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Transcapillary escape rate of ^{125}I-albumin in relation to timing of blood sampling: the need for standardization

Youssef Chahid[1,2*], Nienke M. G. Rorije[3], Soufian el Boujoufi[1], Ron A. A. Mathôt[2], Liffert Vogt[3] and Hein J. Verberne[1]

* Correspondence: y.chahid@amsterdamumc.nl
[1]Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands
[2]Department of Clinical Pharmacy, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands
Full list of author information is available at the end of the article

Abstract

Background: Increased vascular permeability is an early sign of vascular damage and can be measured with the transcapillary escape rate of albumin (TER_{alb}). Although TER_{alb} has a multi-exponential kinetic model, most published TER_{alb} data are based on mono-exponential kinetic models with variation in blood sampling schemes. Aim of this posthoc study was to evaluate the influence of variation in blood sampling schemes and the impact of mono- or bi-exponential analyses on the calculation of TER_{alb}. Study participants were part of a cross-over intervention study protocol, investigating effects of sodium loading on blood pressure, endothelial surface layer and microcirculation. Multiple blood samples were drawn between 3 and 60 min after injection of radioactive iodide labeled human serum albumin (rHSA).

Results: In total 27 male participants with 54 measurements were included. For all participants the maximum serum radioactivity was reached within 20 min, while 85% of the participants had their maximum serum activity within 10 min. The TER_{alb} calculated with the subsequently chosen $T_{20–60\ min}$ reference scheme (6.19 ± 0.49%/h) was significantly lower compared to the TER_{alb} of the $T_{3–60\ min}$, $T_{5–60\ min}$, and $T_{max\ –\ 60\ min}$ schemes. There was no significant difference between the $T_{20–60\ min}$ reference scheme and the $T_{10–60\ min}$ and $T_{15–60\ min}$ schemes. Bi-exponential kinetic modeling did not result in significant different observations compared to the mono-exponential kinetic analysis.

Conclusions: As there is variation in the timing of the maximum serum radioactivity of rHSA, blood sampling schemes starting before 10 min after administration of rHSA will result in a significant overestimation of TER_{alb}. In addition, variation in kinetic modeling did not result in significant changes in TER_{alb}. Therefore, we emphasize the need to standardize TER_{alb} and for practical and logistical reasons advocate the use of a mono-exponential model with blood sampling starting 20 min after rHSA administration.

Keywords: Radioactive iodide labeled human serum albumin, Transcapillary escape rate of albumin, TERalb, Vascular permeability

Background

Diabetes mellitus and hypertension are characterized by an increased risk of vascular complications. An early sign of vascular damage is increased vascular permeability, which can be determined by the transcapillary escape rate of albumin (TER_{alb}) (Broekhuizen et al., 2010).

TER_{alb} is the rate in which intravenous albumin escapes from the intravascular to the extravascular volume in the first hour after injection of radioactive iodide labeled human serum albumin (rHSA) (Parving, 1975). The pharmacokinetics of rHSA could be described as the sum of three exponential components, with respective half-life's of 6.8 h, 1.29 days and 19.4 days (Berson et al., 1953; Bauman et al., 1955; CIS bio International, 2010). The disappearance of rHSA, in the first hour after injection, could be described as a bi-exponential decay curve with a inflection point after approximately 10 min (Margarson & Soni, 2002).

Despite the fact that rHSA has a multi-compartment kinetic model, all published TER_{alb} data analyses are based on a mono-exponential kinetic model. This mono-exponential TER_{alb} model has four assumptions: the rHSA behaves like endogenous albumin; the albumin metabolism is in steady state during the TER_{alb} test; rHSA has a mono-exponential blood pool elimination during the first hour after injection, with a rate constant equal to that of time zero; the initial blood pool elimination reflects extravasation and is not influenced by the rHSA metabolism rate (Parving & Gyntelberg, 1973).

The original protocol of Parving et al. describes that a small amount of I-125 or I-131 labeled rHSA is injected in an arm vein, and eight venous blood samples were drawn from the contralateral arm at 10, 15, 20, 30, 40, 50, 55, and 60 min after the injection. The radioactivity of the rHSA in each blood sample was measured in duplicate. The TER_{alb} was calculated and expressed as the percentage decline of radioactivity during the first hour (%/h) (Parving & Gyntelberg, 1973).

