REFILLING COEFFICIENT *Kr* IN HAEMODIALYSIS AND ITS RELATIONSHIP TO HYDRAULIC PERMEABILITY OF BLOOD CAPILLARIES: CHECKING THE STARLING FORCES

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Background

The filtration coefficient (*Lp*) in the Starling equation (Equation 1) is an important determinant of plasma refilling flow (*RF*) during haemodialysis (HD).

Being impossible to measure in a clinical setting, its value is usually estimated fitting a mathematical model to patient data. In the past it has been proposed an alternative way of estimating *Lp* directly from blood volume data [1]; the main assumption behind this method was that the only drive for refilling flow is the change in capillary oncotic pressure, and the remaining Starling forces (and lymphatic absorption) have negligible effect.

This approximation of *Lp* was called *refilling coefficient* (*Kr*), and it was observed to be decreasing during HD (Figure 1).

$$\frac{dV_p}{dt} = Lp\left[P_i - P_p - \left(\Pi_i - \Pi_p\right)\right] + Lymph - UF$$

Equation 1. *Lp: filtration coefficient; P_i and P_p: interstitial and capillary hydraulic pressures; Π_i and Π_p: interstitial and capillary oncotic pressures; Lymph: lymphatic reabsorption flow of water; UF: ultrafiltration flow*

