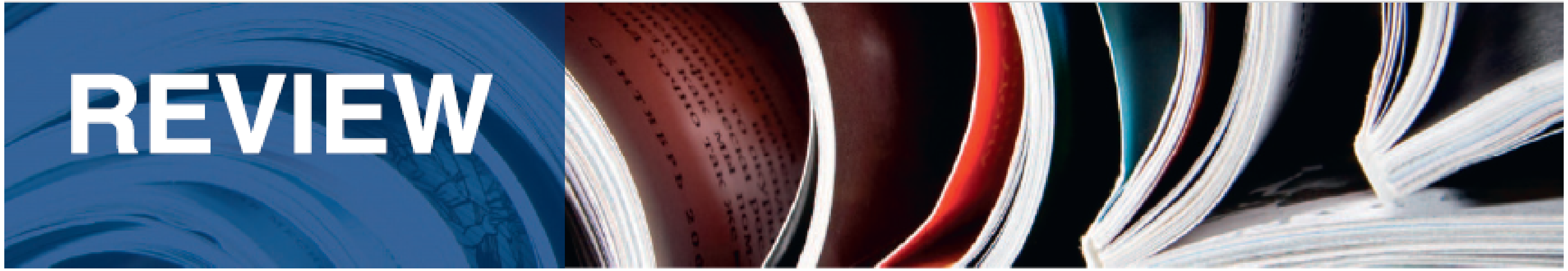
Classification of Uremic Toxins and their Role in Kidney Failure

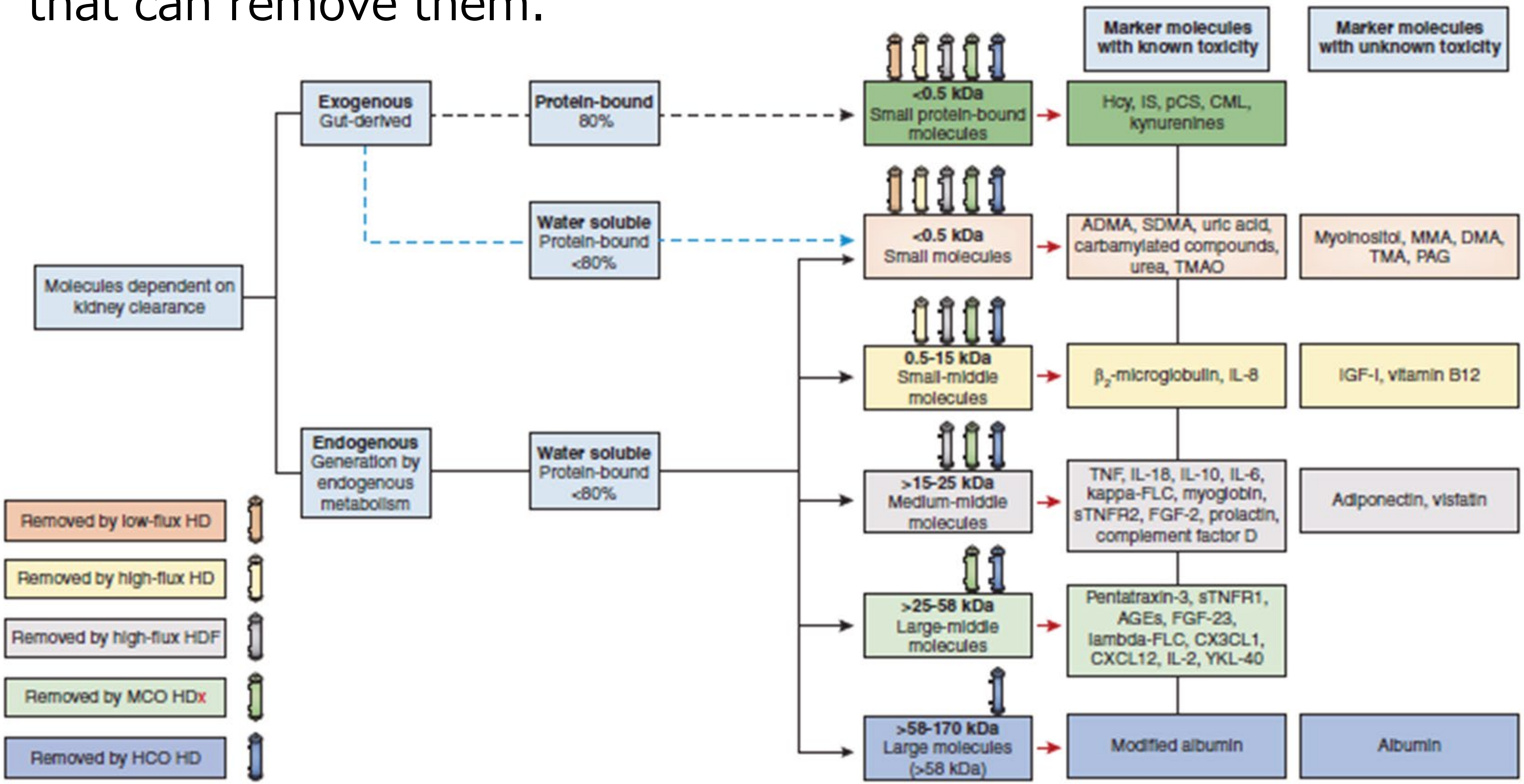


Classification of Uremic Toxins and Their Role in Kidney Failure

Mitchell H. Rosner,[1] Thiago Reis,[2,3] Faeq Husain-Syed,[4] Raymond Vanholder,[5] Colin Hutchison,[6,7] Peter Stenvinkel,[8] Peter J. Blankestijn,[9] Mario Cozzolino,[10] Laurent Juillard,[11,12] Kianoush Kashani,[13] Manish Kaushik,[14] Hideki Kawanishi,[15] Ziad Massy,[16,17] Tammy Lisa Sirich,[18,19] Li Zuo,[20] and Claudio Ronco[21,22]

CJASN 2021;16 :1918-1928

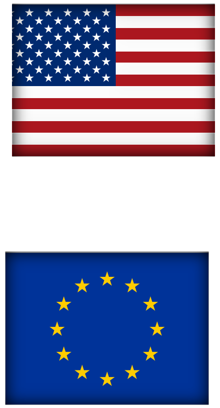
Corresponding molecular weight of the uremic toxins to the modality that can remove them.



CJASN 2021;16 :1918-1928

Classification of Membranes in Japan and Europe/America

QB=350-450mL/min



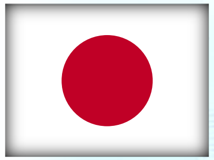
Parameter		Low-flux	Mid-flux	High-flux
Ultrafiltration(UF)	mL/mmHg/h	<20	20-30	30-50
Urea	Kd(mL/min)	<180	180-200	200-220
	KoA(mL/min)	<500	500-600	600-700
	eKt/V	<1.2	1.2-1.4	1.4-1.6
β2MG	Kd(mL/min)	**<20**	**20-40**	**40-60**
	KoA(mL/min)	<30	30-50	50-100
Albumin leakage	g/session	0	0	<2