However most studies using TER_{alb} values show variation in sampling schemes ranging from 3 to 13 blood samples (Margarson & Soni, 2002; Jensen et al., 1992). Some of the schemes started already 1 min after the injection of rHSA, while others started blood sampling 20 min after the administration of rHSA (Margarson & Soni, 2002; Norberg et al., 2015).

This variation in sampling schemes does impact the calculated TER_{alb}. Sampling schemes that started 5 min after administration found TER_{alb} in the range of 6.9–9.1%/h (Dell'omo et al., 2006; Dell'Omo et al., 2000; Haskell et al., 1997; Pedrinelli et al., 2000; Pedrinelli et al., 1999; van Eijk et al., 2005; Rorije et al., 2018). While studies which started sampling 10 min after injection found a lower TER_{alb} of approximately 5.5%/h (Parving, 1975; Jensen et al., 1992; Nannipieri et al., 1997; Jensen, 1995; Nannipieri et al., 1995; Staberg et al., 1982; Zietse et al., 1995). These differences in TER_{alb} were not related to differences in patient population, but are in line with the multi-exponential kinetics of rHSA.

As the use of TER_{alb} for clinical research seems to gain in popularity, standardization of the technique is essential: i.e. reducing variation in performing the test and thereby reducing variation in the test result. As we observed large variations between different publications in TER_{alb} sampling schemes and most likely thereby variation in TER_{alb} results, we therefore aimed to study the influence of

different sampling schemes and the use of a mono- or bi-exponential analysis on the calculation of TER_{alb}.

Methods

Study population and study design

Selected participants of this post hoc study were part of a cross-over intervention study protocol investigating whether an acute intravenous sodium load, as compared to a chronic dietary sodium load, differs in its effects on blood pressure, the endothelial surface layer and microcirculation (Rorije et al., 2018). Participants included healthy men, and both male type 1 diabetes mellitus and hereditary multiple exostosis patients (i.e., patients with, respectively, acquired and genetically determined glycocalyx changes) (Mooij et al., 2014). Exclusion criteria were hypertension (≥ 140/90 mmHg), obesity (body mass index (BMI) ≥ 30 kg/m^2), history of primary hyperlipoproteinemia, coagulation disorders, and renal or cardiovascular diseases. All participants were randomized to a low sodium diet (LSD, < 50 mmol Na^+ daily) or to a high sodium diet (HSD, > 200 mmol Na^+ daily) for 8 days, separated by a crossover period of at least 1 week. The study was performed at the Amsterdam UMC, location AMC, Amsterdam, The Netherlands. All participants provided written informed consent and approval was obtained from the local ethics committee. The trial is registered in the Netherlands Trial Register (NTR4095 and NTR4788).

Transcapillary escape rate of rHSA

An intravenous (IV) bolus of saline solution with rHSA labeled with 100 kBq I-125 was administered in a cubital vein. Blood samples were drawn from the contralateral arm at baseline and between 3 and 60 min after injection of rHSA. Radioactivity in plasma was measured in duplicate with a Wizard2 2480 automatic gamma counter (PerkinElmer, Waltham, Massachusetts, USA) with a coefficient of variation of < 3%. The routine quality controls of the gamma counter were performed according to the standard GLP features of PerkinElmer, including detector energy resolution, background, absolute - and relative detector efficiency, detector stability probability and calibration.

The TER_{alb} was calculated with PKSolver, a free Microsoft Excel add-in for pharmacokinetic (PK) and pharmacodynamic (PD) data analysis (Zhang et al., 2010). PKSolver has been validated and has been used in different PK/PD studies (Zhang et al., 2010; Kulo et al., 2017; de Velde et al., 2016; Nezic et al., 2014; Balakumar et al., 2013; Wenstedt et al., 2020).

TER_{alb} was expressed as percentage decline in plasma radioactivity per hour (%/h). The TER_{alb} calculation with PKSolver was performed for an IV bolus administration. The formula used for the calculation of TER_{alb} was:

$$TER_{alb} = (A_{0\ min} - A_{60\ min})/A_{0\ min}$$

The predicted activity of rHSA at $T_{0\ min}$ ($A_{0\ min}$) and at $T_{60\ min}$ ($A_{60\ min}$) were calculated by PKSolver (Microsoft Excel 2016) based on a mono- and bi-exponential kinetic model. This program also calculated the correlation coefficient (R) between the observed and predicted data.

