Transcapillary Escape Rate of 125I-albumin in Relation to Timing of Blood Sampling: The Need for Standardization.

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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 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 subjects 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 minutes after injection of radioactive iodide labeled human serum albumin (rHSA).

Results

In total 27 male subjects were included. For all subjects the maximum serum radioactivity was reached within 20 minutes, while 86% of the subjects had their maximum serum activity within 10 min. The TER_{alb} calculated with the subsequently chosen $T_{20-60\ min}$ reference scheme (5.97 ± 0.39%/h) was significantly lower compared to the TER_{alb} of the $T_{3-60\ min}$, $T_{5-60\ min}$, $T_{10-60\ min}$, and $T_{max-60\ min}$ schemes. There was no significant difference between the $T_{20-60\ min}$ reference scheme and the $T_{15-60\ min}$ scheme. 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 15-20 minutes 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 minutes after rHSA administration.

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}).(1)

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).(2) The pharmacokinetics of rHSA could be described as the sum of three exponential components, with respective half-life's of 6.8 hours, 1.29 days and 19.4 days.(3–5) 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 minutes.(6)

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.(7)

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 minutes 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).(7)

However most studies using TER_{alb} values show variation in sampling schemes ranging from 3 to 13 blood samples.(8) Some of the schemes started already 1 minute after the injection of rHSA, while others started blood sampling 20 minutes after the administration of rHSA.(9, 10)

This variation in sampling schemes does impact the calculated TER_{alb}. Sampling schemes that started 5 minutes after administration found TER_{alb} in the range of 6.9–9.1%/h.(11–17) While studies which started sampling 10 minutes after injection found a lower TER_{alb} of approximately 5.5%/h.(2, 8, 18–22) 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 study subjects 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.(17) 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).(23) 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 subjects were randomized to a low sodium diet (LSD, <50 mmol Na^+ daily) or to a high sodium diet (HSD, >200 mmol Na^+ daily) for eight days, separated by a crossover period of at least one 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 minutes 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.(24) PKSolver has been validated and has been used in different PK/PD studies.(24-29)

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 minutes
- $T_{5-60\ min}$: 5, 10, 15, 20, 30, 45, and 60 minutes
- $T_{10-60\ in}$: 10, 15, 20, 30, 45, and 60 minutes

- $T_{15-60\ min}$: 15, 20, 30, 45, and 60 minutes
- $T_{20-60\ min}$: 20, 30, 45, and 60 minutes
- $T_{max-60\ min}$: from individual A_{max} till 60 minutes

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

Statistics

TER_{alb} values were excluded if the correlation coefficient (R) was below <0.80.(30) All data were log-transformed and 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 25, 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.(31) 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. All presented values represent non - transformed data.

Results

Patient demographics

In total 27 men were included resulting in 54 PK curves (23 linked to the LSD and 27 linked to the HSD), based on 450 (50*9 samples) blood sample analyses. A total of 4 PK curves were excluded because of R < 0.80. 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 40 years old with a mean age of 25.3 ± 6.2 years. Other patient characteristics are displayed in table 1.

Table 1
Patient characteristics

Patient characteristics	Result
Health status (n)	27
Healthy	12
DM type I	8
HME*	7
Age (years ± SD**)	25.3 (6.2)
Healthy	22.7 (4.1)
DM type I	28.1 (5.7)
HME	26.6 (8.5)
Length (cm ± SD)	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*** (ml/min ± SD)	118.1 (10.3)
Healthy	114.7 (12.1)
DM type I	120.3 (9.6)
HME	121.6 (6.3)
* HME (hereditary multiple exostoses), ** SD (standard deviation), *** eGFR based on CKD-EPI equation.	

A typical blood serum disappearance of rHSA of a healthy male (subject number 5) is shown in figure 1. The graphic shows a bi-exponential slope of decay curve with inflexion point at 20 minutes.

