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EFFECT OF SAMPLING FREQUENCY ON PERFUSION VALUES IN CT PERFUSION OF LUNG TUMORS

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Abstract

Purpose—To assess the impact on CT perfusion (CTp) values of increasing sampling intervals (SI) in lung CTp acquisition, as a potential means of limiting radiation exposure.

Materials and Methods—24 lung CTp datasets in 12 patients with lung tumors (>2.5 cm diameter), were analyzed by distributed parameter modeling to yield tumor blood flow (BF), blood volume (BV), mean transit time (MTT), and permeability (PS) values. Scans were undertaken 2–7 days apart, without intervening therapy, on a 16-row multidetector CT scanner. CTp values for the gold-standard sampling interval of 0.5s (SI_{0.5}) were compared with those of SI datasets of 1s, 2s, and 3s, which included relative shifts to account for uncertainty in pre-enhancement set-points, by linear mixed model analyses. Scan-rescan reproducibility was assessed by between-visit coefficient of variation (wCV).

Results—With increasing SIs, mean (95% CI) BF and BV values were increasingly overestimated by up to 14% (11% – 18%) and 8% (5% – 11%) at 3s SI, and MTT and PS values under-estimated by up to 11% (9% – 13%) and 3% (1% – 6%), compared to SI_{0.5}. The differences were significant for BF, BV and MTT for SIs of 2s and 3s (p = 0.0002), but not for SI of 1s. wCVs increased with subsampling for BF (32.9–34.2%), BV (27.1–33.5%) and PS (39.0–42.4%) compared to SI_{0.5} (21.3%, 23.6% and 32.2%, respectively).

Conclusion—Increasing sampling intervals beyond 1s yield significantly different CTp parameter values compared to gold-standard (up to 18% at 3s sampling); scan-rescan reproducibility was also adversely affected.

INTRODUCTION

CT perfusion (CTp) is evolving as a tool in oncologic imaging, with potential to assist in treatment monitoring, prognostication and pathophysiological understanding [1–4]. A

variety of perfusion parameters can be derived from CTP depending on the particular physiological model that is used to describe the behavior of tissue perfusion.

CT images for CTP analysis are acquired at relatively high temporal sampling frequencies, typically with a temporal sampling intervals of 1 second or less, during intravenous (IV) administration of contrast medium. Any reductions in the temporal sampling frequency, or “subsampling”, would decrease radiation dose exposure, and would be advantageous. However, it is clearly important to understand the impact of any reductions in sampling frequency, or increases in sampling interval (SI), on resultant perfusion parameter values before implementing such acquisition strategies.

There have been relatively few studies which have investigated the effects of temporal sampling intervals on resulting CTP values [5–10]. These studies, which have been undertaken with a variety of different physiological and CTP models, have yielded somewhat mixed conclusions, with some suggesting that reducing sampling intervals to 3s are satisfactory, while others have advocated against sampling intervals of less than 1s [7, 8].

One physiological model that is implemented in a commercially available CTP platform is based on the distributed parameter model, or deconvolution analysis. A range of tissue perfusion parameters can be derived from the resulting time-attenuation (density) curves acquired from the tissue region(s) of interest ROI(s) and vascular (arterial) input [11, 12]. These CTP parameters include blood flow (BF), blood volume (BV), mean transit time (MTT) and permeability-surface area product (PS).

The aim of this study was to evaluate the effects of reductions in the sampling frequency of CT data acquisition on resultant CTP parameter values, utilizing the distributed parameter model, in lung tumors. We also assessed the impact of sampling interval on scan-rescan reproducibility.

MATERIALS AND METHODS

Patients and CTP Scanning Technique

The prospective study that provided the patients for this study was approved by our institutional review board, and written informed consent had been obtained from all patients. The study complied with HIPAA regulations.

Details of the patient inclusion criteria and CTP scanning protocol have been presented previously [13]. In brief, patients with lung lesions larger than 2.5 cm in longest axial diameter were eligible for participation, and underwent two CTP scans 2–7 days apart on a 16-row multidetector CT scanner (LightSpeed, GE Healthcare, Waukesha, WI).