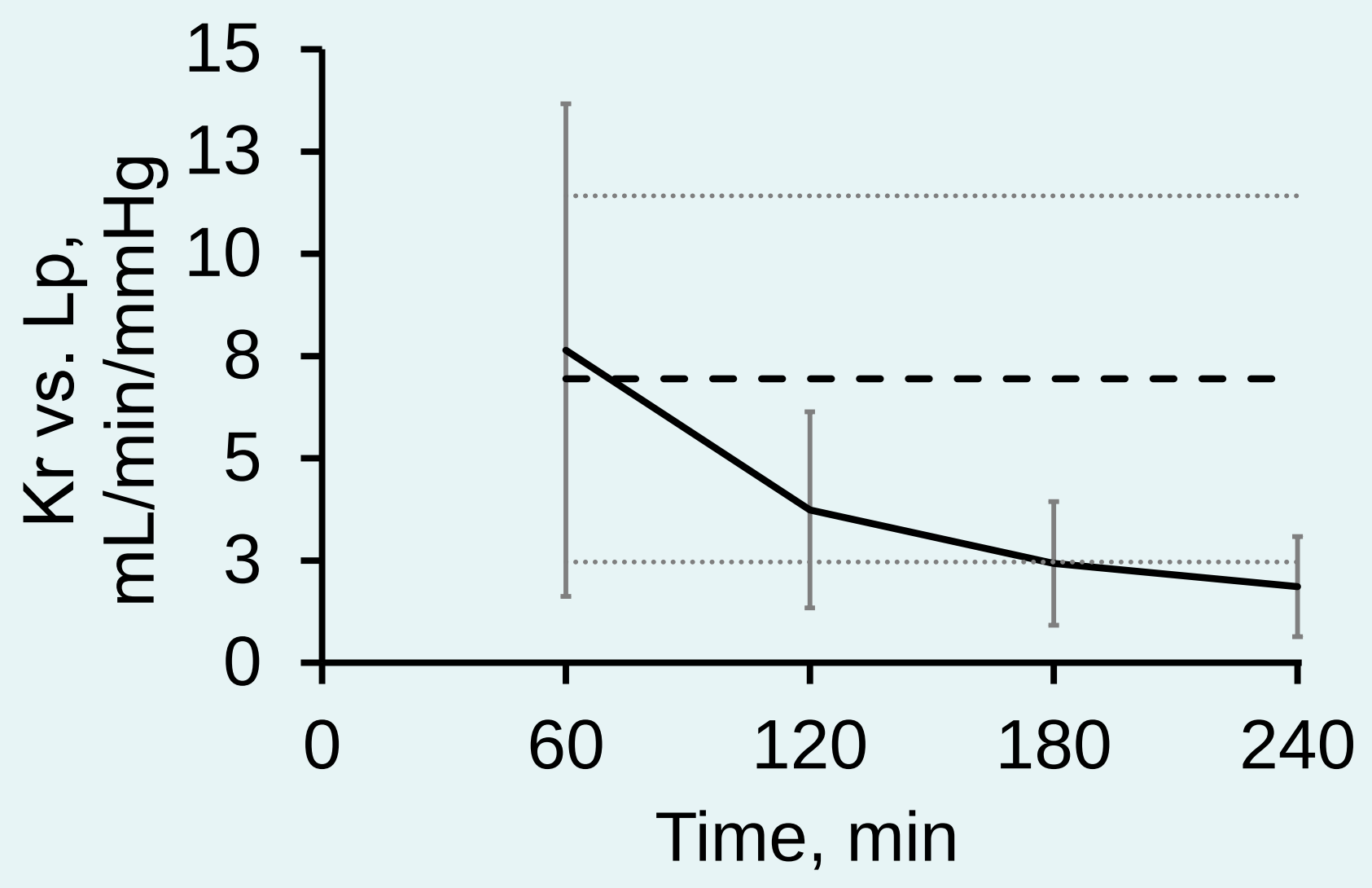

Figure 1. *Average Lp estimated by the model (dashed line) compared with Kr (continuous line)*