T_{max} after rHSA administration

The T_{max} after rHSA administration showed a large inter-individual variability (Figure 2). The mean T_{max} was 6.6 ± 0.6 minutes. In 86% of the subjects A_{max} of rHSA was reached within 10 minutes, while T_{max} was reached at 20 minutes after administration for all subjects 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 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 42 of the 50 PK curves. The other 12 PK curves were excluded because of a $R < 0.80$. The mean TER_{alb} of the $T_{3 - 60\ min}$ scheme resulted in the highest calculated TER_{alb}: 8.69 ± 0.61%/h (Figure 3). The TER_{alb} calculated with the $T_{20 - 60\ min}$ reference scheme (5.97 ± 0.39%/h) was significantly lower compared to the TER_{alb} of the $T_{3 - 60\ min}$ (mean difference = -2.72%/h, CI = -3.64 – -1.79%/h, $p < 0.001$), $T_{5 - 60\ min}$ (mean difference = -1.48%/h, CI = -2.22 – -0.74%/h, $p < 0.001$), $T_{10 - 60\ min}$ (mean difference = -0.76%/h, CI = -1.44 – -0.09%/h, $p = 0.014$), and $T_{max - 60\ min}$ (mean difference = -1.84%/h, CI = -2.55 – -1.13%/h, $p < 0.001$) schemes. There was no significant difference between the mean TER_{alb} of the $T_{20 - 60\ min}$ reference scheme and the $T_{15 - 60\ min}$ 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 6.22 ± 0.38%/h vs. 5.75 ± 0.35%/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 = -3.13%/h, CI = -4.80 – -1.45%/h, $p < 0.001$), $T_{5 - 60\ min}$ (mean difference = -2.36%/h, CI = -3.77 – -0.95%/h, $p < 0.001$), $T_{10 - 60\ min}$ (mean difference = -1.79%/h, CI = -3.11 – -0.46%/h, $p = 0.001$), and $T_{max - 60\ min}$ (mean difference = -1.74%/h, CI = -3.10 – -0.38%/h, $p < 0.002$) schemes. As with mono-exponential kinetic analysis of $T_{15 - 60\ min}$ scheme, there were no significant differences between the mean TER_{alb} of the $T_{20 - 60\ min}$ reference scheme and the $T_{15 - 60\ min}$ scheme based on bi-exponential kinetic analysis (Figure 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 0.5%/h between the different time schemes without a significant trend over the data range (2.7 – 12.7%/h) and with a consistent variability over the data range.

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.(6) 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 minutes.(2, 8, 11–22) 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 within 15–20 minutes. Apparently rHSA may need up to 20 minutes 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.(6, 32) To minimize the number of blood samples, we advocate the use a mono-exponential model with blood sampling starting 20 minutes 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, the sample size of the study was too small to detect differences between healthy subjects, type 1 diabetes mellitus and hereditary multiple exostosis patients. So we had to combine them, resulting in relative large standard error of the mean. 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 hours 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 15–20 minutes 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 minutes 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

Declarations

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.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Not applicable.

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.

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Authors' information

Not applicable.