The CTP scans were obtained in two phases: Phase 1, cine acquisition during a 30 second breath-hold, followed 20 seconds later by Phase 2, six short breath-hold helical scans acquired at 15 second intervals. The final Phase 2 acquisition commenced 125s after the start of the Phase 1 acquisition. The Phase 1 cine images were reconstructed to a temporal sampling interval of 0.5 second. Data acquisition started 5 seconds after intravenous injection of 50 mL of a nonionic contrast agent (ioversol [Optiray], 320 mg of iodine/100 mL; Mallinckrodt, Inc., St. Louis, MO) using an automatic injector (MCT/MCT Plus; Medrad, Pittsburgh, PA) and an injection rate of 7 mL/second. This was followed by a saline chase of 50 mL also at 7 mL/second.

CT Perfusion analyses

The images were analyzed using CTP software on a workstation (Body CT Perfusion 4 version 4.3.1; Advantage Windows 4.4, GE Healthcare, Waukesha, WI). Before the CT perfusion analyses were undertaken, the Phase 1 and Phase 2 images of each patient dataset were anatomically registered, as previously described [13, 14]. This resulted in a CT perfusion dataset consisting of fifty-nine 4-slice cine images temporally sampled at 0.5s from the Phase 1 acquisition, together with six anatomically matched 4-slice images from the Phase 2 acquisition. These images formed the gold-standard dataset (SI_{0.5}).

Gold-standard CTP analysis—For each gold-standard dataset obtained above, a circular ROI was placed in the thoracic aorta, which provided the arterial input function for generation of perfusion maps within the software. A *pre-enhancement* set point (T_1) was determined, based on the time when the arterial signal first begins to rise (t_0). *Last first phase* (or “*Post-enhancement*” (T_2)) and *last second phase* (T_3) set points were also assigned, namely, at the final time point of the Phase 1 data acquisition, and the final Phase 2 image (T_3), respectively (Figure 1, top row; Figure 2a).

For each of the four axial slice locations of each dataset, lung lesion ROIs were drawn freehand around the periphery of the lesion, using an electronic cursor and mouse, with reference to the source cine CT images and perfusion maps, displaying the images at soft tissue windows (width = 350 HU, level = 40 HU) [E.F.A and D.H.H in consensus]. Mean BF, BV, MT and PS values were obtained from each CT levels (Figure 2b–2e).

All ROIs were saved within the software to enable identical placement in all the subsequent subsampling analyses.

Temporal subsampling CTP analysis—The above gold-standard datasets for each patient, which were based on a temporal sampling of 0.5 seconds from the Phase 1 component of the acquisition (SI_{0.5}), were re-analysed with temporal sampling intervals of 1, 2 and 3 seconds applied to the Phase 1 data. CTP analyses were undertaken of the combined subsampled Phase 1 images and the reference Phase 2 images.

Thus, the 1s sampling interval (SI₁) dataset was achieved by selecting alternate images from the original SI_{0.5} 4-slice Phase 1 cine dataset, and loading these with the corresponding six Phase 2 images into the software. The 2s sampling interval (SI₂) dataset was achieved in a similar fashion by selecting every fourth image from the SI_{0.5} data. The 3s sampling interval (SI₃) dataset was achieved by selecting every sixth image from the original SI_{0.5} dataset (Figure 1, 2nd row).

It should be noted that subsampling was carried out only on the cine Phase 1 data, and not the six delayed Phase 2 data; thus, final subsampled datasets consisted of subsampled Phase 1 data combined with unaltered Phase 2 data.

Temporal shifting CTP analysis—The above analyses were initially undertaken with T_1 fixed at the timepoint that had been determined for the gold-standard dataset ($T_1=t_0$).