Sampling schemes

After acquiring the PK curves of rHSA, we calculated the TER_{alb} according the following simulated blood sampling schemes:

- $T_{3–60\ min}$: 3, 4, 5, 10, 15, 20, 30, 45, and 60 min
- $T_{5–60\ min}$: 5, 10, 15, 20, 30, 45, and 60 min
- $T_{10–60\ in}$: 10, 15, 20, 30, 45, and 60 min
- $T_{15–60\ min}$: 15, 20, 30, 45, and 60 min
- $T_{20–60\ min}$: 20, 30, 45, and 60 min
- $T_{max\ –\ 60\ min}$: from individual A_{max} till 60 min

All blood samples before A_{max} of the PK curves were excluded for the calculation of $TER_{alb,}$ irrespective of the sampling scheme.

Statistics

The effect of different blood sampling schemes on the TER_{alb} values were analyzed by fitting a mixed model as implemented in IBM SPSS Statistics (version 26, IBM, USA). This mixed model uses a compound symmetry covariance matrix and is fitted using maximum likelihood. In the absence of missing values, this method results in the same p values as multiple comparisons tests (e.g. repeated measures ANOVA) that are less able to deal with missing values. Therefore, in the presence of missing values, the results can be interpreted like repeated measures ANOVA (Harrison et al., 2018). We used Bonferroni correction as post hoc test and p values < 0.05 were considered statistically significant. Results were reported as mean ± standard error of the mean (SEM). Bland-Altman plots were used to evaluate the level of agreement between two different blood sample schemes.

Results

Patient demographics

In total 27 men were included resulting in 54 PK curves (27 linked to the LSD and 27 linked to the HSD), based on 486 (54*9 samples) blood sample analyses. The study population consisted of 12 healthy volunteers, 8 diabetes mellitus type I patients, and 7 patients with hereditary multiple exostoses. All volunteers were between 18 and 38 years old with a median age of 24 (range 18–38 years). Other characteristics of study participants are displayed in Table 1.

The blood serum disappearance of rHSA of the study participants is shown in Fig. 1. The pharmacokinetic graphic shows a bi-exponential slope of decay curve with inflexion point at 15–20 min.

T_{max} after rHSA administration

The T_{max} after rHSA administration showed a large inter-individual variability (Fig. 2). The mean T_{max} was 6.9 ± 0.6 min. In 85% of the participants A_{max} of rHSA was reached within 10 min, while T_{max} was reached at 20 min after administration for all participants without an effect of subject category (HME, DM type 1 or healthy volunteer) or the diet followed (LSD vs HSD). Therefore $T_{20–60\ min}$ was used as the reference

Table 1 Characteristics of study participants

Characteristics of participants	Result
Health status (n)	27
Healthy	12
DM type I	8
HME[a]	7
Age (years median, range)	24 (18–38)
Healthy	21 (18–31)
DM type I	26 (21–37)
HME	21 (19–38)
Length (cm ± SD[b])	183.7 (5.8)
Healthy	185.6 (6.3)
DM type I	184.3 (5.0)
HME	179.9 (4.1)
Weight (kg ± SD)	77.0 (7.6)
Healthy	75.7 (6.8)
DM type I	77.4 (9.4)
HME	78.8 (7.3)
BMI (kg/m^2 ± SD)	22.9 (2.5)
Healthy	22.0 (2.2)
DM type I	22.8 (2.5)
HME	24.4 (2.9)
eGFR[c] (ml/min ± SD)	118.1 (10.3)
Healthy	114.7 (12.1)
DM type I	120.3 (9.6)
HME	121.6 (6.3)

[a]HME (hereditary multiple exostoses), [b]SD (standard deviation), [c]eGFR based on CKD-EPI equation