Albumin leakage

MCO

MCO HDx corresponds to a subset of super high flux HD

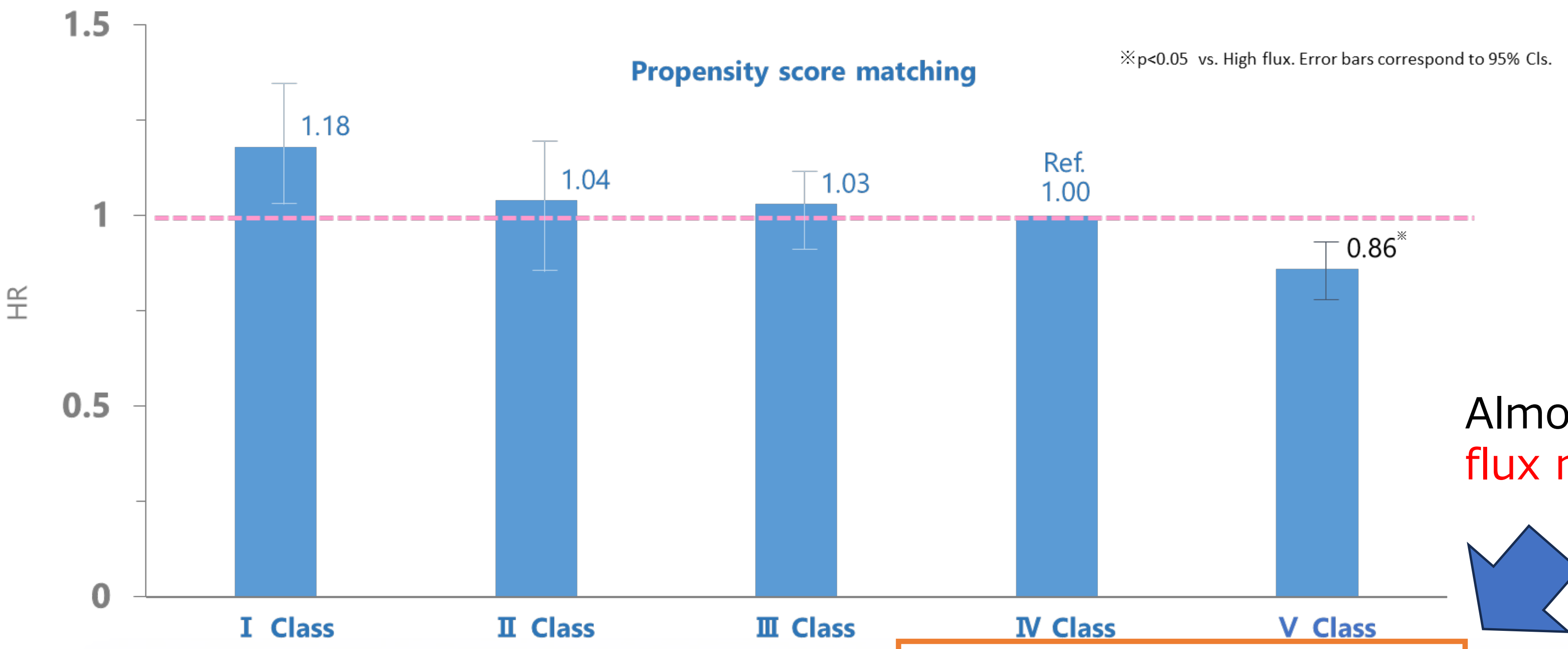
QB=200mL/min



Classification in Japan~2013		I	II	III	IV	V
					Super-high-flux	Super-high-flux
β2MG clearance	mL/min	**<10**	**10-30**	**30-50**	**50-70**	**≧70**
2014～		I	I	I	I	IIa / IIb
		Low flux (ELISIO-L)	Middle flux (ELISIO-M)	Middle-high flux (ELISIO-K)	High flux (ELISIO-H)	**Super high flux (ELISIO-HX)**: **PES-Sα** (IIa) / **PES-Dα** (IIb)

We need performance indicators measured under the same conditions as basic performance.

Impact on life prognosis



	I Class	II Class	III Class	IV Class	V Class
	Low flux	Middle flux	high flux	Super high flux	Super high flux
n	2,087	1,721	8,349	165,082	25,796
	1.0%	0.8%	4.1%	81%	13%

Almost all patients use super high flux membrane for HD in Japan.

Abe M et al. High-performance dialyzers and mortality in maintenance hemodialysis patients. Sci Rep. 2021.

Abe M et al. High-performance dialyzers and mortality in maintenance hemodialysis patients. Sci Rep. 2021.

Objectives of our research project

- Objectives of the present research project (it's still ongoing) are to comprehensively and scientifically clarify the advantages and disadvantages of single-use and reuse of dialyzers.
- To this end, we quantitatively evaluate reused dialyzer in vitro and in vivo, whether reused dialyzer could affect solute permeability, safety risk, and biocompatibility compared to single-use dialyzer.

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in vitro experiment

◆Dialyzer used
→ELISIO-210HR(NIPRO Sales Co., Ltd)

◆4 types of dialyzers with different number of reuse times were compared.

- single use (first use)
- reused* 5 times
- reused* 10 times
- reused* 15 times

*The dialyzers were used in a clinical setting in Thailand or Philippines.

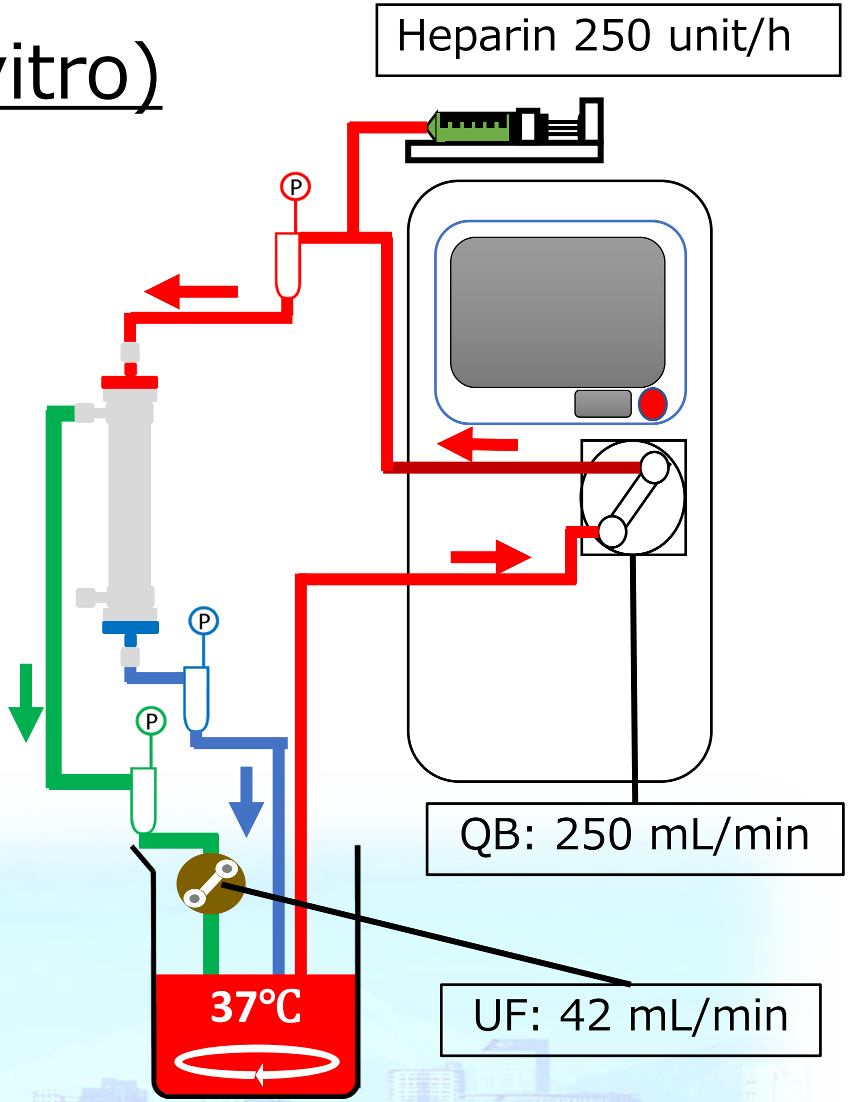
Properties of the dialyzer used

	ELISIO 210 HR
Membrane Material	Polyether-sulfone
Effective surface area [m^2]	2.1
Inner diameter [μm]	200
Effective Length [mm]	280
Membrane Thickness [μm]	40
Priming Volume[mL]	130
UFR [mL/hr/100 mmHg)]	413

Hemofiltration experiment (in vitro)

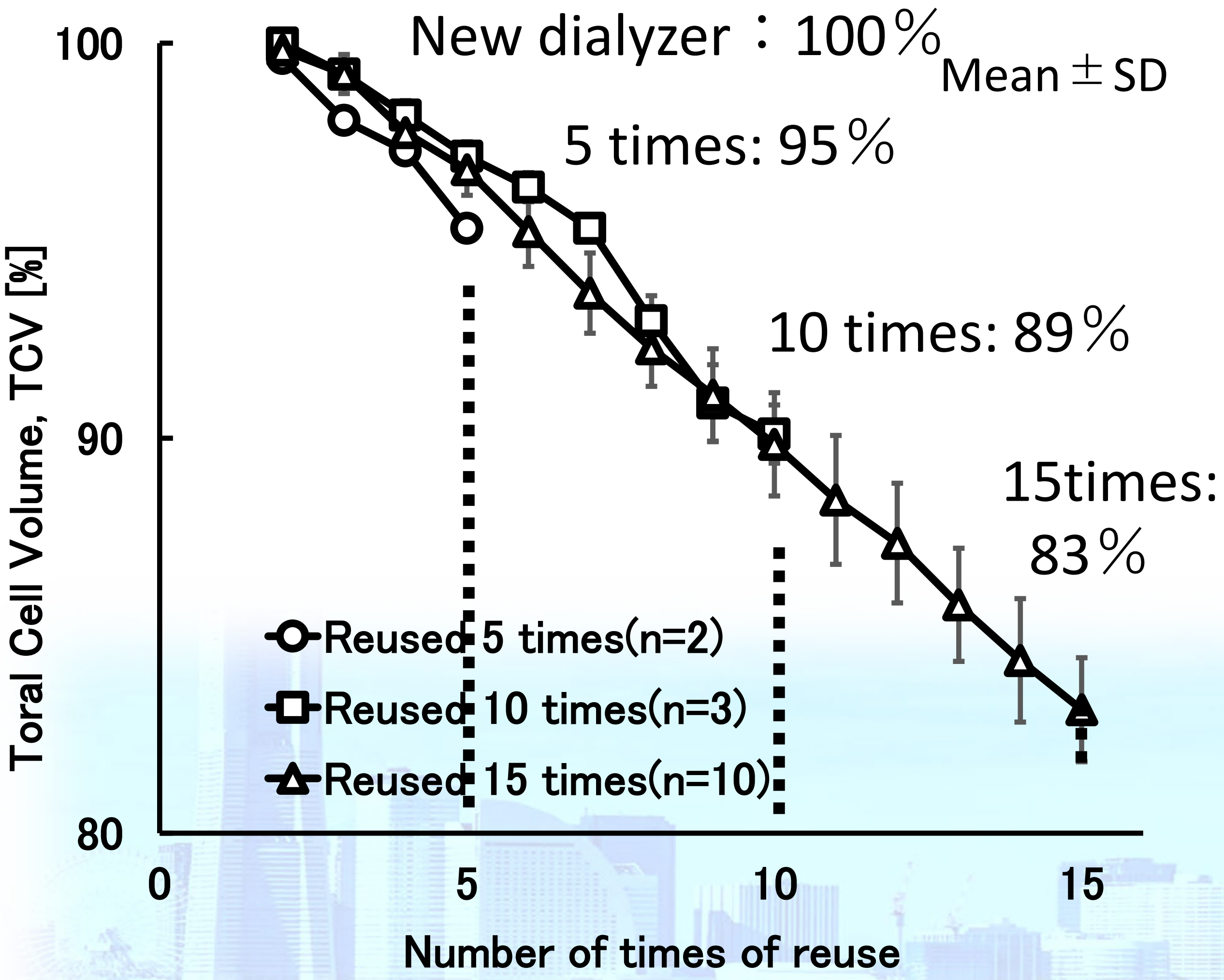
- Change in TCV (total cell volume), change in volume of liquid that can fill inside the hollow fiber, due to reuse.
- Visual observation of blood flow in side the hollow fiber and blood leaks.
- Water permeability
- Measurement of sieving coefficient of β-lactoglobulin (large middle molecules)