Subsequently, each subsampled data was analyzed following application of a “temporal shift”. The need to include temporal shifting in consideration of an analysis of subsampling is that there may be uncertainty as to the T_1 timepoint of the more sparsely populated subsampled data, and indeed the precise time point in the gold-standard 0.5s data considered to represent $T_1=t_0$ may not have been actually acquired or represented in the subsampled data. In order to simulate the reality of such subsampled datasets, we applied both positive and negative temporal shifts to the subsampled T_1 time point. Although in principle one

could explore the full range of possible shifts for any subsampled data, we considered that although observers may stray on the side of the upslope of the time attenuation curve of the aorta, in practice only small incursions were likely. Thus, for the SI₁ dataset, temporal shifts in T₁ relative to t₀ of -0.5s, 0s and +0.5s were investigated. This was achieved by analyzing the 1s sampling interval dataset a further two times in addition to the T₁=t₀ described above, each time using a different pre-enhancement set point time (T₁), which was shifted from the original reference pre-enhancement set point time at t₀ by -0.5s and +0.5s. For the SI₂ dataset, two further temporal shifts, of -1.0s and -1.5s, were added to those of the SI₁ shifts of -0.5s, 0s and +0.5s (i.e., a total of 5 temporal shifts). For the SI₃ dataset, the following 7 temporal shifts were investigated, -2.5s, -2.0s, -1.5s, -1.0s, -0.5s, 0, +0.5s (Figure 1, third and bottom rows).

We also controlled for the potential bias in baseline attenuation values that might be introduced due to subsampling and/or shifting. This was in recognition that subsampling/shifting inevitably affects the number of available data points from the gold-standard data prior to T₁ from which baseline vascular and tissue attenuation values for the algorithm are determined; and this is exacerbated by baseline data which may be intrinsically noisy. We therefore ensured that there were the same number of pre-T₁ data points in the subsampled/shifted datasets as in the 0.5s gold-standard; this was achieved by randomly inserting the necessary number of baseline imaging data points (from the reference 0.5s data) to the subsampled/shifted data, maintaining a constant number of baseline (or pre-T₁) datapoints.

All the resultant subsampled/shifted datasets were analysed in the CTp software using the same arterial and tissue ROIs as for the reference analyses. Mean BF, BV, MTT and PS values were obtained for each tissue ROI at each CT level (Figure 2b–2e).

Statistical Analysis

Summary statistics of raw BF, BV, MTT, and PS data were provided in the form of median and range. All data were transformed to the logarithmic scale prior to any statistical analysis.

The differences between the gold-standard (original SI_{0.5} dataset with no shift) and subsampled measurements were estimated using a linear mixed model on the logarithmic scale for each pair of data by sampling interval and shifting. The estimated differences were back-transformed (anti-log) to the original scale to obtain ratios between subsampled measurements and the gold-standard. Summaries of the ratios were provided by estimated ratio and 95% confidence interval of the estimated ratio. The linear mixed model was used to assess if the difference was significantly different from zero, i.e., if the subsampled measurements were significantly different from the gold-standard. The mixed model took into account the correlations between measurements from the same patients.

In order to assess the relative contributions of sampling interval or shifting to the overall difference between subsampled and gold-standard measurements, a variance component analysis was carried out to assess variations due to sampling interval and shifting. A component with higher variation indicates that that factor makes a larger contribution to the overall difference.

For each shift within a sampling interval, the BF, BV, MTT and PS measurements from all the ROIs were plotted against the gold-standard measurement. A unity line was plotted to illustrate if there was over- or under-estimation.

We assessed the impact on scan-rescan reproducibility by evaluating the between-visit coefficient of variation (wCV) [15]. After each variance component analysis, the within-patient coefficient of variation (wCV) was calculated using the formula $wCV = (e^{wSD} - 1)$,

in which the within-patient standard deviation (wSD) is the square root of the *within*-patient variation. The 95% confidence interval (CI) of the wCV was calculated on the basis of the CI of the wSD.

All tests were two-sided and p-values of 0.05 or less were considered statistically significant. Statistical analysis was carried out using SAS version 9 (SAS Institute, Cary, NC). Plotting was carried out using SPlus 7 (Insightful Inc., Seattle, WA).

RESULTS

In total, 24 CTP datasets formed the study cohort. This consisted of 12 patients (mean age 55.1 years (range, 21.6–74.8); 8 male, 4 female), each with two CTP studies. The median size of the lung tumors was 4.5 cm (range, 2.5–9.7 cm), and the median axial-section area of tumor ROIs was 604 mm² (range, 440–3250 mm²). The median size of aortic ROIs was 57 mm² (range, 16–123 mm²). The primary sites of malignancy of the lung lesions were: lung (n=5), melanoma (n=3), sarcoma (n=2), rectal (n=1), renal (n=1).

