Quantitative Ultrasound Perfusion Analysis In Vitro

Mezl M, Jirik R, Harabis V, Kolar R
Department of Biomedical Engineering, FEEC, BUT, Brno, Czech Republic
xmezlm00@stud.feec.vutbr.cz

Abstract. This study describes quantitative perfusion analysis by ultrasound. The main task of this study is to apply a general perfusion model for intravascular contrast agents to ultrasound perfusion analysis. For this investigation a phantom model using a dialyser tubing as the model of the tissue was constructed. Two quantitative parameters (mean transit time and fractional blood volume) are estimated and compared with reference values.

1 Introduction

Perfusion imaging techniques are important for diagnosis and treatment monitoring of ischemic and oncologic diseases. In these methods, image sequences following an intravenous contrast agent administration are acquired. Based on physical or mathematical models, the sequences are processed to estimate tissue perfusion parameters in desired regions, as diagnostically important values.

In ultrasonography, these techniques lead to estimation of semi-quantitative indices related to tissue perfusion, which are however also dependent on acquisition parameters. The aim of this study is to contribute to introduction of fully quantitative perfusion analysis, as used in MRI, CT, PET and SPECT, to ultrasonography. The presented method leads to estimation of perfusion parameters which are physical quantities directly describing the perfusion process on the microvascular level, to a certain degree independent on the acquisition parameters. The proposed ultrasound quantitative perfusion analysis is demonstrated on a phantom mimicking a perfused tissue region. A fairly good fit between estimated and known reference values is reported.

2 Data Acquisition

A phantom mimicking a perfused tissue was constructed using a dialyser (F60S, Fresenius, Bad Homburg, Germany) with silicone tubing and peristaltic pump (Peri-Star Pro, World Precision Instruments, Sarasota, USA). Schematic illustration of the constructed model is presented in Fig. 1. Arterial input function (AIF) and venous output function (VOF) were measured in locations with thicker tubes (diameter 12 mm). The system was filled with saline solution (0.9% w/v of NaCl) and immersed in water as a coupling medium for ultrasound probe. Manual contrast agent bolus of ultrasound contrast agent (UCA) and the flush saline bolus were applied using two syringes connected by standard luerlock T-connector to 16-gauge needle. The UCA (SonoVue^{TM}, Bracco, Italy) was diluted 1:64 with saline, according to our previous in vitro studies. [3]

A commercial ultrasound scanner (VingMed Vivid 5, GE Healtcare, Waukesha, USA) with 2.4 MHz transducer was used for radiofrequency (RF) data recording on the second harmonic. Low mechanical index (MI=0.1) was used to prevent UCA destruction. Image sequences of approximately 180 images were recorded and further processed. The preprocessing contained filtering in the frequency domain to separate the first and second harmonic RF data. The next step was envelope detection. These data were subsequently interpolated from polar to rectangular coordinates and the logarithmic compression was done for imaging on a screen. Example B-scan images in different times after injection are shown in Fig. 2.