Blood samples were taken from the inlet and outlet of blood side and filtrate samples were taken from filtration to measure the concentration of β-lactoglobulin and the sieving coefficient was calculated.



Hct : 30 ± 1%,
TP : 6.5 ± 0.1 g/dL

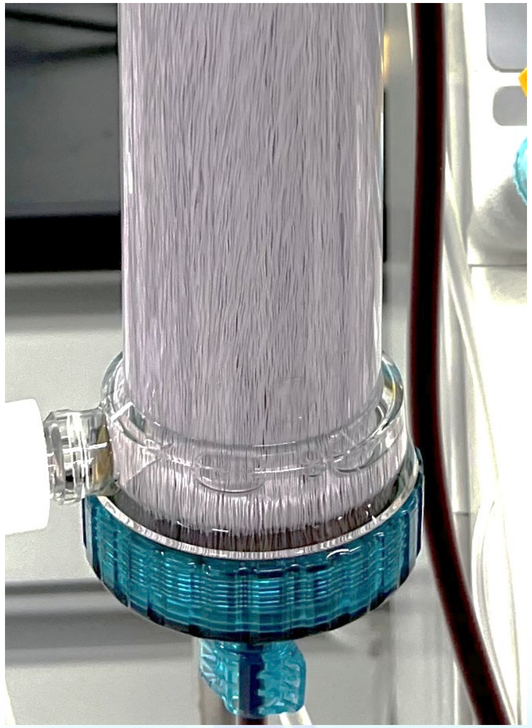
TCV of dialyzer used in the experiment and blood filling into hollow fiber in dialyzer after blood replacement (Thailand)



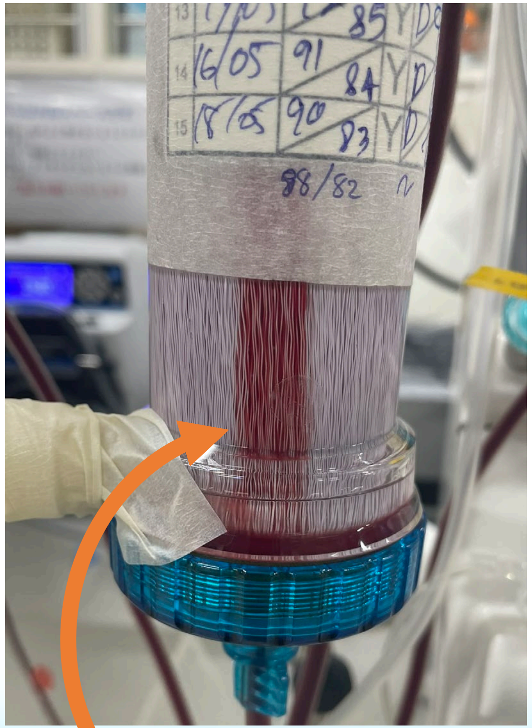
TCV decreased with number of times of reuse.

White hollow fibers not filled with blood were observed in those with a high number of reuses.

Number of times the leak has occurred



normal



Blood leaking from the hollow fiber

Experimental Group	Number of occasion	Foreign object
First-time use(n=5)	0	0
Reused 5 times(n=5)	0	1
Reused 10 times(n=5)	1	0
Reused 15 times(n=10)	6	0

※The experiment was conducted under conditions where the membranes were more susceptible to damage due to transportation from Thailand to Japan and long storage periods.

Repeated reuse resulted in the membranes being more likely to be damaged.

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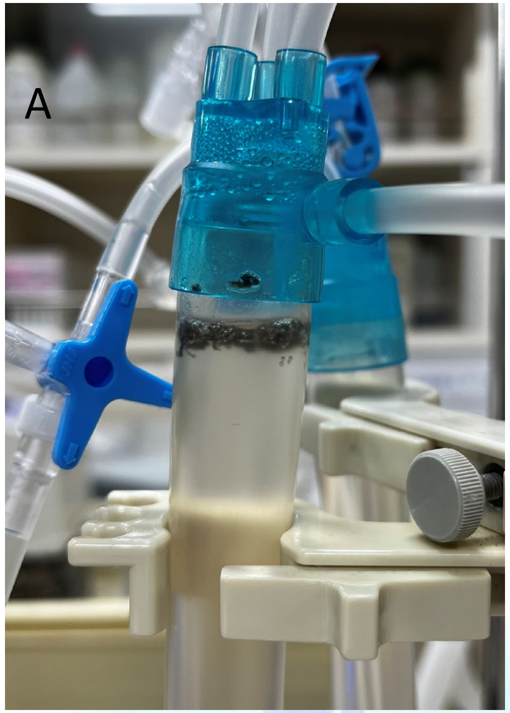
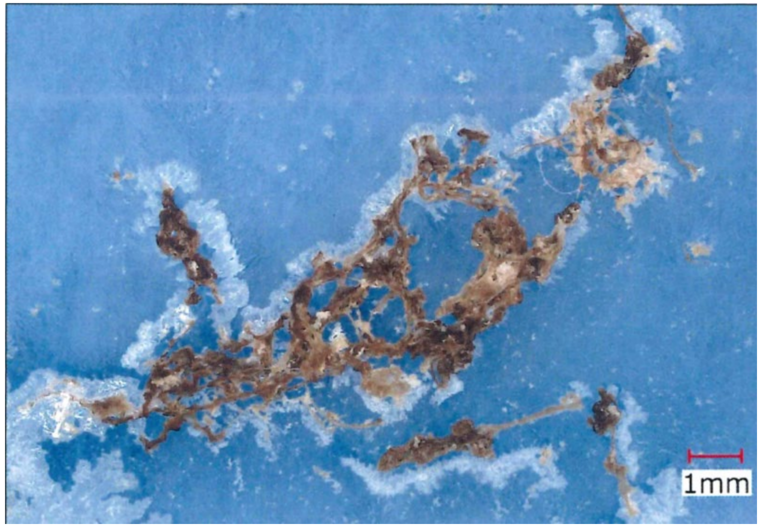
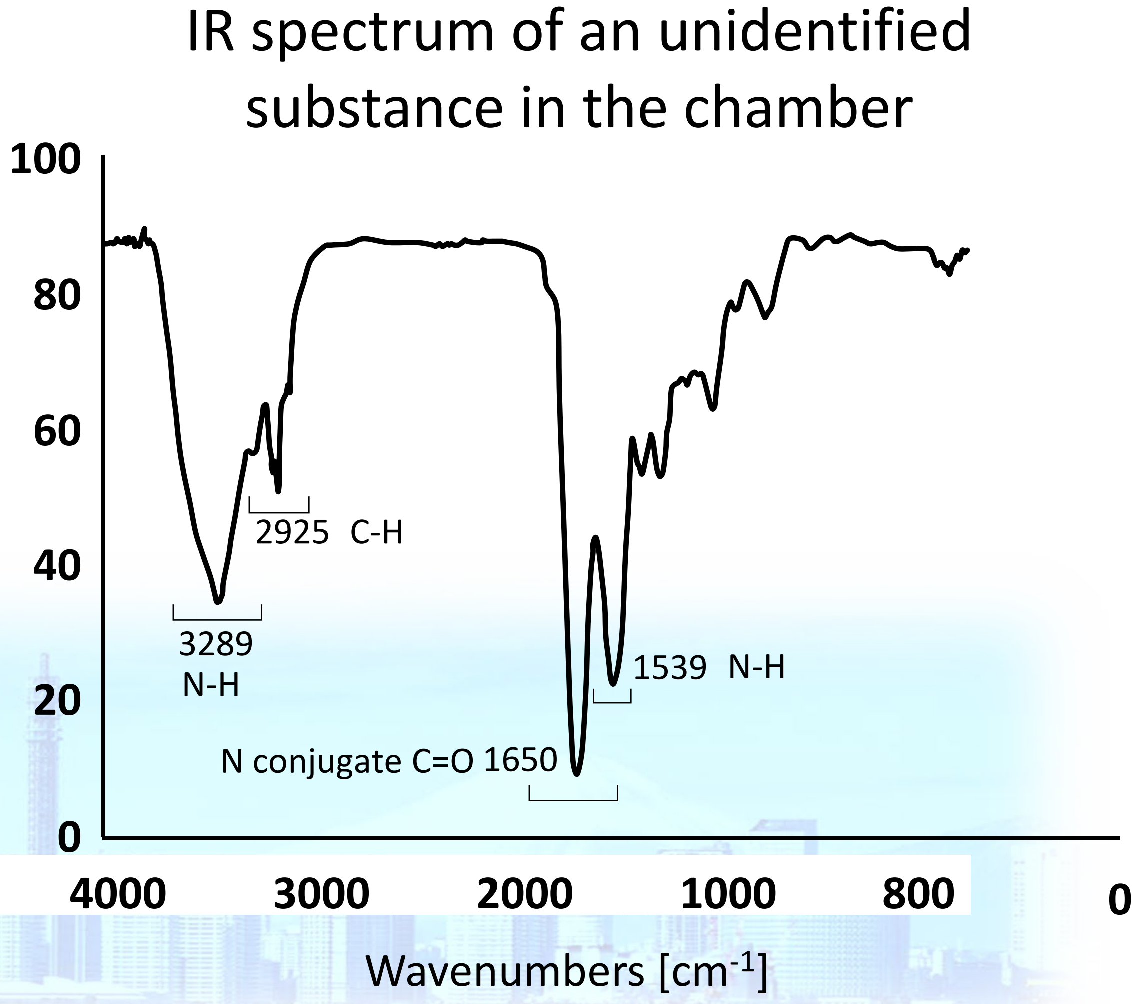
After the HF experiment, an unidentified black, thin, fiber-like substance that appeared to be residue in the chamber