For our gold-standard analysis (SI_{0.5}), median BF, BV, MTT, and PS values were 55.3 mL/min/100g, 2.83 mL/100g, 4.0 seconds, 27.5 mL/min/100g, respectively. With increases in sampling interval, median BF and BV values increased, and MTT values decreased (Table 1). No specific trend in PS values with subsampling was evident. There were no significant differences in the four CTP parameter values compared to gold-standard for 1s sampling intervals (p>0.05).

However, BF, BV and MTT values were significantly different from gold-standard for sampling intervals greater than 1s (p = 0.0002), and for PS values for sampling intervals greater than 2s (p<0.0001) (Table 1). For example, back transforming (i.e. anti-logging) for 3s sampling interval with the inclusion of all associated shifts, mean (95% CI) BF, BV, MTT and PS values compared to gold-standard were: 14% (11% - 18%) higher, 8% (5% - 11%) higher, 11% (9% - 13%) lower, and 3% (1% - 6%) lower, respectively.

Incorporation of shifting yielded a wider range of values across all CTP parameters compared to corresponding subsampled datasets *without* shifting, although median values were similar (Table 1). Plots of the raw data by subsampling interval with incorporation of all shifts in T₁ for each subsampling interval are presented in Figure 3. It will be noted that the datapoints are heavily skewed, supporting the need to log-transform the data. For comparative purposes, plots of the raw data by subsampling interval without incorporation of shifts in T₁ for each subsampling interval are also presented, in Figure 4; these plots show less dispersion than for the corresponding plots which incorporate all shifts.

Variance components analyses indicated that for BF and BV, shifting made a greater relative contribution than sampling interval to the overall observed differences from gold-standard (Table 2). The opposite was observed for MTT and PS.

The impact of subsampling on scan-rescan reproducibility is presented in Table 3. This shows wCVs for BF, BV, MTT and PS for the gold-standard dataset of 21.3%, 23.6%, 26.5% and 32.2%, respectively. Median wCVs for BF (32.9–34.2%), BV (27.1–33.5%) and PS (39.0–42.4%) increased with subsampling, with a suggestion of a trend towards increasing variability with increasing sampling intervals; the converse was observed for MTT.

DISCUSSION

Our results indicate that reductions in sampling interval, or subsampling, can significantly affect the absolute values of CTP parameters when sampling intervals are greater than 1s. With increases in sampling intervals greater than 1s, BF and BV were increasingly over-estimated and MTT increasingly under-estimated. At 3 seconds sampling interval, BF values were over-estimated by up to 18% (upper 95% confidence interval), and on average 14%. Similarly, BV values were over-estimated by up to 11%, on average 8%; and MTT values, under-estimated by up to 13%, on average 11%. Subsampling had a smaller effect on PS values.

There have been relatively few previous studies which have investigated the effects of subsampling using the distributed parameter physiological model, and they have yielded somewhat mixed conclusions amongst themselves. Kamena et al. [7] investigated the effects of 1s, 2s, 3s and 4s temporal sampling in a study of 30 patients with strokes and a brain CTP acquisition protocol spanning 49s. In comparison to a gold-standard of 0.5s, they concluded, using a Wilcoxon analysis, that subsampling generated significant differences for BF, BV and MTT, and they recommended a sampling interval of 0.5s.

In a study of 45 patients with colorectal tumors and a CTP acquisition protocol spanning 65s, Goh et al. [9] similarly investigated the effects of 1s, 2s, 3s and 4s temporal sampling on CTP parameters. In comparison to a gold-standard of 1s, they found that BF was significantly over-estimated with 3s and 4s data, and that MTT was significantly underestimated. They found no significant trends with BV and PS. Of note, they came to their conclusions based on a statistical evaluation using an analysis of variance. This methodology and also the Wilcoxon analysis used by Kamena et al. [7] above do not take into account potential correlations between measurements from the same patients. A more appropriate statistical evaluation should take the latter into consideration, as has been undertaken in the current analysis by means of using a mixed model.