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Figures

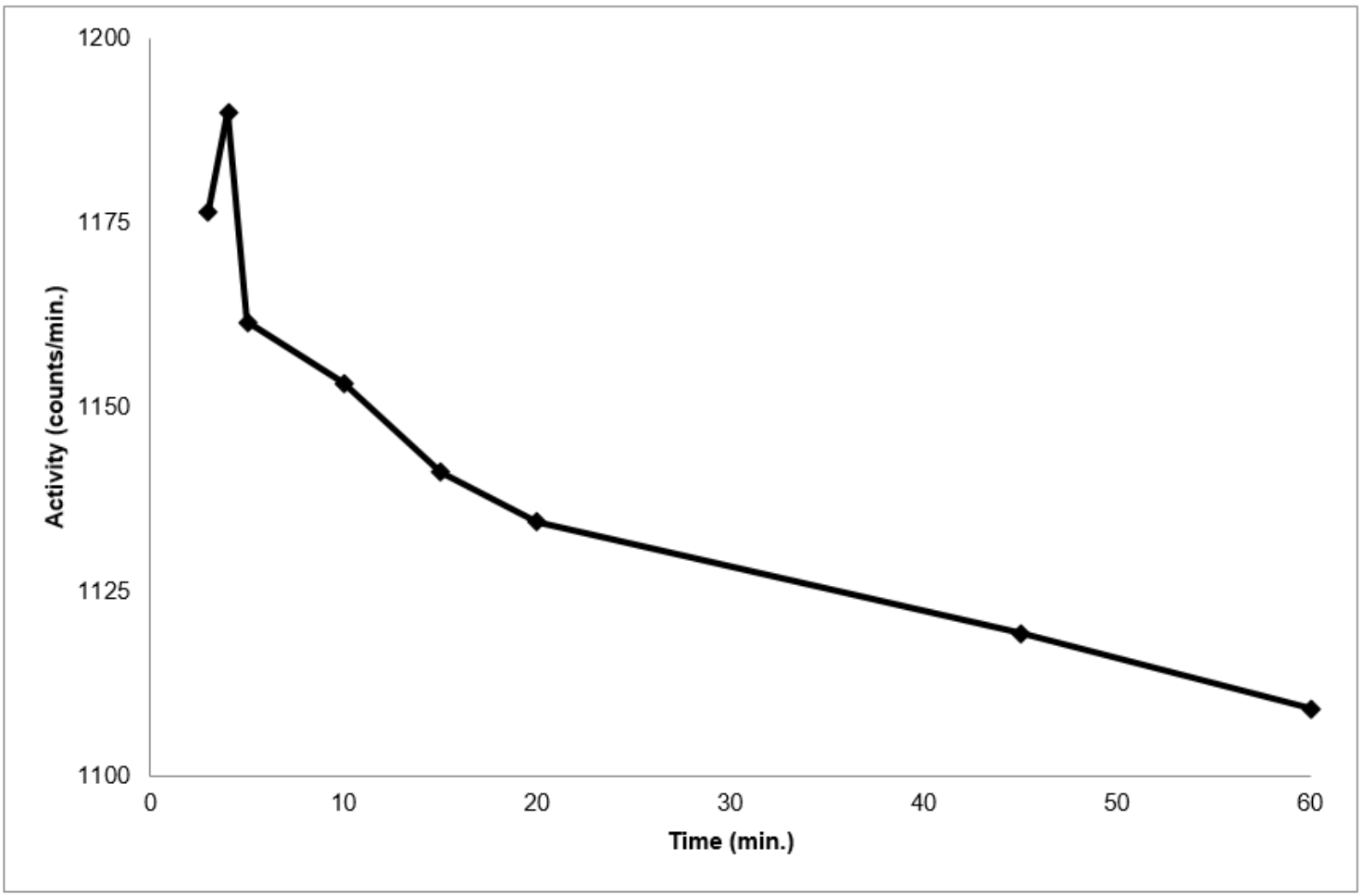

Figure 1

Decrease of plasma activity over the first hour after administration of rHSA (subject number 5, low sodium diet).