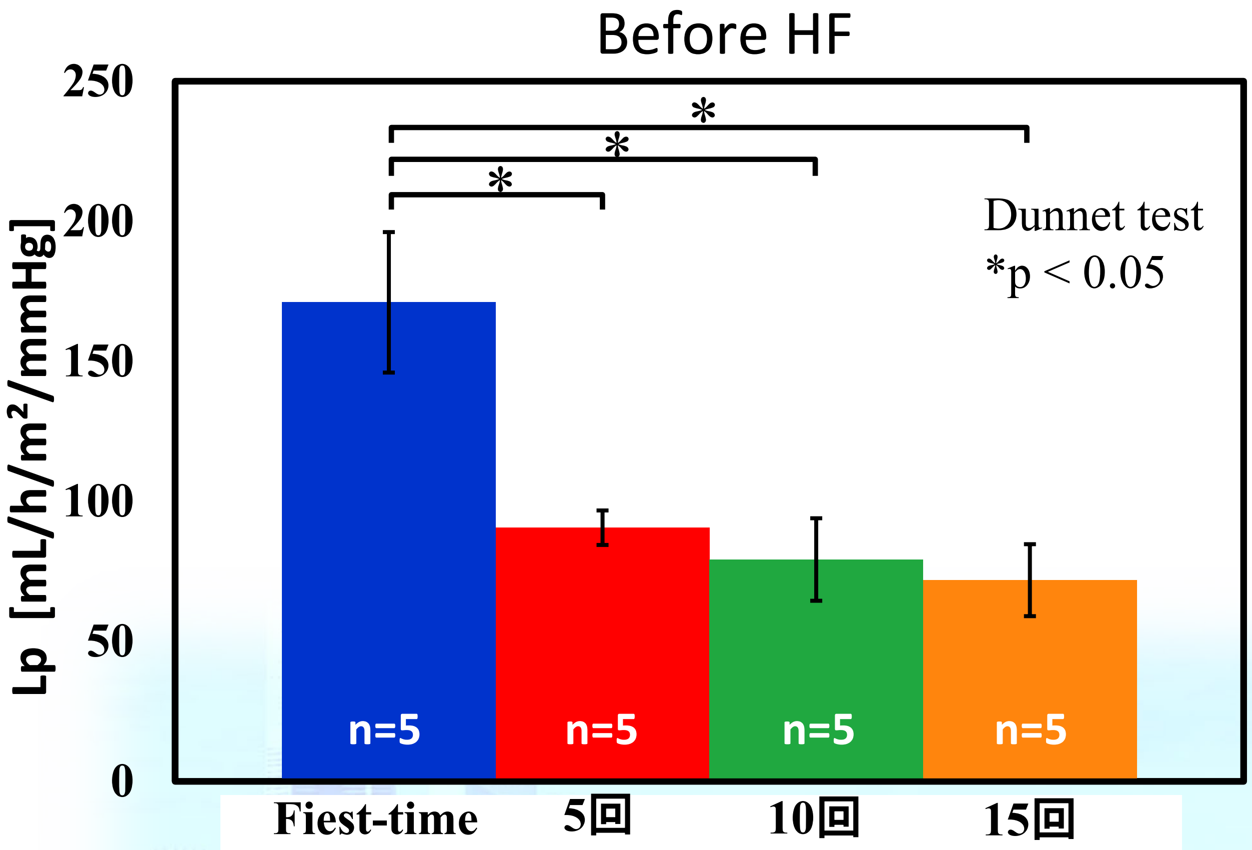


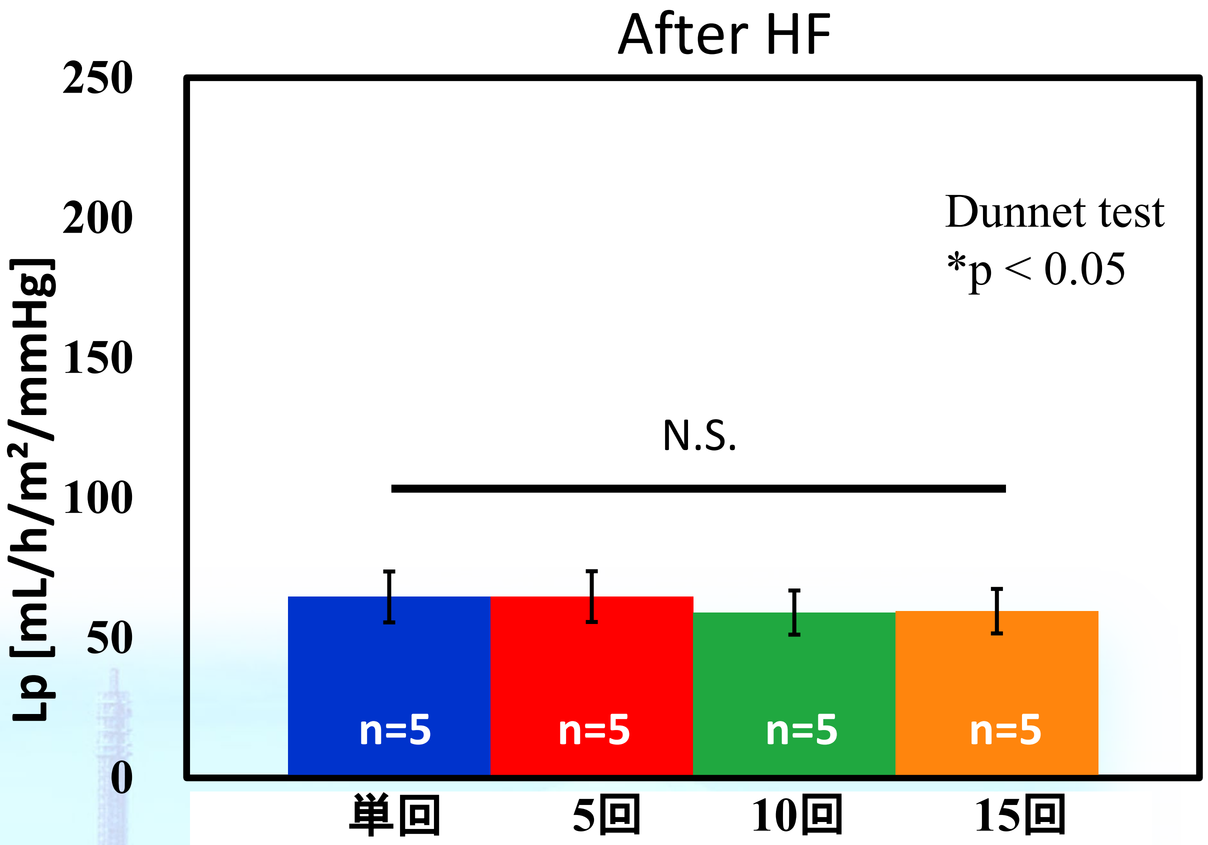




The major component of the unidentified substance was a protein component (natural polyamide).
The unidentified substance was speculated to be residual thrombus denatured by a disinfectant solution (peracetic acid).