Kambadakone et al. [10] undertook an investigation of the effects of 1s, 2s, and 3s temporal sampling in a study of 30 patients with rectal and retroperitoneal tumors and a two phase CTP acquisition protocol, similar to ours, spanning 210s. In comparison to their gold-standard of 0.5s temporal sampling, they concluded that increasing the sampling interval to 2s maintained good *correlations* for all CTP parameters ($r=0.8-0.99$), but that 3s subsampling led to loss of correlation ($r=0.51$ to 0.96). Unlike the results of Goh et al. [9] and ours, their results indicated that BF values were under-estimated and MTT values were over-estimated with subsampling.

Of note, the conclusions of Kambadakone et al. [10] were based on an assessment of correlation coefficients. In such an approach, high Pearson correlation coefficients (r close to ± 1) indicate that two sets of data lie close to a straight line, but this gives no indication as to the relative value of the two variables (i.e., their slope).

The latter two studies suggest that 2s sampling intervals are satisfactory, while Kamena et al. [7] have suggested that any sampling interval greater than 0.5s significantly affects CTP parameter values. In comparison, our study suggests that sampling intervals beyond 1s significantly impact on CTP parameter values. The extent to which differences in tumors, precise CTP acquisition protocols and software might influence these results has not been investigated. As regards the latter, our study utilized a later version of the GE CT Perfusion software (Perfusion 4) than the above three studies, which employed GE CT Perfusion 3 software.

In our evaluation of subsampling, we incorporated analysis of the effects of shifting in T_1 , which has not been previously undertaken. Consideration of shifting is necessary because in an actual acquisition employing wider sampling intervals, one cannot ensure that the actual $T_1=t_0$ timepoint will be acquired or even represented in the dataset. Scatter-plots of the raw data showed that the incorporation of shifting to subsampling increased the extent of scatter for each sampling interval across all CTP parameter (plots without shifting have not been presented). This was confirmed by the wider ranges observed in CTP parameter values for shifted compared to non-shifted data (as evident in Table 1). The contribution of shifting to the overall variation was further demonstrated by our variance component analysis, which notably indicated that shifting makes a larger contribution than does sampling interval itself to overall variation for BF and BV parameter values. Thus, studies which have not, or do not, include shifting in their analyses will likely underestimate the impact of reductions in sampling frequency.

The distributed parameter model is only one of several other physiological models that have been applied in CT perfusion imaging, these include the central volume principle and maximum slope model. Studies using these models have also yielded slightly conflicting results, as with previous studies utilizing the distributed parameter model. For example, Wintermark et al. [5] in a study using data from brain perfusion, temporal sampling ranging from 0.5s to 6s, and the central volume principle has reported that sampling intervals greater than 1s do not alter accuracy. Weisman et al. [6] in a similar study using data using temporal sampling ranging from 0.5s to 3s has reported that there is less than 10% error in BF, BV and MTT with sampling rates up to 3s. Kloska et al. [8] in a study using data from brain perfusion, temporal sampling ranging from 1s to 4s, and the maximum slope model has reported that sampling intervals greater than 1s can significantly affect cerebral blood flow values.

The nature of our source data, acquired 2–7 days apart without any intervening therapy, allowed us to investigate the impact of subsampling on scan-rescan variability. This showed a deterioration in reproducibility of BF, BV and PS with subsampling: with between-visit wCVs increasing from 21.3%, 23.6% and 32.2%, respectively, for the gold-standard dataset to 32.9%, 27.1% and 39.0%, respectively, for a sampling interval of 1s. There was a suggestion of a trend towards increasing wCVs for these parameters with increasing sampling intervals of 2s and 3s. Overall, our results suggest that sampling intervals affect not only the absolute values of perfusion parameters, but also the reproducibility with which they can be determined.

We recognize and acknowledge several limitations in our study. We had a relatively small number of patients, and our study was limited only to lung lesions. A separate study would be required to explore other lesions and other tissues.