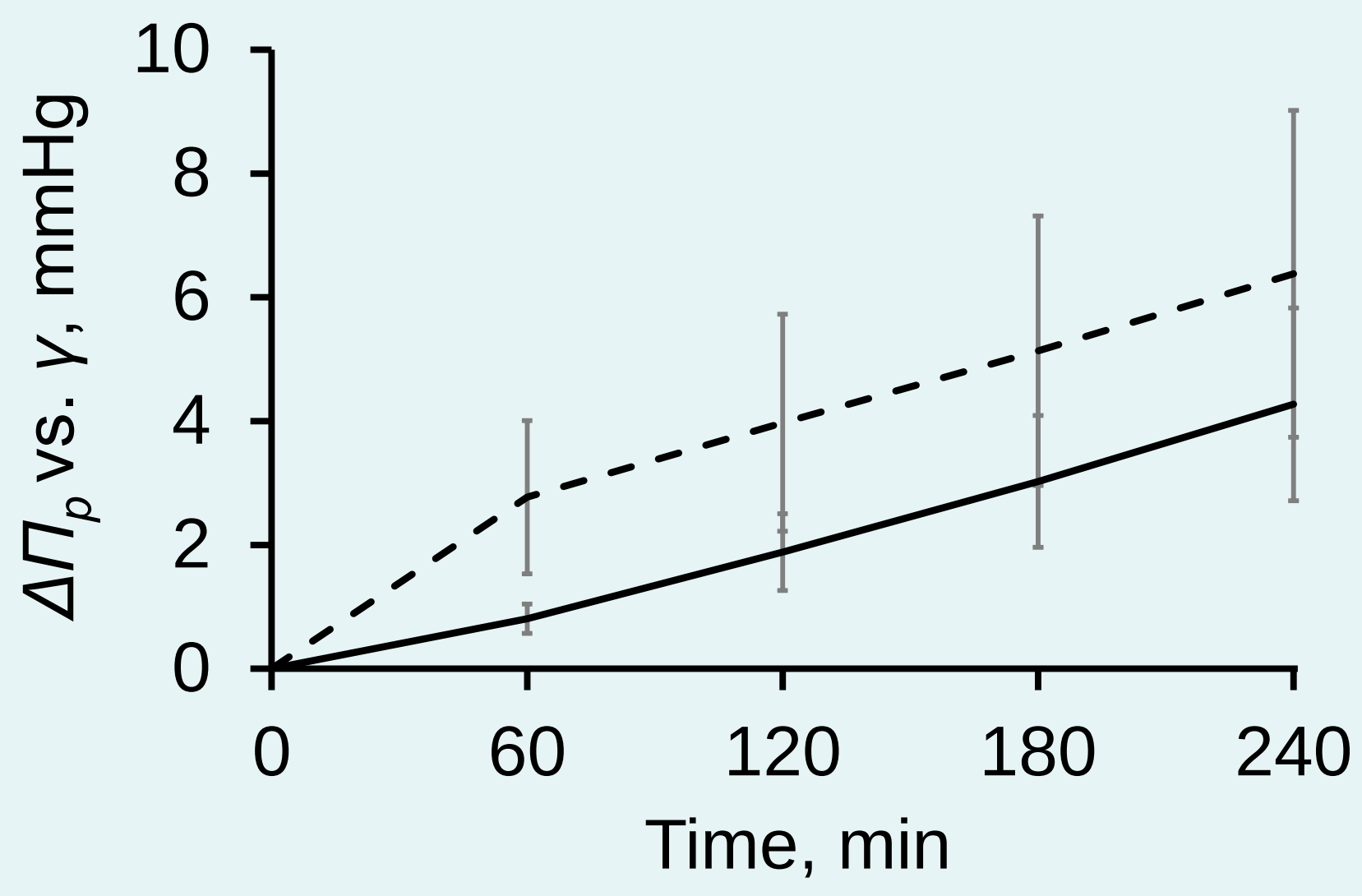

Figure 3. *Values of $\Delta\Pi_p$ (dashed line) and γ (continuous line)*

Objective

The aim of our study was to use mathematical modelling to test the assumptions proposed in [1], necessary for calculating *Kr* from the clinical data .

Methods

- Bioimpedance (BCM), serum total protein concentration, and online blood volume (CritLine) data were acquired in 20 patients undergoing standard maintenance HD.
- The refilling coefficient was calculated as the ratio between *RF* and the increase in plasma oncotic pressure ($\Delta\Pi_p$) from the start of the HD session [1].

  Refilling coefficient (Kr) :

$$Kr(t) = \frac{\frac{dV_p}{dt} + UF}{\Delta\Pi_p(t) - \gamma(t)} \cong \frac{RF}{\Delta\Pi_p(t) - \gamma(t)}$$

$$\gamma(t) \nearrow \gamma(t) = 0 \quad \textit{(under Kr assumptions)}$$

$$\gamma(t) \searrow \gamma(t) \approx \Delta\Pi_i - \Delta P_i - \Delta Lymph$$

Without particular assumptions, γ represents the combined effect of the other Starling forces.

- The mathematical model used to estimate γ is represented in Figure 2. In the model, the only Starling force assumed to be constant was capillary hydraulic pressure [2].
- The estimate of γ was used to calculate a conversion factor *μ* between the constant *Lp* and *Kr*. The correction factor (*μ*) was calculated imposing the equality of the refilling rates calculated both with *Kr* assumptions and without:

$$\begin{cases} RF = Kr \cdot \Delta\Pi_p \\ RF = Lp\left(\Delta\Pi_p - \gamma\right) \end{cases} \Rightarrow \quad \mu(t) = \frac{Kr}{Lp} = \frac{\Delta\Pi_p - \gamma}{\Delta\Pi_p}$$