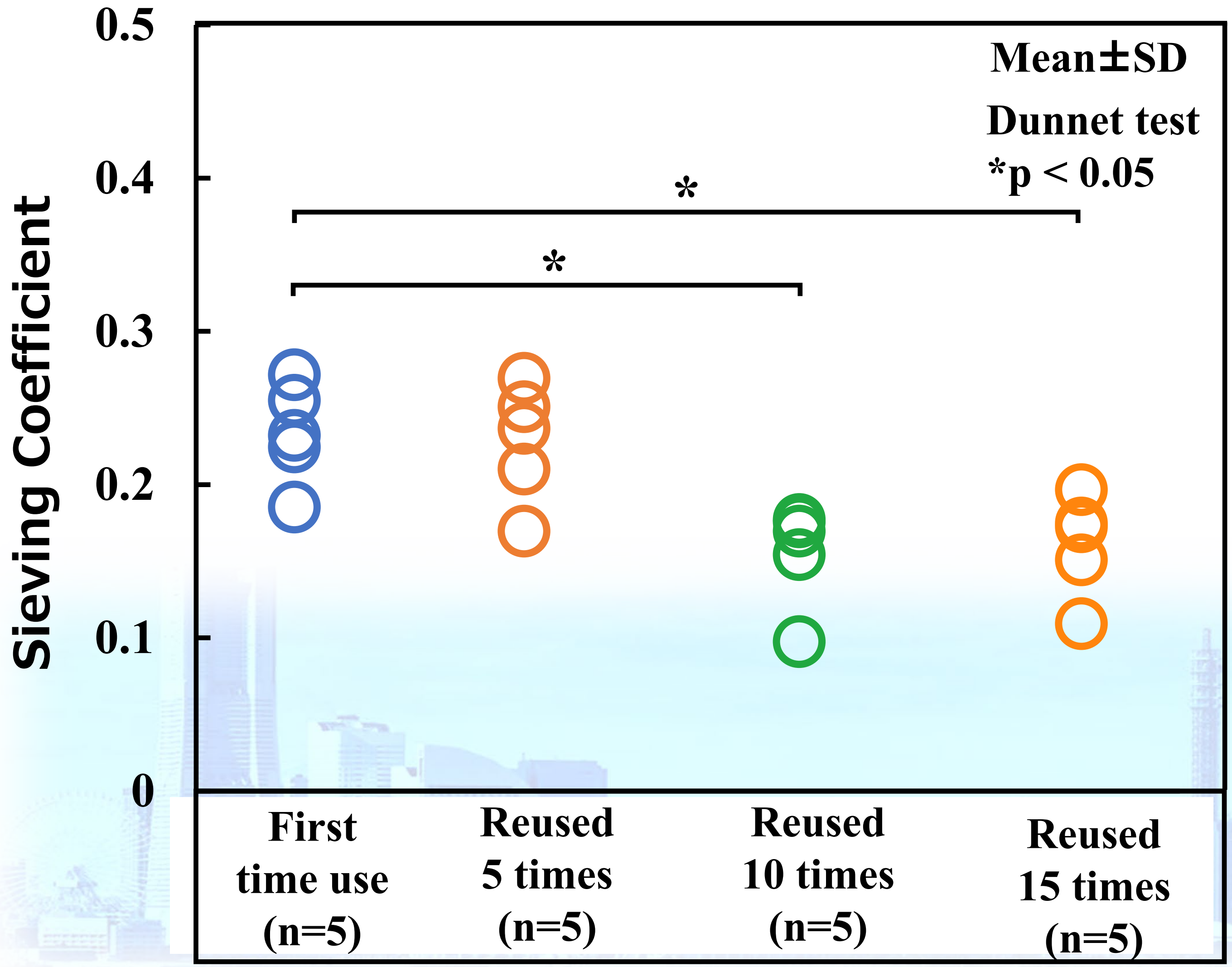
Water permeability (Lp) of the dialyzer before and after the hemofiltration experiment (Thailand)





Lp decreased in the reused dialyzer compared to the one-time use.
No difference in Lp was observed between the number of times the dialyzer was reused.

Sieving coefficient of β-lactoglobulin in in-vitro hemofiltration experiments with porcine blood (Thailand)



The sieving coefficients in the large middle molecule were significantly lower for the 10-reuse and 15-reuse dialyzers compared to the single use.

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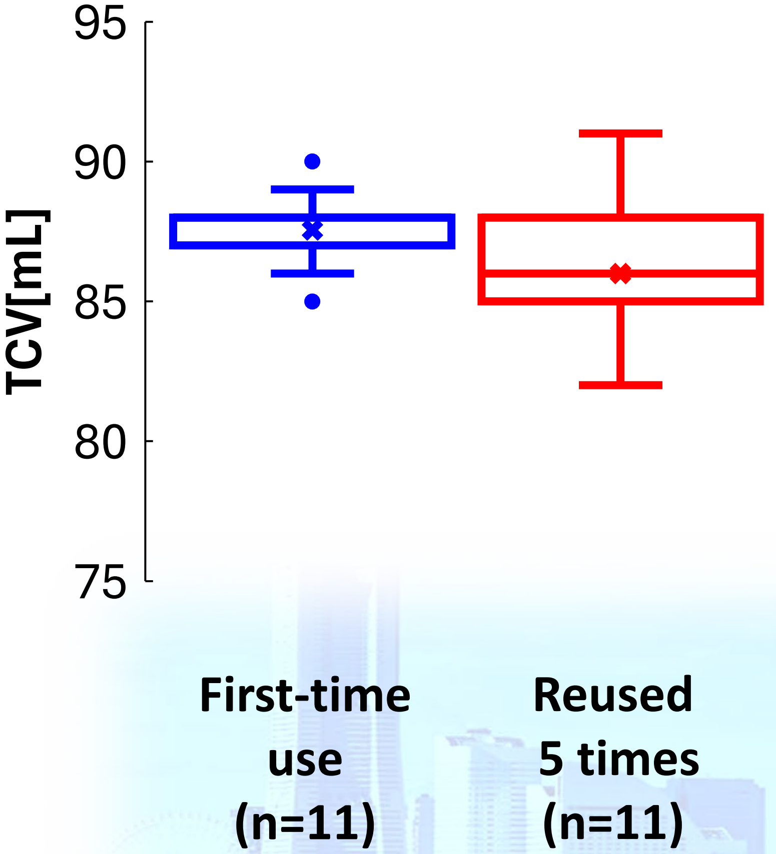
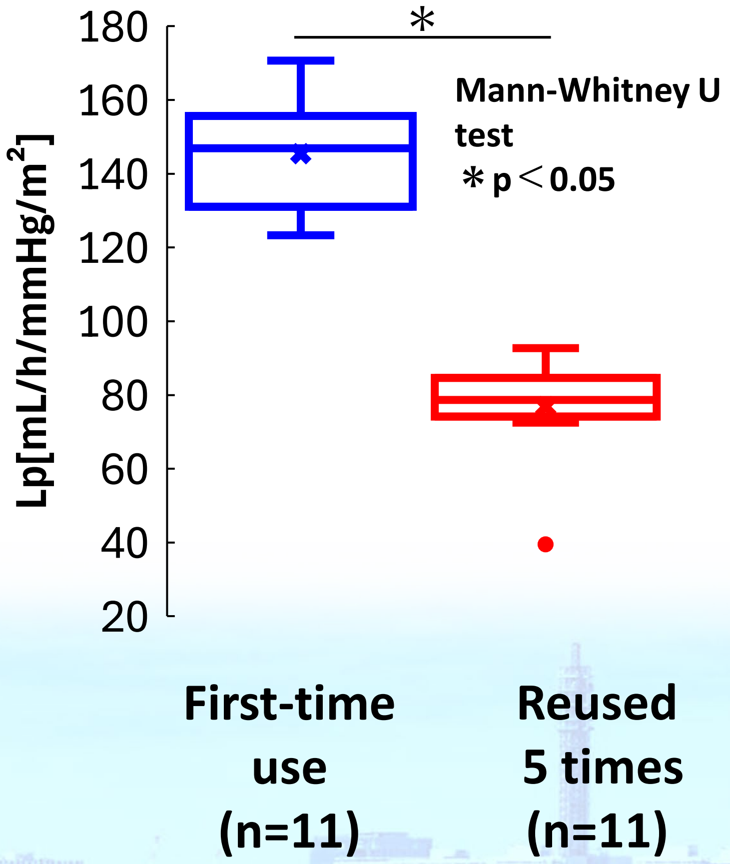
Performance change by reuse at Viet Nam