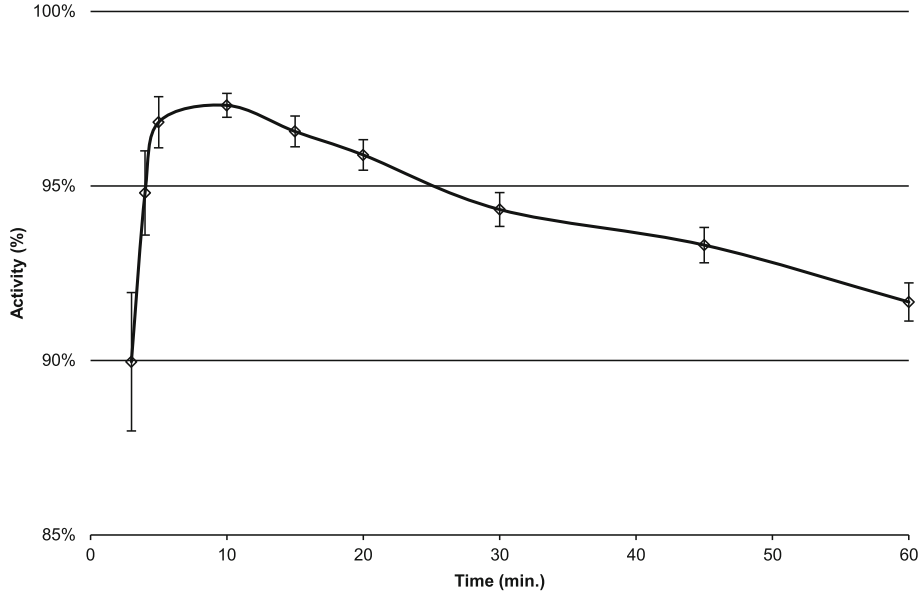

Fig. 1 Relative plasma activity in the first hour after administration of rHSA (Tmax is 100% activity for each individual participant)

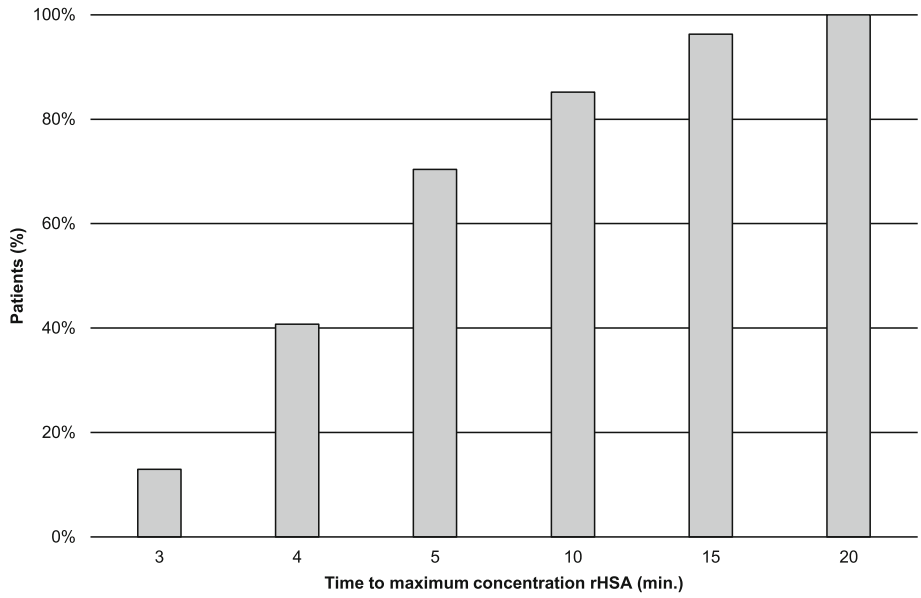

Fig. 2 Percentage of participants reaching serum maximum rHSA activity after administration of rHSA (T_{max})

scheme. The mean TER_{alb} values of the other time schemes were compared to the reference scheme $T_{20–60\ min}$ based on mono-exponential kinetic analysis.