Our analysis was based on data obtained using a specific CTP acquisition protocol, and it is possible that our findings may be influenced, at least in part, by the nature of that data. Our Phase 2 data was essentially already subsampled and fixed, at 15s, and our subsampling manipulations were undertaken in Phase 1 only. An ideal dataset with which to investigate the impact of subsampling might be one which was acquired at a high temporal sampling throughout. Acquisition of such data would impose high radiation burdens and have practical difficulties in acquisition, at least for lung lesions, because of breathing motion.

Our analysis has been limited to the distributed parameter CTP model; it is possible that there might be substantial differences across model platforms. Evaluation of the effects of subsampling with other physiological models was beyond the scope of this work.

In conclusion, our study of subsampling in the context of the distributed parameter model suggests that sampling intervals beyond 1s result in significant differences in CTP values when compared to 0.5s gold-standards. Sampling intervals between 1s and 3s were associated with under- and over-estimation in CTP values up to -13% and +18%, respectively, compared to gold-standard. Scan-rescan reproducibility was adversely affected by subsampling. Further work is required to determine if these effects of subsampling on the estimation of CTP values are within acceptable limits for clinical purposes.

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Figure 1. Schematic of subsampling and shifting

Top row: Gold-standard dataset (SI_{0.5}). 0.5s temporal interval in Phase 1, combined with 6 anatomically registered Phase 2 images. T₁, pre-enhancement setpoint; T₂, Post-enhancement setpoint; T₃, last second phase setpoint.

Second row: Subsampled dataset, T₁=t₀. Orange block, baseline datapoints added to ensure comparability of baseline values across all sampling intervals.

Third row: Subsampled dataset. Sampling interval same as second row, but T₁=shifted forward

Bottom row: Subsampled dataset. Sampling interval same as second row, but T₁=shifted backward

Figure 2. 65 year old man with lung carcinoma in right upper lobe

(a): Arterial time-attenuation curve. T1 = pre-enhancement set point. T2 = last first phase (or “Post-enhancement”) set point, T3 = last second phase (T₃) set point
Parametric maps for (b) BF, (c) BV, (d) MTT, and (e) PS with illustrative examples of gold-standard (SI_{0.5}), SI₃ with no shift, and SI₃ with −2.5s shift. BF, in mL/min/100g; BV, in mL/100g; MTT, in seconds; PS, in mL/min/100g.
(Purple outline = tumor ROI. The color scales are identical for each triplet set of parametric maps)

Figure 3.

Raw data plots for a) BF, b) BV, c) MTT, and d) PS by sampling interval, with all shifts for each sampling interval.

Solid line = slope of unity. BF, in mL/min/100g; BV, in mL/100g; MTT, in seconds; PS, in mL/min/100g.

Figure 4.

Raw data plots for a) BF, b) BV, c) MTT, and d) PS by sampling interval, without shifts in T_0 .

Solid line = slope of unity. BF, in mL/min/100g; BV, in mL/100g; MTT, in seconds; PS, in mL/min/100g.

(Note there are necessarily fewer datapoints than in Figure 3).

TABLE 1

Summary statistics for CTP parameter values by subsampling interval, *without* and *with* all shifts in T₁, and comparisons with gold-standard of 0.5s sampling interval.