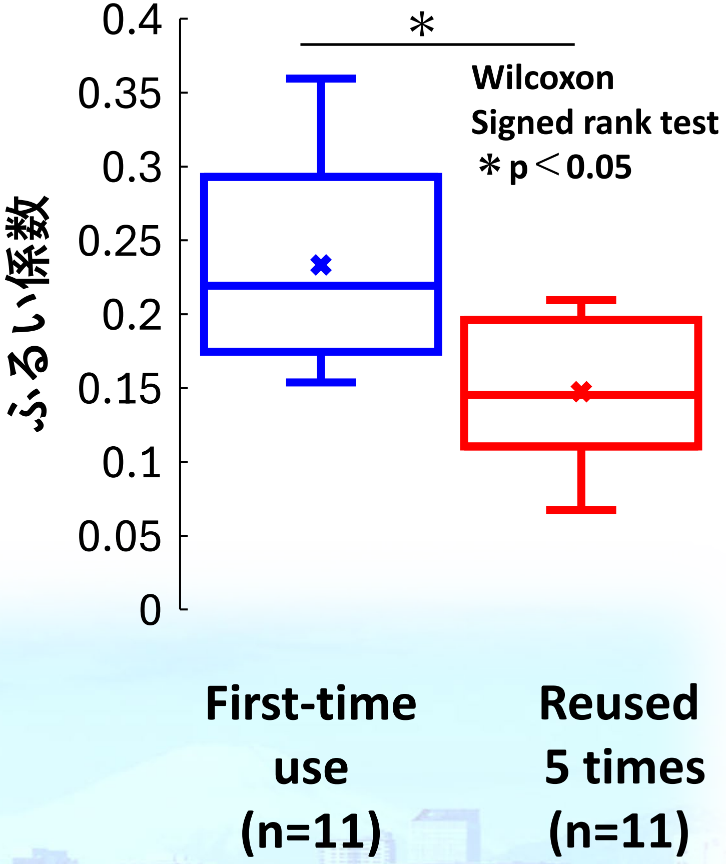
Total cell Volume (TCV)



Water permeability (Lp)



Sieving Coefficient of β-LG



The 5 reuse in Viet Num decrease in removal performance of large-middle molecules.

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Hypothesis before start of clinical trial

- We hypothesize that switching from reuse to single-use may change the following points.

(1) Inflammation

(2) Oxidative stress

(3) Function of leukocytes

Research methods and the location of the experiment/data collection

Research design

- Crossover comparative study (2 groups, 2 periods)

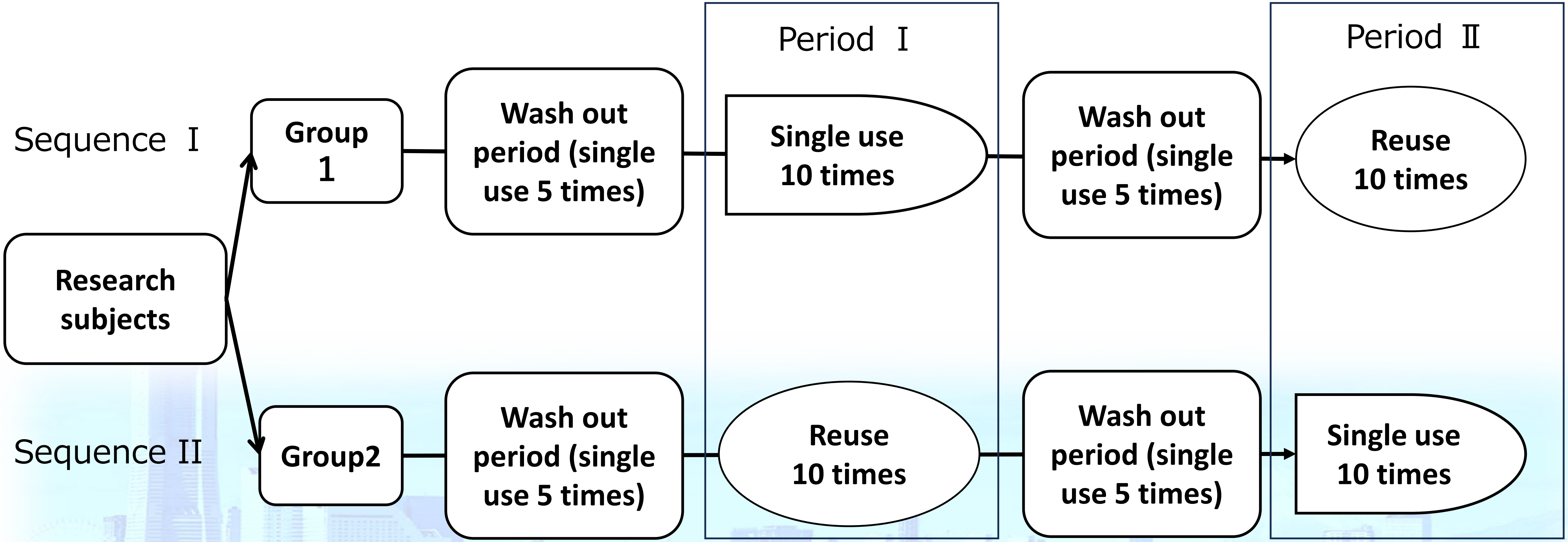
Target population

- Dialysis patients who stably received dialysis therapy on 4-hour dialysis x 3 times/week at Phare Cristian Hospital and other clinic.

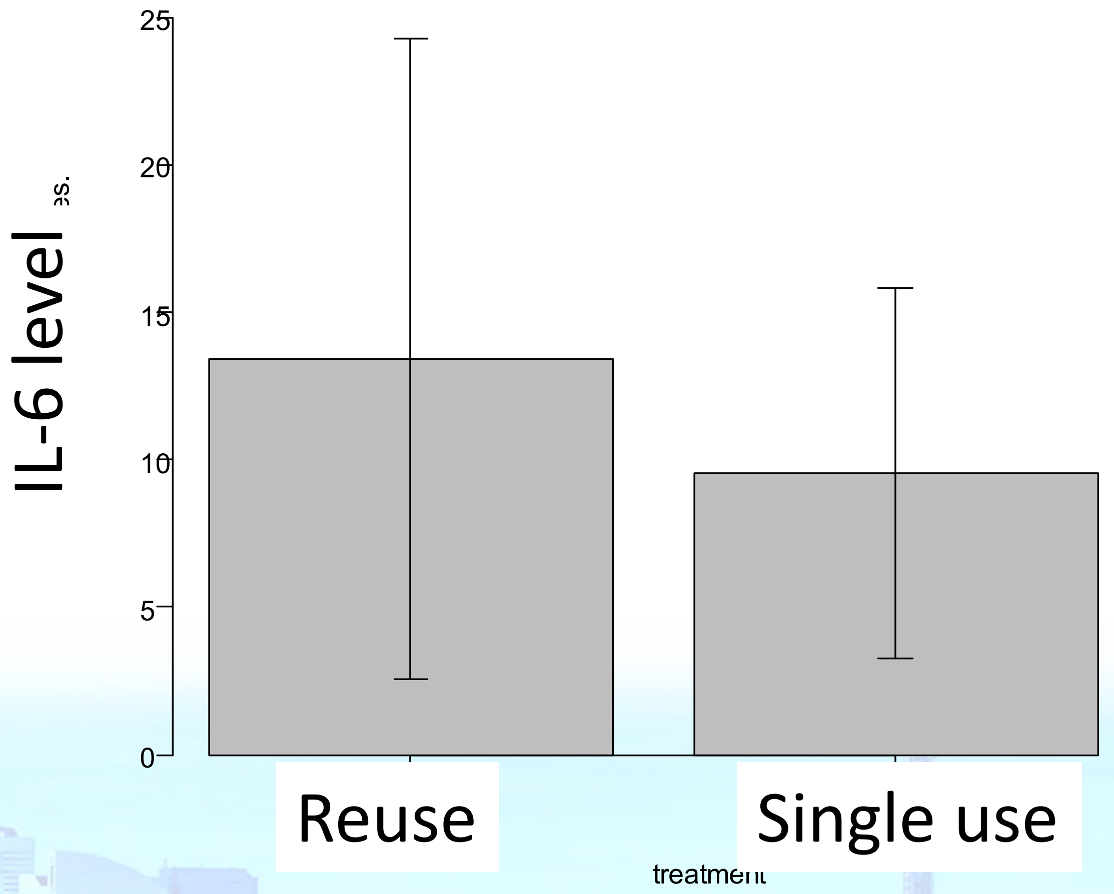
Consent of the Study

- All subjects have been explained the details of the project and agree to participate in the project.