TER_{alb} based on mono-exponential kinetic analysis

The reference $T_{20–60\ min}$ scheme included 54 of the 54 PK curves. The mean TER_{alb} of the $T_{max\ -\ 60\ min}$ scheme resulted in the highest calculated TER_{alb}: 8.30 ± 0.49%/h

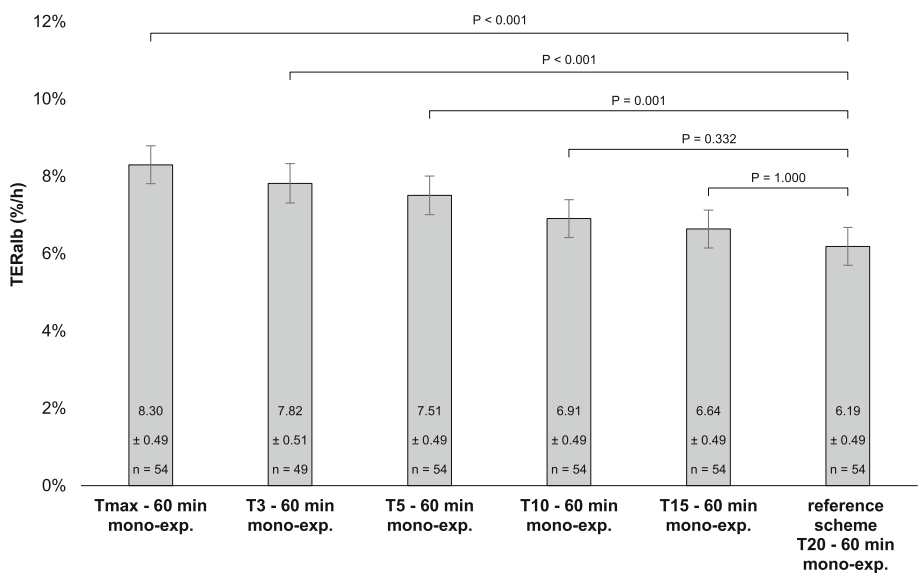

Fig. 3 TER_{alb} for the different blood sampling time schemes based on a mono-exponential kinetic analysis and compared with the $T_{20–60\ min}$ reference scheme

(Fig. 3). The TER_{alb} calculated with the $T_{20–60\ min}$ reference scheme (6.19 ± 0.49%/h) was significantly lower compared to the TER_{alb} of the $T_{3–60\ min}$ (mean difference = – 1.63%/h, CI = – 2.65 – – 0.61%/h, $p < 0.001$), $T_{5–60\ min}$ (mean difference = – 1.32%/h, CI = – 2.27 – – 0.36%/h, $p = 0.001$), and $T_{max\ –\ 60\ min}$ (mean difference = – 2.11%/h, CI = – 3.04 – – 0.48%/h, $p < 0.001$) schemes. There were no significant difference between the mean TER_{alb} of the $T_{20–60\ min}$ reference scheme and the $T_{10–60\ min}$ and $T_{15–60\ min}$ scheme.

TER_{alb} based on bi-exponential kinetic analysis

Using a bi-exponential analysis according to the $T_{20–60\ min}$ scheme did not result in significant different TER_{alb} values when compared to the mono-exponential analysis based $T_{20–60\ min}$ reference scheme (respectively 6.19 ± 0.46%/h vs. 6.05 ± 0.46%/h, $p = 1.000$). The mean TER_{alb} of the reference $T_{20–60\ min}$ scheme was significantly lower compared to the mean TER_{alb} of the bi-exponential kinetic analysis of the $T_{3–60\ min}$ (mean difference = – 1.49%/h, CI = – 2.68 – – 0.29%/h, $p = 0.004$), $T_{5–60\ min}$ (mean difference = – 1.09%/h, CI = – 2.18 – – 0.01%/h, $p = 0.050$), and $T_{max\ –\ 60\ min}$ (mean difference = – 1.87%/h, CI = – 2.95 – – 0.80%/h, $p < 0.001$) schemes. There were no significant difference between the mean TER_{alb} of the $T_{20–60\ min}$ reference scheme and the $T_{10–60\ min}$ and $T_{15–60\ min}$ schemes based on bi-exponential kinetic analysis (Fig. 4).

Figure 5 shows the Bland-Altman plot with agreement between the bi-exponential analysis based on $T_{20–60\ min}$ scheme and $T_{20–60\ min}$ reference scheme. The TER_{alb} showed a bias of – 0.1%/h between the different time schemes without a significant trend over the data range (1.7–12.8%/h) and with a consistent variability over the data range.