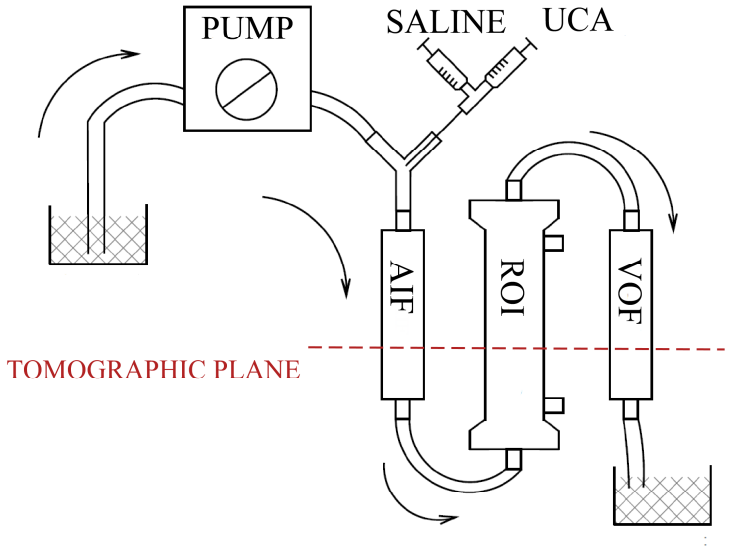

Fig 1.Experimental setup

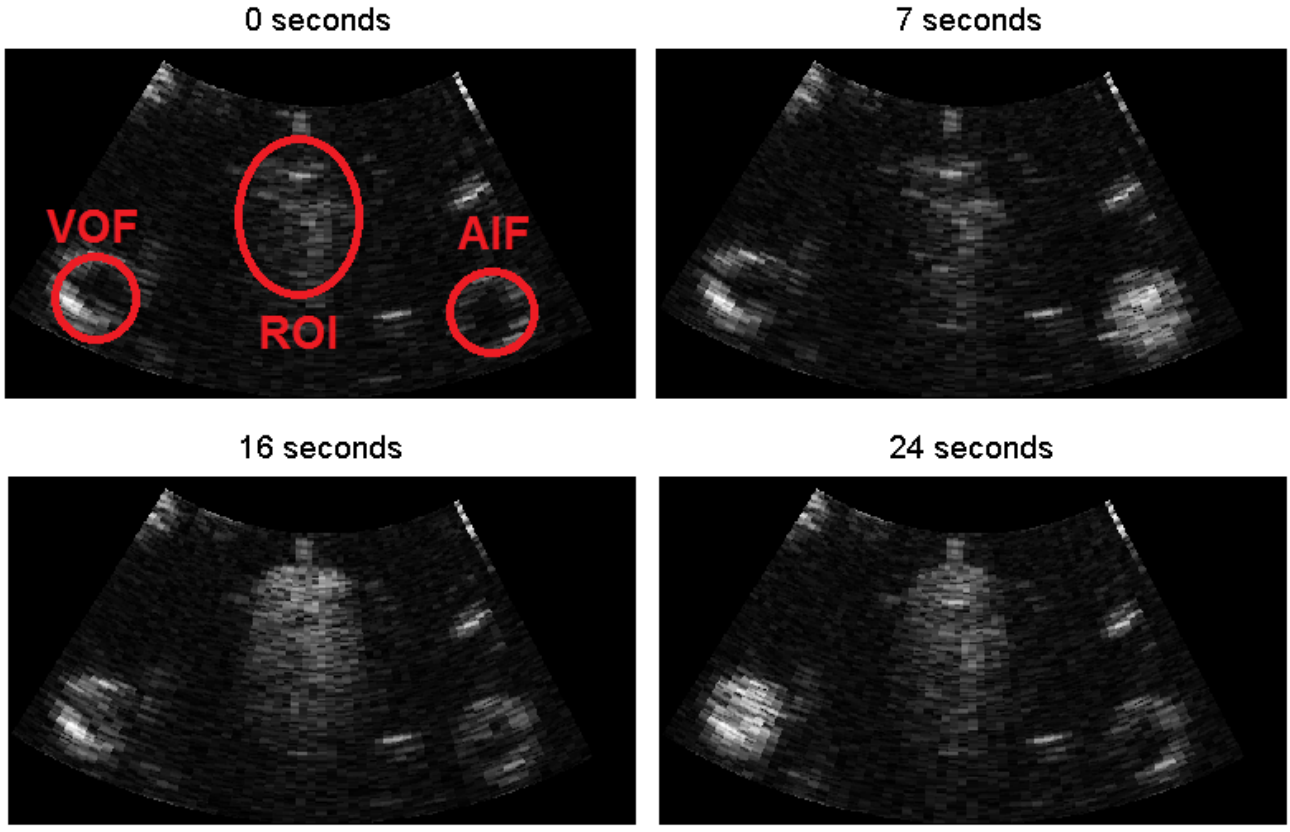

Fig 2. Four example B-scans of the scene in different times after injection

In each experiment three image regions were chosen, AIF, VOF and a dialyser region. The tomographic plane is drawn by a dashed line in Fig. 1. The location of the image regions is illustrated in Fig. 2. For each region a vector of the mean backscattered ultrasound intensity development in time was computed.

The ultrasound intensity is proportional to the UCA concentration for small concentrations. However, for high concentrations (as in the AIF region) the relationship is nonlinear [4]. Hence, a new correction for nonlinearity was designed, based on the power function approximation of the non-linearity and on the mass conservation law applied to the concentration time-curves in the AIF and VOF regions. For each time vector of the mean backscattered ultrasound intensity the power constant k was computed as

$$k = \arg\min \sum_n \left(C_A^k(n) - C_V^k(n)\right)^2, k \in \Re^+ \quad (1)$$

where $C_V(n)$ is the mean UCA concentration in the VOF region and $C_A(n)$ is the mean UCA concentration in the AIF region.

3 Estimation of Perfusion Parameters

As the UCAs are intravascular tracers, a general perfusion model for intravascular contrast agents used in other imaging modalities, e.g. in MRI [1], can be applied. Surprisingly, it has not been applied in ultrasound perfusion analysis before, to our knowledge. The contrast agent concentration within the region of interest (ROI), $C_R(n)$, is modelled as a convolution of the tissue residual function, $R(t)$, the contrast agent concentration in the AIF, $C_a(n)$, and the blood flow F, as

$$C_R(n) = C_A(n) * R(n) \cdot F. \quad (2)$$

After deconvolution of these two measured functions, three perfusion parameters can be directly estimated: Mean transit time (*MTT*) of a tracer particle through the ROI, fractional blood volume in the ROI (V_b), and blood flow per unit tissue volume or mass (F). Only two parameters (here *MTT* and V_b) need to be estimated because the third parameter can be directly derived from them.