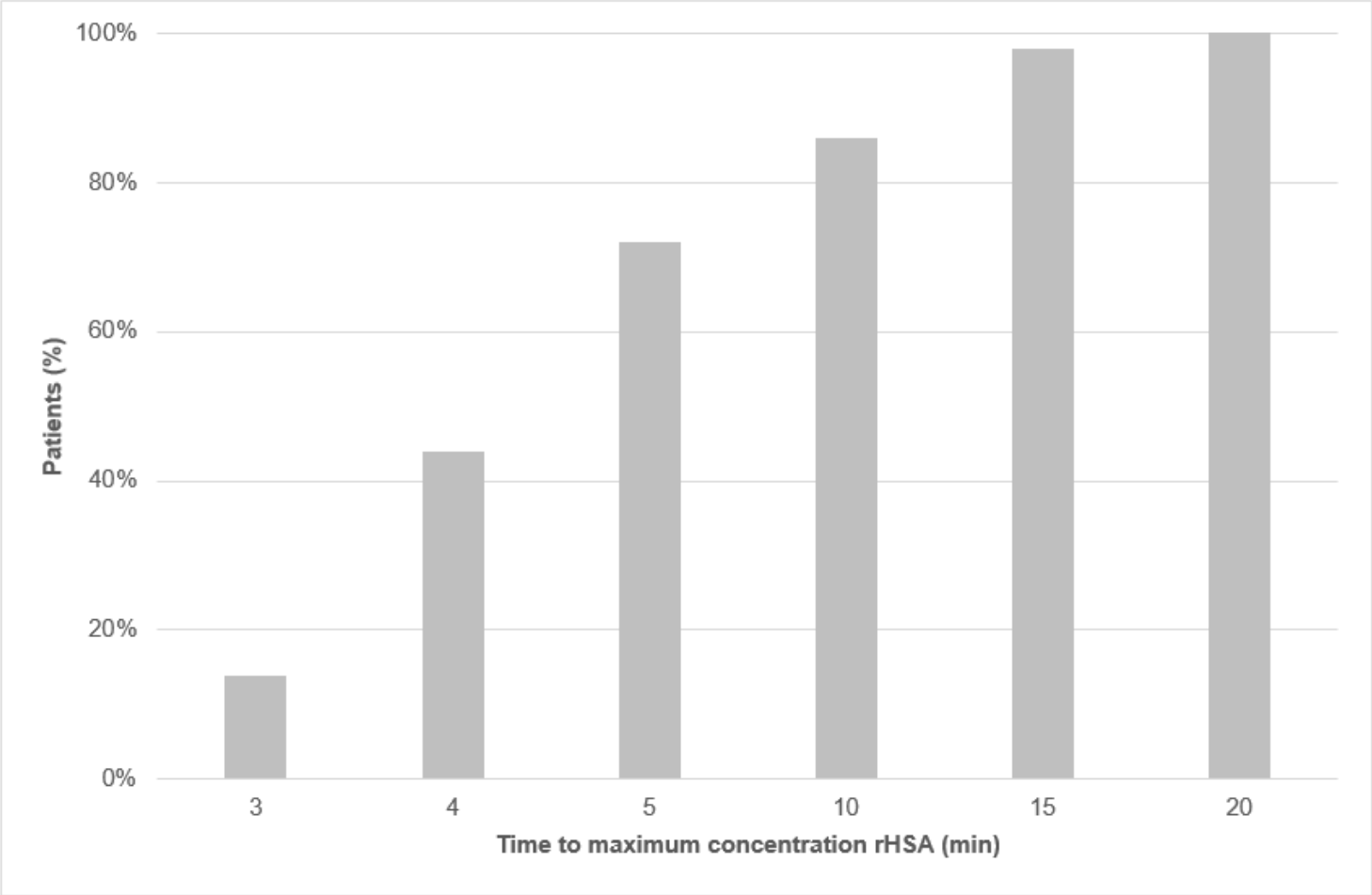

Figure 2

Percentage of patients reaching serum maximum rHSA activity after administration of rHSA (Tmax).