Schematic diagram of the crossover comparative study

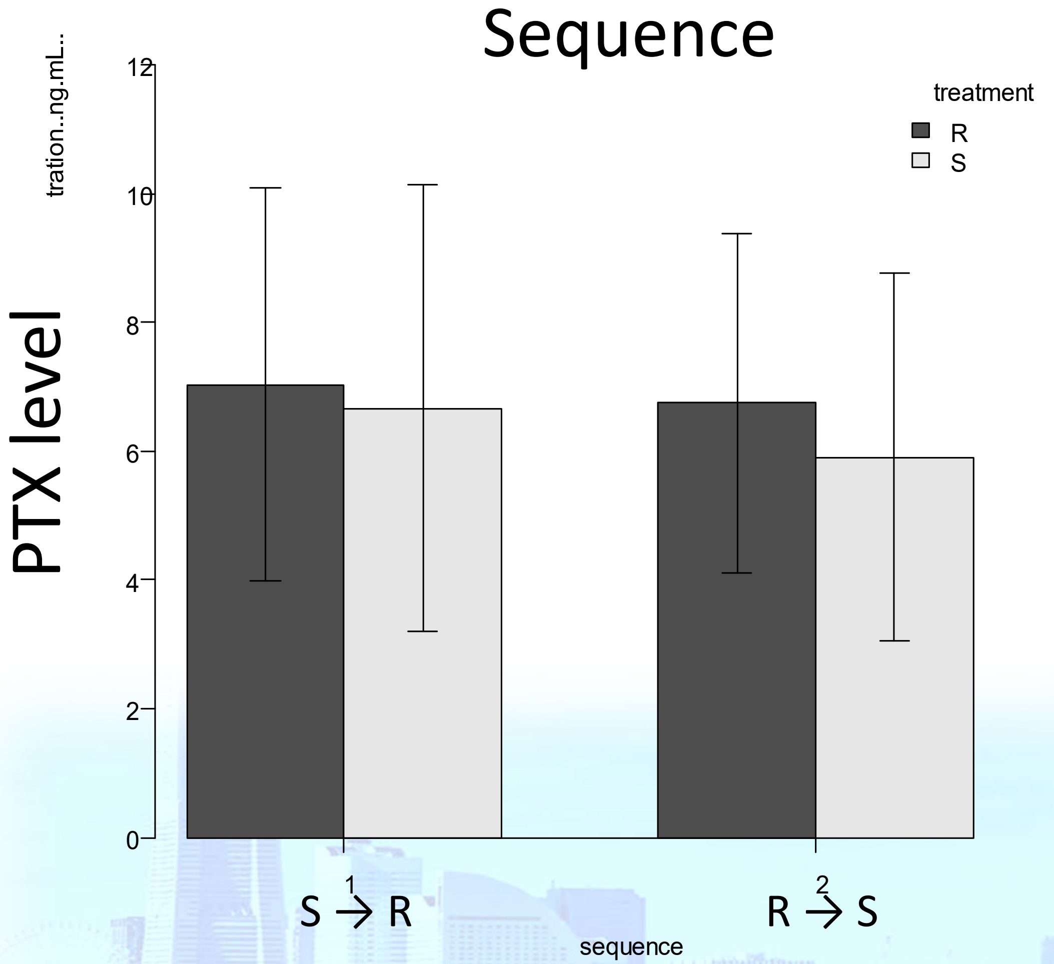


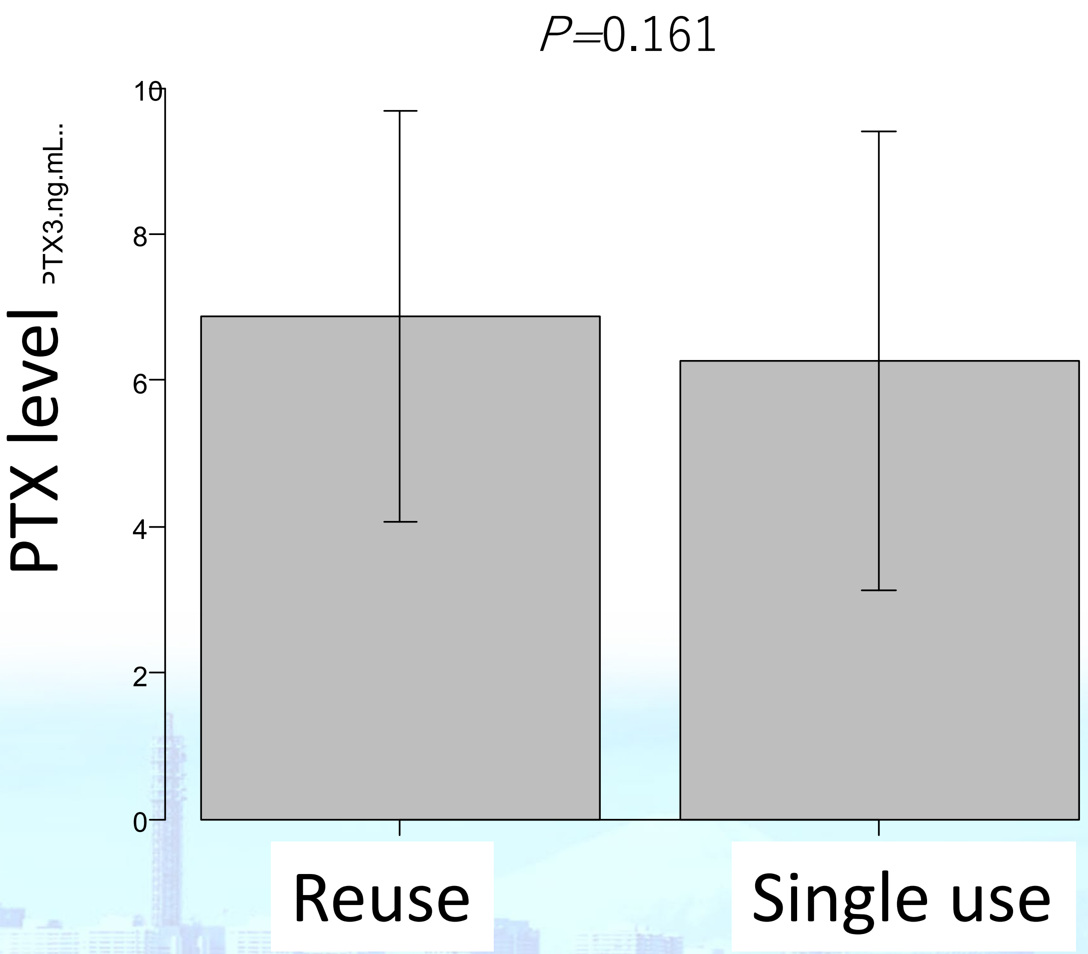
IL-6 (inflammation marker)



Reuse had a higher level of IL-6

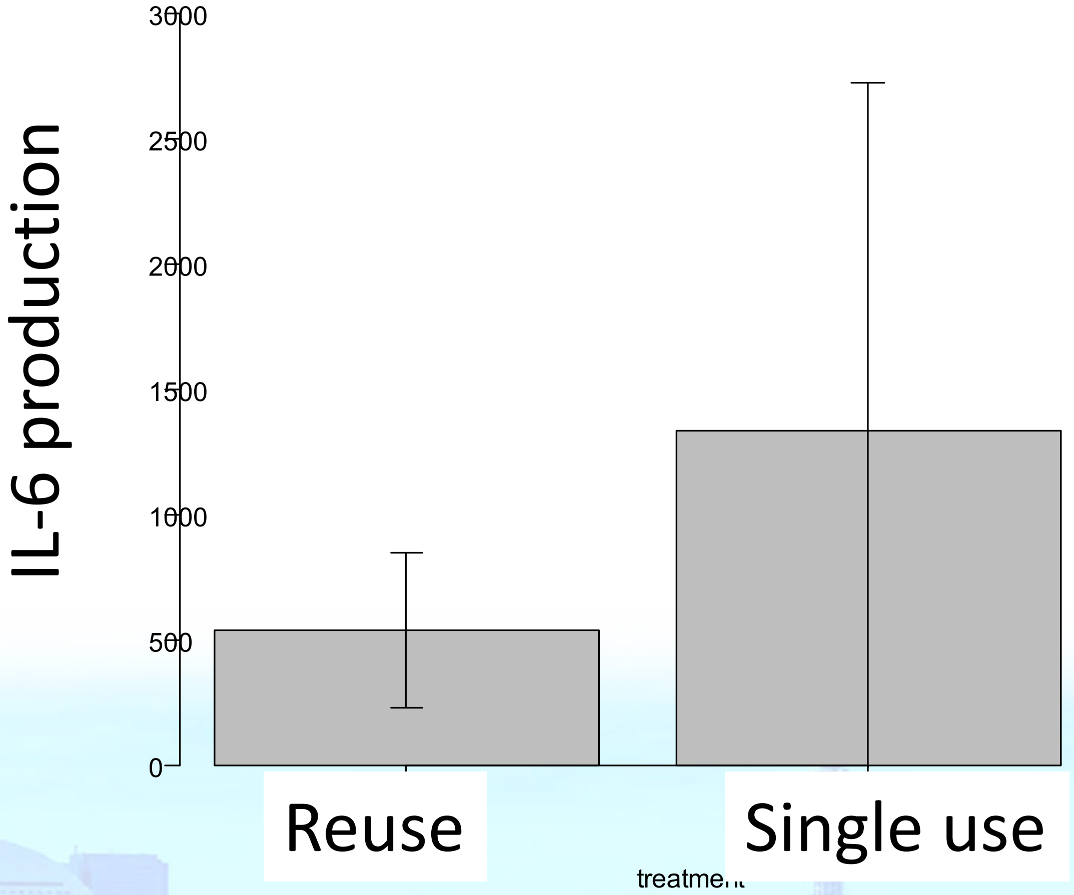
PTX (inflammation marker)





PTX was also high in patients using reused dialyzer.