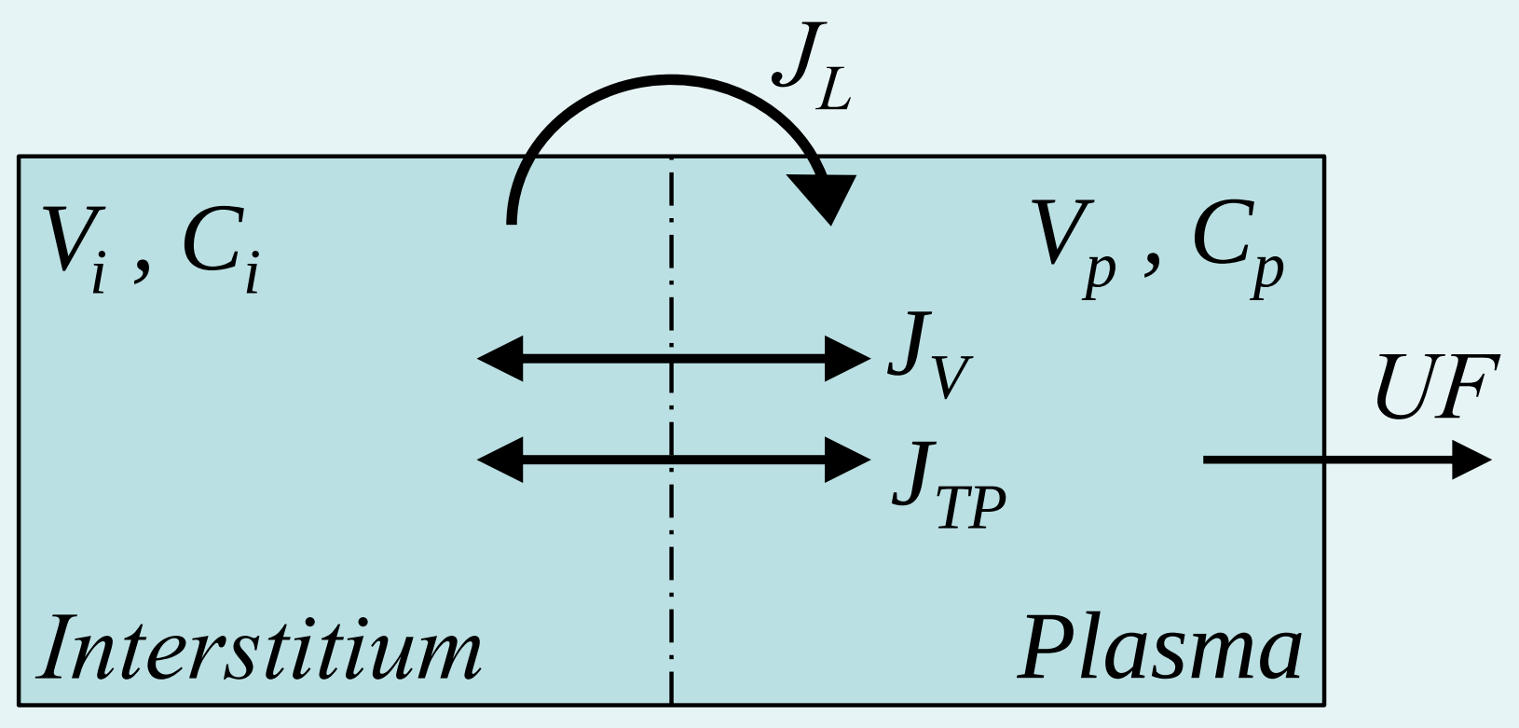

Figure 2. *Structure of the mathematical model*

J_L – lymph flow
J_{TP} – protein flow
J_V – fluid flow
V – volume
C – protein concentration

Results

- The values of $\Delta\Pi_p$, and the increase in the other Starling forces are shown in Table 1. Their sum, γ, resulted to be non-negligible compared to $\Delta\Pi_p$ (Figure 4).
- *Lp* was estimated by the model as a constant value of 5.6 ± 4.2 mL/min/mmHg. After applying the correction factor, the result was a decreasing function of time, similar in shape and values to *Kr* (Figure 4, right).
- The correction factor *μ(t)* was found to be time-dependent (Figure 3, left).
- In a subgroup of 6 patients, initial *Kr* was higher than initial corrected *Lp* (*Lp*); these patients showed also significantly higher values of *Lp* (Table 2).