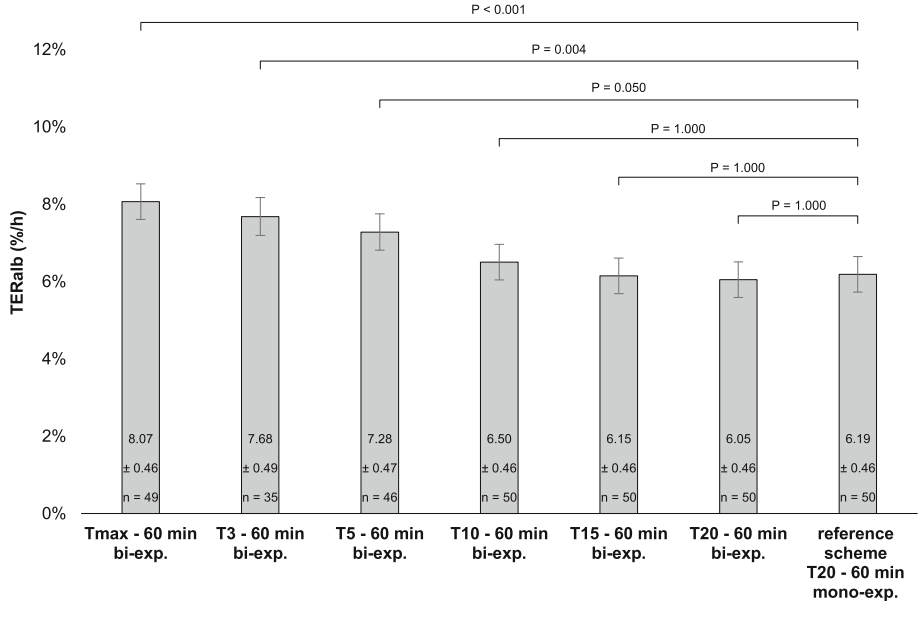

Fig. 4 TER_{alb} for the different blood sampling schemes based on a bi-exponential kinetic model, compared with the $T_{20–60\ min}$ reference scheme

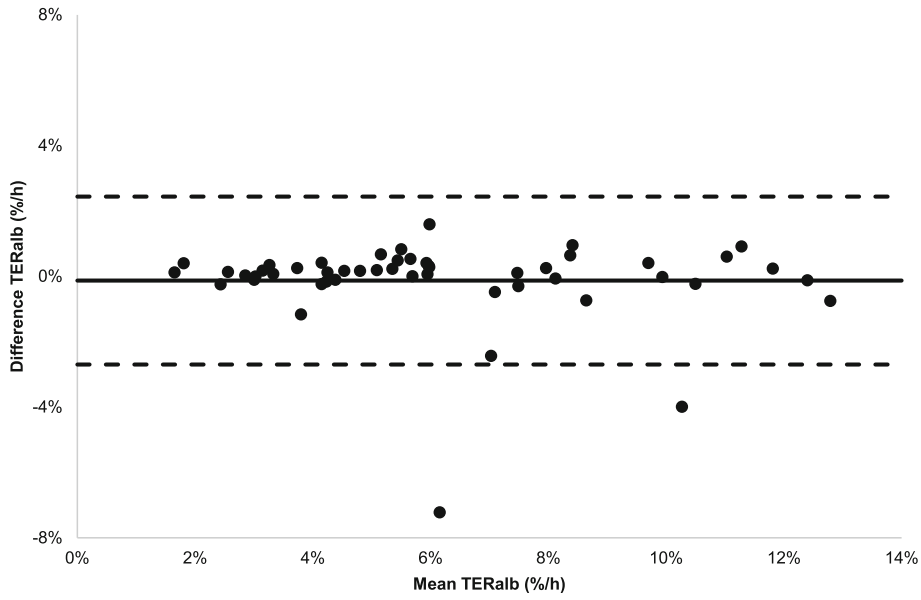

Fig. 5 Bland-Altman plot with differences between TER_{alb} values calculated according $T_{20–60\ min,\ bi\text{-}exp.}$ scheme and the $T_{20–60\ min}$ reference scheme. Solid line: bias (− 0.1%/h) between the two sampling schemes, dotted lines: 95% limits of agreement (− 2.7–2.4%/h)

Discussion

To our knowledge, this study is the first to examine the influence of different blood sampling schemes and the impact of mono- or bi-exponential analyses on the calculation of TER_{alb}. Our findings emphasize the necessity to standardize TER_{alb} calculations.

