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Abdominal parametric perfusion imaging with respiratory motion-compensation based on contrast-enhanced ultrasound: *In-vivo* validation

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ABSTRACT

Parametric perfusion imaging (PPI) based on dynamic contrast-enhanced ultrasound (DCEUS) is a multi-parametric functional method that is increasingly used to characterize the hemodynamic features of abdominal tumors. Periodic respiratory kinetics adversely affects the signal-to-clutter ratio (SCR) and accuracy of abdominal PPI. This study proposed respiratory motion-compensation (rMoCo) employing non-negative matrix factorization combined with fast block matching algorithm to effectively remove these disturbances on abdominal PPI, which was validated through *in-vivo* perfusion experiments. The mean calculation efficiency of rMoCo was improved by 83.6% when the algorithm was accelerated in a unique matching sequence, which was formed from dozens of DCEUS subsequences at the same respiratory phase. The horizontal and vertical displacements induced by respiratory kinetics were estimated to correct the extraction of time-intensity curves and the peak SNR remained at 22.58 ± 2.90 dB. Finally, the abdominal PPIs of four perfusion parameters were formed with non-negative rMoCo, and their SCR was improved by 3.99 ± 0.49 dB ($p < 0.05$). Compared with the results without rMoCo, the continuity and visualization of abdominal arterioles were clearly enhanced, and their perfusion details were accurately characterized by PPIs with non-negative rMoCo. The proposed method benefits clinicians in providing accurate diagnoses and in developing appropriate therapeutic strategies for abdominal diseases.

1. Introduction

Tissue perfusion characterization is increasingly utilized for clinical diagnosis and postoperative evaluation, especially in abdominal tumors (Mulé et al., 2011). Tissue perfusion characteristics, particularly for tumor angiogenesis, are assessed by multi-parametric functional imaging based on dynamic contrast-enhanced ultrasound (DCEUS), computed tomography, or magnetic resonance imaging (Miller et al., 2005; Provenzale 2007; Kuenen et al., 2013; Pitre-Champagnat et al., 2015). DCEUS presents several advantages over computed tomography and magnetic resonance imaging, namely, cost-effectiveness, no radiation, ease of use at the bedside, and excellent temporal resolution (Kuenen et al., 2013; Pitre-Champagnat et al., 2015; Wang et al., 2015).

Contrast-specific imaging techniques largely exploit the nonlinear acoustic responses of microbubbles, suppress the linear signal from tissues, and improve the contrast and spatial resolution of microvascular visualization in DCEUS (de Jong et al., 2000; Wang et al., 2016). Therefore, quantitative DCEUS is an excellent tool for the delineation of perfused tissues and assessment of microcirculation to monitor tumor pathological processes (Guibal et al., 2010; Mulé et al., 2011; Orlacchio et al., 2011). Parametric perfusion imaging (PPI) estimated from contrast-enhanced time-intensity curves (TICs) is a quantitative DCEUS imaging technique that can quantify and depict the detailed hemodynamic distribution of tumor angiogenesis (Gu et al., 2010; Pitre-Champagnat et al., 2015). Many

Abbreviations: PPI, parametric perfusion imaging; DCEUS, dynamic contrast-enhanced ultrasound; TIC, time-intensity curve; rMoCo, respiratory motion-compensation; ICA, independent component analysis; PCA, principal components analysis; NMF, non-negative matrix factorization; FS, full search; TSS, three step search; FSS, four step search; SES, simple and efficient search; ARPS, adaptive rood pattern search; MSE, mean square error; SNR_P, peak signal-to-noise ratio; SCR, signal-to-clutter ratio; WIT, wash-in time; WOT, wash-out time; PV, peak value; AUC, area under curve.

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abdominal tumors, such as hepatic cirrhosis, hemangioma, hepatocellular carcinoma, and other metastasis cancers, are currently effectively detected and characterized through PPI (Sugimoto et al., 2008; Rognin et al., 2010; Wang et al., 2015).