Parameter	Sampling interval (s)	No shift					All shifts				
		Median	Range	Est ratio	95% CI of ratio	P-value	Median	Range	Est ratio	95% CI of ratio	P-value
BF	0.5	55.3	8.5 - 226.1	(1.00)			55.3	8.5 - 226.1	(1.00)		
BF	1	58.0	9.2 - 222.0	1.06	0.99 - 1.13	0.08	55.9	5.1 - 290.5	0.98	0.95 - 1.02	0.39
BF	2	60.3	13.0 - 275.1	1.19	1.12 - 1.27	<0.0001	57.5	6.5 - 311.4	1.10	1.06 - 1.13	<0.0001
BF	3	65.6	9.5 - 160.0	1.18	1.10 - 1.26	<0.0001	60.3	5.0 - 339.3	1.14	1.11 - 1.18	<0.0001
BV	0.5	2.8	0.5 - 24.7	(1.00)			2.8	0.5 - 24.7	(1.00)		
BV	1	3.1	0.5 - 25.9	1.05	1.00 - 1.12	0.07	3.1	0.2 - 30.4	0.99	0.96 - 1.03	0.69
BV	2	3.2	0.7 - 30.8	1.11	1.05 - 1.18	0.0003	3.1	0.3 - 39.6	1.05	1.02 - 1.08	0.0002
BV	3	3.2	0.5 - 21.6	1.16	1.05 - 1.18	0.0002	3.2	0.2 - 53.9	1.08	1.05 - 1.11	<0.0001
MTT	0.5	4.0	2.3 - 7.9	(1.00)			4.0	2.3 - 7.9	(1.00)		
MTT	1	4.0	2.2 - 8.2	0.98	0.94 - 1.02	0.32	4.0	2.2 - 8.3	1.00	0.98 - 1.03	0.89
MTT	2	3.5	2.3 - 7.2	0.89	0.86 - 0.93	<0.0001	3.6	2.2 - 8.7	0.93	0.91 - 0.95	<0.0001
MTT	3	3.3	2.4 - 11.2	0.88	0.85 - 0.92	<0.0001	3.4	2.3 - 11.2	0.89	0.87 - 0.91	<0.0001
PS	0.5	27.5	4.1 - 85.4	(1.00)			27.5	4.1 - 85.4	(1.00)		
PS	1	28.4	4.3 - 82.3	0.98	0.96 - 1.08	0.58	29.1	3.1 - 85.5	1.01	0.97 - 1.04	0.67
PS	2	26.1	2.3 - 92.0	0.95	0.92 - 1.04	0.54	27.3	0.9 - 96.2	0.99	0.96 - 1.02	0.39
PS	3	27.1	3.7 - 77.7	0.87	0.90 - 1.10	0.11	26.1	1.9 - 91.5	0.97	0.94 - 0.99	<0.0001

BF, in mL/min/100g; BV, in mL/100g; MTT, in seconds; PS, in mL/min/100g

Est ratio and 95% CI = estimated ratio, and 95% confidence interval of ratio compared to gold-standard of 0.5s sampling interval. The estimated ratio was back calculated based on the difference on the logarithmic scale. A ratio > 1 indicates over-estimation, and < 1 indicates under-estimation compared with gold-standard.

p-values are in comparison to the gold-standard of 0.5s sampling interval (bold values are non-significant).

TABLE 2

Summary of variance component analysis for the difference (on log-scale) between gold-standard and subsampled data. Higher estimated variance means relatively more contribution to the difference.

Parameter	Source of Variation	Estimated Variance	95% CI range
BF	subsampling	0.00237	0.0 - 0.00838
BF	shifting	0.00299	0.00024 - 0.00575
BV	subsampling	0.00049	0.0 - 0.0819
BV	shifting	0.00211	0.0 - 0.0201
MTT	subsampling	0.00179	0.0 - 0.00488
MTT	shifting	0.00053	0.0 - 0.00111
PS	subsampling	0.00142	0.0 - 0.00342
PS	shifting	0.00022	0.0 - 0.00084

TABLE 3

Summary of between-visit wCVs for gold-standard and subsampled data.

Parameter	Sampling interval (s)	Median wCV (%)	Lower – Upper Bounds of wCV (%)
BF	0.5	21.3	12.3 – 31.0
BF	1	32.9	16.9 – 52.1
BF	2	33.3	16.3 – 54.5
BF	3	34.2	17.2 – 55.3
BV	0.5	23.6	13.6 – 34.6
BV	1	27.1	13.9 – 41.1
BV	2	31.2	13.4 – 57.0
BV	3	33.5	15.4 – 59.1
MTT	0.5	26.5	15.1 – 38.9
MTT	1	25.0	13.8 – 41.9
MTT	2	20.3	9.8 – 33.2
MTT	3	17.7	9.1 – 30.8
PS	0.5	32.2	18.3 – 47.9
PS	1	39.0	19.9 – 60.9
PS	2	42.0	21.3 – 72.7
PS	3	42.4	20.1 – 71.7

wCV, between – visit coefficient of variation