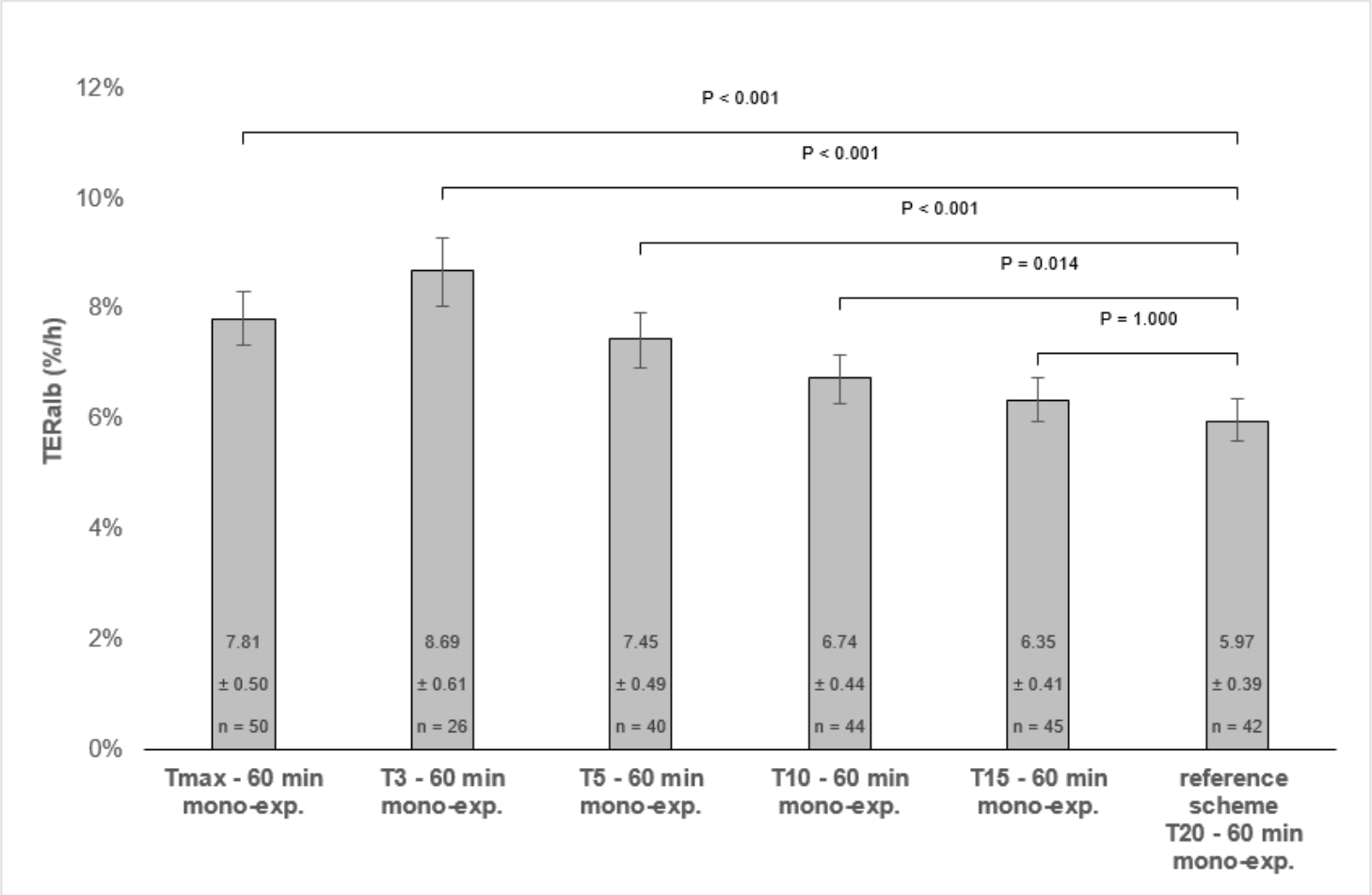

Figure 3

TERalb for the different blood sampling time schemes based on a mono-exponential kinetic analysis and compared with the T20 – 60 min reference scheme.