We found that the TER_{alb} became lower when blood sample collection started later. This phenomenon has been reported previously (Margarson & Soni, 2002). In this context it is remarkable that the majority of published studies used a fixed time sampling scheme with the first blood sampling within 10 min (Dell'omo et al., 2006; Dell'Omo et al., 2000; Haskell et al., 1997; Pedrinelli et al., 2000; Pedrinelli et al., 1999; van Eijk et al., 2005; Rorije et al., 2018). This practice will have caused a overestimation of the reported TER_{alb}. In addition, this makes the reported findings based on TER_{alb} difficult to reproduce and troublesome to extrapolate. Especially when TER_{alb} values of different sampling schemes are compared with each other.

Although the blood serum disappearance of rHSA should be described as a bi-exponential kinetic model, as shown in Fig. 1, the mean TERalb values between mono- and bi-exponential analysis were not significant different. Therefore, we concluded that the mono-exponential kinetic analysis, which is common used for TER_{alb} analysis, is a robust and easy to use approach to calculate the TER_{alb} in the daily practice.

Our data showed that biodistribution of rHSA seems to be complete after 15–20 min. Apparently rHSA may need up to 20 min to reach an equilibrium. This inter-individual variation may be explained by the rate of lymphatic return or redistribution into the hepatic and splenic interstitium (Margarson & Soni, 2002; Henriksen & Schlichting, 1981). To minimize the number of blood samples, we advocate the use a mono-exponential model with blood sampling starting 20 min after rHSA administration for the daily practice. For scientific purposes, we suggest to use the T_{max} scheme to correct for the inter- and intra-individual variability. It should be

noted that these TERalb values are significant higher compared to the daily practice scheme.

This study has several limitations that need to be addressed. First, we pooled data, because no differences between healthy participants, type 1 diabetes mellitus and hereditary multiple exostosis patients were detected. One would have expected higher TERalb values in type 1 diabetes mellitus patients. However, our study included young male with uncomplicated type 1 diabetes without albuminuria. Likely, at this stage of the disease, TERalb is still unaffected. Secondly, we did not collect any blood samples after $T_{60\ min}$. Blood sampling for longer time periods after administration, for example up to 24 h after rHSA injection, could have helped in better understanding the kinetics of rHSA blood clearance.

Conclusions

To our knowledge, this study examined for the first time whether different blood sampling schemes impact TER_{alb} values. We found significant differences between the blood sampling schemes which will cause bias in reporting TER_{alb} and makes it difficult to reproduce and extrapolate outcomes of TER_{alb}.

As there is a large variation in the timing of the maximum serum radioactivity of rHSA, blood sampling schemes starting before 10 min after administration of rHSA will result in a significant overestimation of TER_{alb}. In addition, variation in mono- or bi-exponential kinetic modeling did not result in significant changes in TER_{alb}. Therefore, we emphasize the need to standardize TER_{alb} and for practical and logistical reasons advocate the use of a mono-exponential model with blood sampling starting 20 min after rHSA administration.

Abbreviations

rHSA: radioactive iodide labeled human serum albumin; TERalb: Transcapillary escape rate of albumin; Tmax: Time to peak drug concentration; Cmax: Peak drug concentration; I-125: Iodine-125; I-131: Iodine-131; BMI: Body mass index; LSD: Low sodium diet; HSD: High sodium diet; GLP: Good Laboratory Practice

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Authors' contributions

YC and HV analyzed and interpreted the data. YC, SB and HV were major contributors in writing the manuscript. NR, LV and RM have substantively revised the manuscript. All authors read and approved the final manuscript.

Authors' information

Not applicable.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All participants provided written informed consent and approval was obtained from the local ethics committee. The trial is registered in the Netherlands Trial Register (NTR4095 and NTR4788).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details
[1]Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands. [2]Department of Clinical Pharmacy, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands. [3]Department of Internal Medicine, Section of Nephrology, Amsterdam University Medical Centers, Amsterdam Cardiovascular Sciences, University of Amsterdam, Amsterdam, The Netherlands.

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