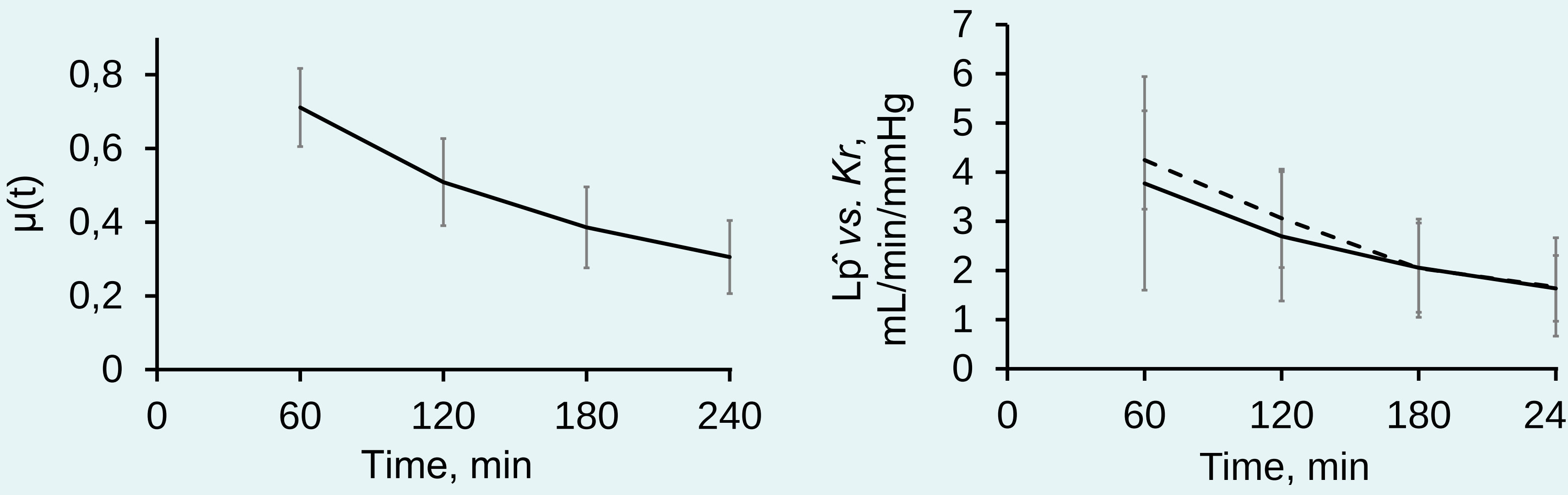

Figure 4. *Left: conversion factor μ(t). Right: Average values of Kr (continuous line) and Lp (Lp after correction with μ, dashed line) for the Baseline group of patients with lower initial Kr.*

$\Delta\Pi_p$	6.4 ± 2.6 mmHg	**% of $\Delta\Pi_p$**
$\Delta\Pi_i$	1.6 ± 0.6 mmHg	25 %
ΔP_i	-1.2 ± 0.3 mmHg	19 %
γ	4.3 ± 1.6 mmHg	67 %

Table 1. *Average increase in the Starling forces after 4 h, calculated by the model. γ is the algebraic sum of $\Delta\pi_i$, ΔP_i and of the change in lymphatic flow during HD.*

	High initial Kr	**Baseline group**
Kr (t = 1h)	15.6 ± 3.6*	4.3 ± 2.6
Lp	13.0 ± 2.7*	6.5 ± 4.4
Lp (t = 1h)	6.0 ± 1.0*	3.8 ± 1.6

Table 2. *Values of Kr, Lp and Lp in the subgroup of patients with high initial Kr, and in the baseline group. * p < 0.05 vs. Baseline.*

Conclusions

The results showed that the decrease observed in *Kr* is likely caused by neglecting important changes in the Starling forces whilst deriving the equation for *Kr*. When these Starling forces are taken into account, constant *Lp* and dynamic *Kr* are equivalent. Rather than indicating a decrease in the hydraulic conductivity of the capillary membrane, *Kr* changes reflect a progressive decrease in refilling efficiency during HD.

References:

1. Tabei K., et al., *An index of plasma refilling in hemodialysis patients.* Nephron, 1996.
2. Pietribiasi M., et al., *Modelling Transcapillary Transport of Fluid and Proteins in Hemodialysis Patients.* PLOS ONE, 2016

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