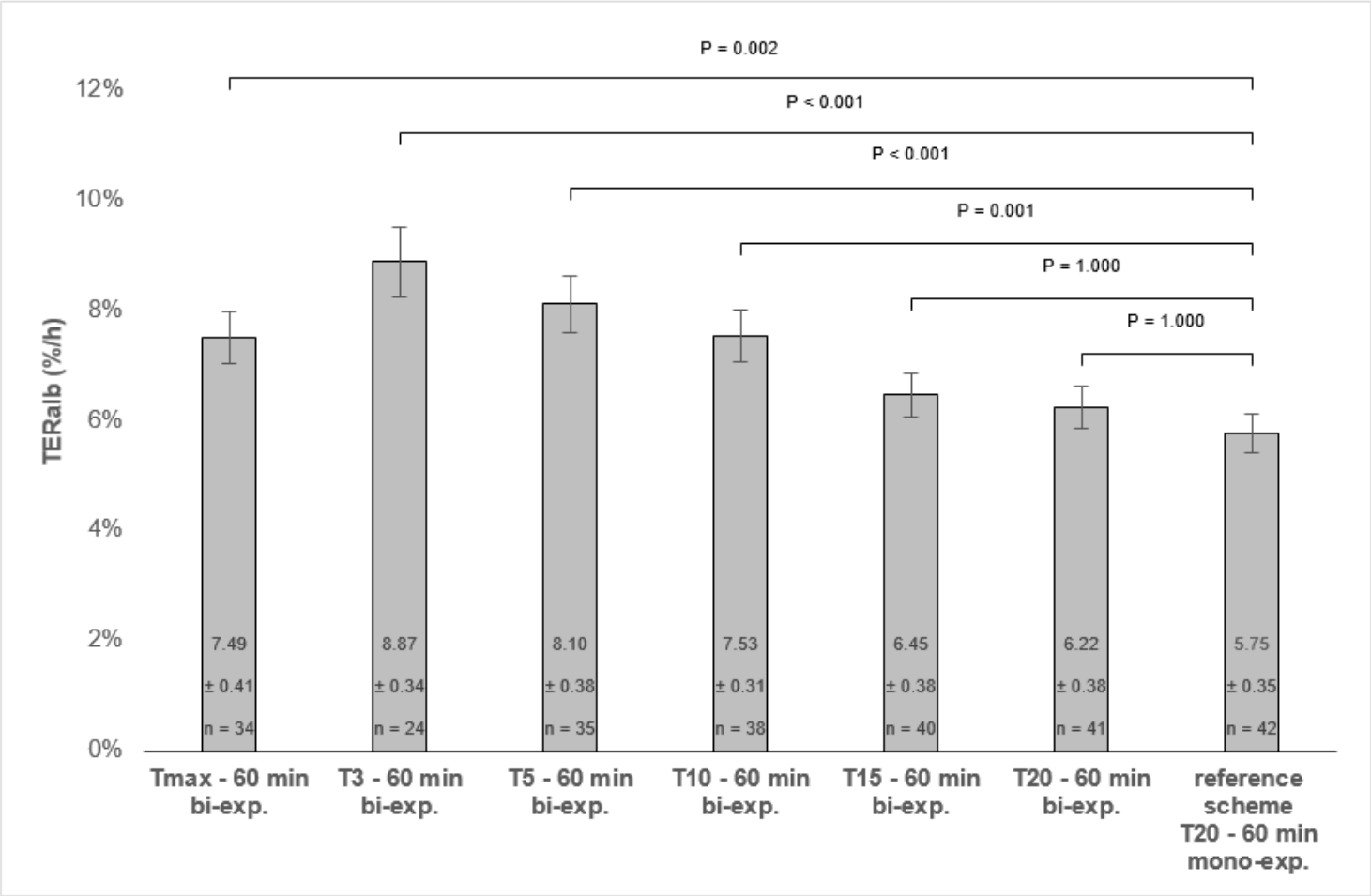

Figure 4

TERalb for the different blood sampling schemes based on a bi-exponential kinetic model, compared with the T20 – 60 min reference scheme.