Here, the ROI is considered to be the dialyser part between the AIF input and the tomographic plane. The corresponding concentration $C_R(n)$ is measured indirectly as the concentration $C_h(n)$ in the cross-section area of the dialyser with the tomographic plane. Deconvolution of $C_h(n)$ with $C_a(n)$ gives an estimate of the vascular transport function $h(n)$ through the ROI. Estimation of $h(n)$ is computed by nonparametric maximum likelihood deconvolution with Tikhonov regularization. The weight of the regularization term was determined experimentally based on smoothness of the estimated $h(n)$. $R(n)$ is then calculated from $h_n(n)$, which is $h(n)$ normalized to unity integral, as [2]:

$$R(n) = 1 - \sum_n h_n(n). \quad (3)$$

Consequently $R(t)$ descends from one to zero. *MTT* and V_b are then estimated as described by (4) and (5).

$$MTT = \sum_n R(n) \quad (4)$$

$$V_b = \frac{\sum_n C_R(n)}{\sum_n C_A(n)} \quad (5)$$

Theoretical reference values of *MTT* and V_b were computed from the peristaltic pump flow and the technical datasheet of the dialyser. The peristaltic pump flow was measured as the total volume of saline which flowed through the system in one minute.

4 Results

The perfusion experiment was repeated for 4 different peristaltic pump flow rates (83, 166, 254 and 352 ml/min). For each experiment theoretical and experimental values of *MTT* were computed. Experimental values were computed two times, once for the whole dialyser region and the second time for several smaller areas inside the ROI. For the latter, the mean value and standard deviation of MTT were computed. The comparison of the reference and experimental values for all measured experiments is shown in Tab 1.

Flow [ml per minute]	**MTT [seconds]**			
	Reference value	Estimation in ROI	Mean value for small ROIs	Standard deviation for small ROIs
83	8.39	8.83	8.73	1.075
166	11.62	12.76	12.93	1.349
254	17.78	18.9	18.82	1.929
352	35.56	41.36	41.78	2.365

Tab 1. Comparison of reference and estimated MTT

Fig. 3 shows a fit between the reference values of MTT and MTT estimated in the dialyser region for all experiments.

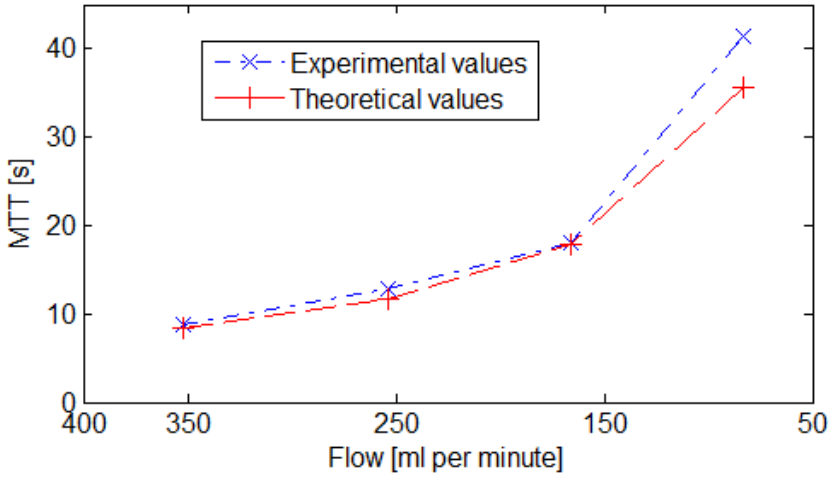

Fig 3.Comparison of the reference and estimated MTT for different flows

For verification of the estimated values were also computed values of mean transit time for whole dialyser (MTT_c). Experimental values of MTT_c was estimated by deconvolution of the signals in AIF and VOF. Reference values of MTT_c were computed from peristaltic pump flow and the length of the dialyser. For this case were the experimental values slightly higher than the related reference ones. The difference between those values were caused by time which is needed for UCA transition from one part of system to other and is more significant for lower flows.

The reference value of V_b was 0.24 ml of blood per ml of tissue. Experimental values of V_b for the experiments were slightly higher: 0.27, 0.27, 0.26, 0.29 ml of blood per ml of tissue. The experimental values were computed only for the whole dialyser region. Estimation of V_b in small regions is problematic due to the ultrasound intensity loss due to diffraction and attenuation. Correction for the attenuation is task of the further investigation.

5 Conclusion and Discussion

The results show possibilities of quantitative perfusion analysis in ultrasonography with estimation of physical parameters. Fairly good fit between theoretical and measured values of MTT is presented in Fig. 3 and Tab. 1. Verification of measured values is done by comparing the reference and experimental values of *MTTc*.

Attenuation of the ultrasound waves is significant in estimation of V_b. Time intensity curves are dependent on relative distance between the probe and investigated region. For further regions the values of V_b were lower than the mean value in the whole dialyser region.

Implications for in vivo applications (suitability of the phantom, sources of errors, correction for attenuation) will be further investigated in the following verification of the method on phantoms and clinical data.

Acknowledgement

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