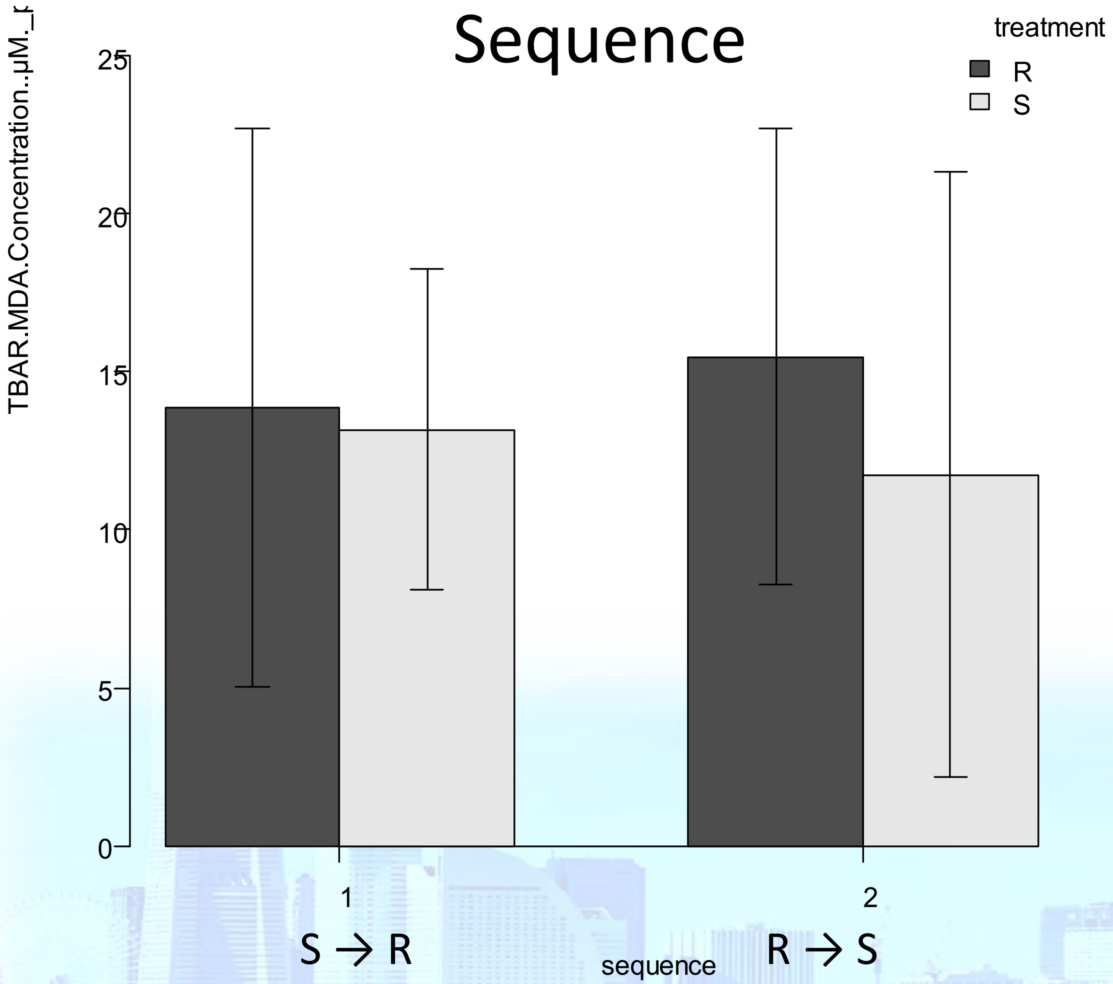
LPS stimulation test (capability of IL-6 production)

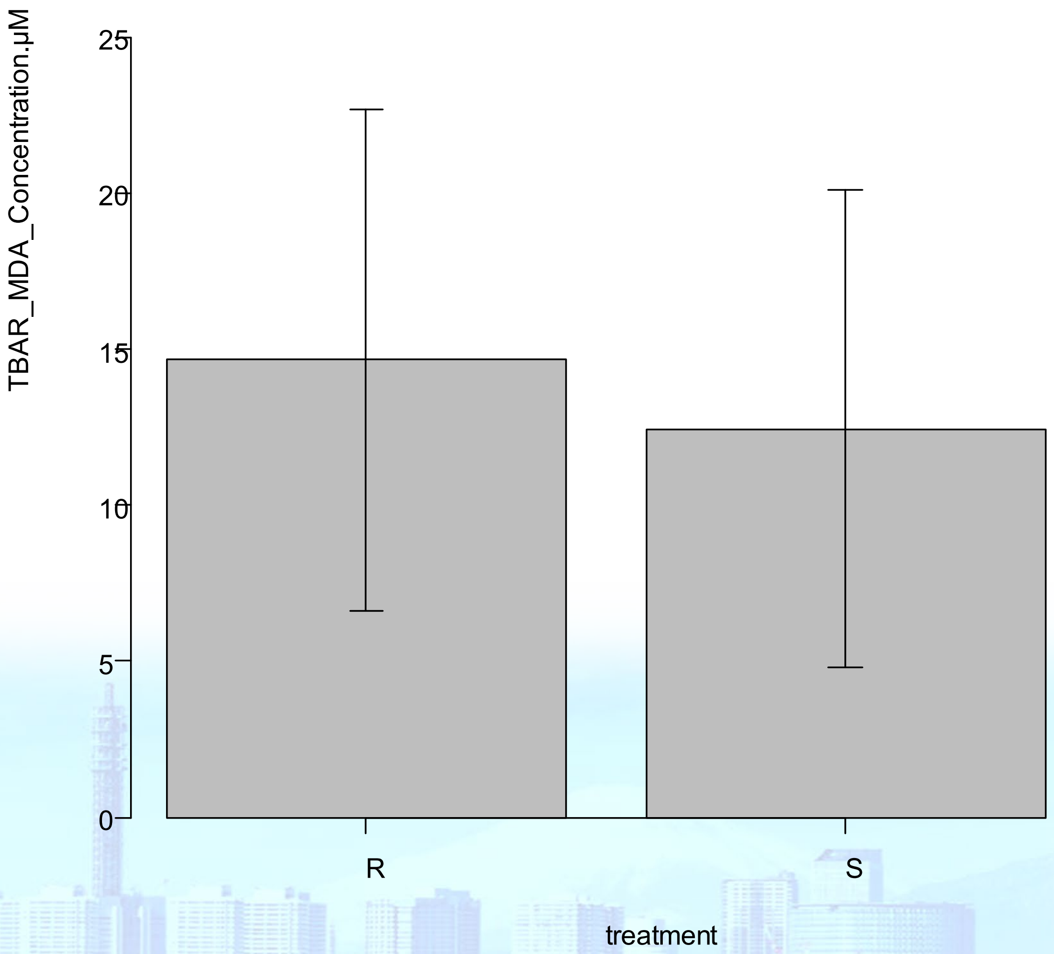


Leukocyte function decreased after contact with reused dialyzer.

TBARS (oxidative stress marker)

P=0.203





Oxidative stress is high in patients using reused dialyzer.

Summary of the results (clinical trial)

(1) Inflammation was likely to slightly increase using reused dialyzer.
→ PTX3, IL-6 slightly increased during hemodialysis using reused dialyzer.

(2) Leukocyte function decreased after contact with reused dialyzer.

(3) Oxidative stress was likely to increased using reused dialyzer

(4) No other factors associated with biocompatibility indicated that reuse was better.

(5) Biocompatibility is not improved by reuse. Rather, biocompatibility of single-use may be slightly better.

Summary (single use vs. reuse)

	Single use	Reuse
Solute permeability	Good	Small molecule: Not affected by reuse. Middle molecule: Decrease after 10 or more reuses.
Biocompatibility	Good	Reuse more than 10 times may alter the reactivity of leukocytes and the propensity of platelets activation.
Safety	Safe	There are potential risks of membrane breakage, residual blood clots, etc.

Implication

TCV decreased with number of times of reuse, meaning that residual blood clot or some protein components that are denatured by the disinfectant clogged inside of the hollow fibers. Detached substances may detach and enter the bloodstream.
The membrane itself was likely to be damaged due to reprocessing and storing process. use.

The decrease in the sieving coefficient of β-LG suggests that reuse results in narrowing of the hollow fiber pores of the dialyzer and decrease in the effective membrane area. Decrease in the removal performance of large middle molecules cannot be avoidable as long as reused dialyzers are used.

Leukocytes that come in contact with membranes that have been reused more than 5 times have reduced cytokine-producing capacity.

Biocompatibility is not improved by reuse. Rather, biocompatibility of single-use may be slightly better in clinical setting.

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TCV decreased with number of times of reuse, meaning that residual blood clot or some protein components that are denatured by the disinfectant clogged inside of the hollow fibers. De… The mem… …ng process. use.

→There are potential risks associated with reuse itself (independent of number of reuse).

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→Reuse more than 5 times causes obvious bat effects. (depend on number of reuse).

Leukocyte… …re than 5 times have reduced cytokine-producing capacity.

Biocompatibility is not improved by reuse. Rather, biocompatibility of single-use may be slightly better in clinical setting.

Take home message

- Even though the reused dialyzer looks clean, the membrane is actually damaged and when the TCV is down, there are clogs somewhere, which reduce solute permeability of large-middle molecules and leukocyte function and increase the potential risk for safety.
- The 5 reuse in Viet Nam can not prevent a decrease in removal performance of large-middle molecules.
- The removal of large-middle molecules is beginning to be recognized as important worldwide.
- In order to get the benefit of higher solute removal performance, It is crucial to use super high-flux membranes and to avoid reuse.

Thank you very much for your attention!