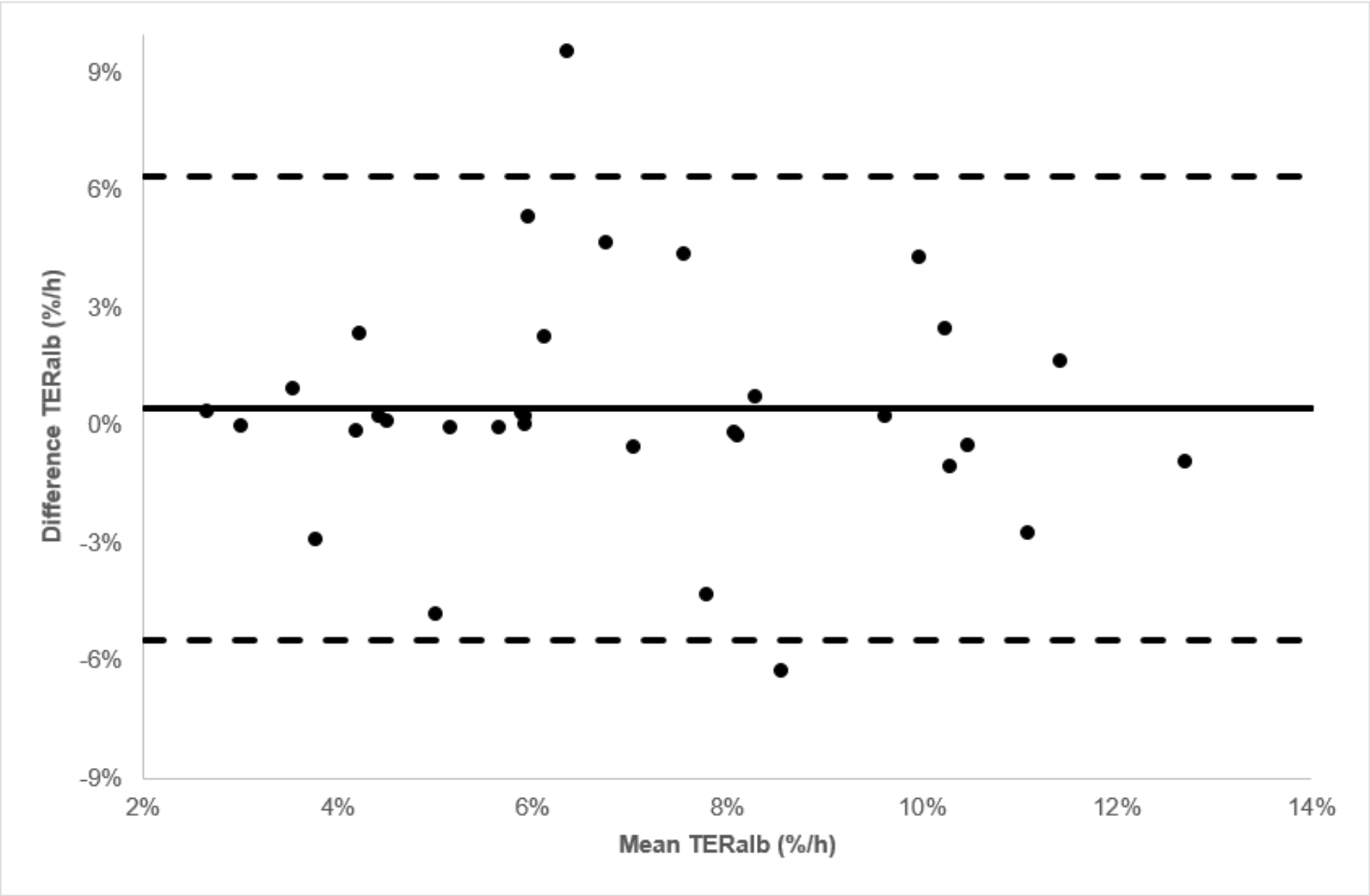

Figure 5

Bland-Altman plot with differences between TERalb values calculated according T20 – 60 min, bi-exp. scheme and the T20 – 60 min reference scheme. Solid line: bias (0.5%/h) between the two sampling schemes, dotted lines: 95% limits of agreement (-5.5 – 6.4%/h).