However, one of the most critical sources of disturbances on TICs and PPIs is motion due to patients respiration, which can cause the malposition of regions-of-interest (ROIs), large periodic fluctuations of TICs, and impairment of TIC kinetics (Mulé et al., 2011; Wang et al., 2015). The signal-to-clutter ratio (SCR) of TICs decreases in the liver due to the respiratory motion (Needles et al., 2010). The respiration motion also causes the incorrect acquisition of perfusion parameters and decreased accuracy of abdominal PPI (Rognin et al., 2010; Mulé et al., 2011). Therefore, it is difficult to accurately quantify perfusion characterization without respiratory motion compensation (rMoCo) in the abdominal tissue and organs. The respiratory motion must be addressed for a robust and accurate abdominal PPI (Rognin et al., 2010; Mulé et al., 2011).

Several rMoCo strategies have been investigated in recent years to minimize the disturbances of respiratory motion on abdominal DCEUS studies. These strategies include the breathing holding, image-based registration, and breathing gating strategies (Mulé et al., 2011; Wu et al., 2015). Breathing holding is difficult to be realized during a perfusion examination because of the acquisition length (*i.e.*, at least 20 s or 30 s ~ up to 2 min)(Renault et al., 2005). Image-based registration involves aligning all DCEUS images to perform rMoCo, which is always guided by an anatomical landmark (Averkiou et al., 2010). Given the complex motion of abdominal tissue and organs induced by respiratory kinetics, the registration strategy is still limited by the time-consuming, the inefficient for out-of-plane motion, and the unavailable landmarks (Needles et al., 2010; Rognin et al., 2010). The third rMoCo strategy includes online and offline breathing gating methods. Subsequences of DCEUS images can be captured online at the same respiratory phase (Tang et al., 2011), which is monitored through external tracking devices (*e.g.*, belt sensors) (Atkinson et al., 2001). These devices are not routinely available clinically and many perfusion images are lost. Thus, this online method is not widely accepted by operators (Renault et al., 2005).

Researchers have applied the independent component analysis (ICA) and principal components analysis (PCA) into the breathing gating to overcome the aforementioned limitations (Renault et al., 2005; Mulé et al., 2011). ICA and PCA can automatically estimate the respiratory kinetics offline by studying the abdominal DCEUS images during free-breathing. The subsequences of DCEUS images are further selected at two extreme phases of end-of-inspiration and end-of-expiration in the respiratory cycles (Renault et al., 2005; Mulé et al., 2011). The contrast-enhanced TICs are then corrected using rMoCo. The respiratory kinetics is one of ICA components (Renault et al., 2005). However, the independent assumption between respiratory and contrast-enhanced kinetics is not ensured in ICA (Renault et al., 2005), which can't guarantee the correct rMoCo for PPI. Thus, PCA has been developed to modify ICA and overcome its limitation. The respiratory kinetics is an orthonormal first component in PCA (Mulé et al., 2011). However, a new problem emerges in PCA. The PCA results may be negative, whereas TICs and PPI must be non-negative (Mulé et al., 2011). To ensure that the extracted respiratory kinetics is non-negative, the respiratory kinetics and hemodynamics can be treated as the non-negative matrix factorization (NMF) problems (Wu et al., 2015). The feasibility and accuracy of NMF on DCEUS have been preliminarily verified through *in-vitro* respiratory kinetic estimation (Wu et al., 2015). Displacements at the two extreme phases of end-of-inspiration and end-of-expiration are then obtained to accurately correct the *in-vitro* TICs (Wu et al., 2015). However, many DCEUS images and detailed perfusion information are lost. The rMoCo performance employing NMF in abdominal PPI has not yet to be considered to the best of our knowledge.

In this study, a fully automatic rMoCo method, NMF combined with fast block matching algorithm, was proposed for abdominal DCEUS-based PPI. During free-breathing, the respiratory kinetics was first estimated from DCEUS sequence by using NMF algorithm. To avoid missing perfusion information, dozens of subsequences of DCEUS were generated at the same respiratory phase. To improve the calculation efficiency of rMoCo, the block matching algorithm was accelerated by a fast search strategy and the horizontal and vertical displacements were estimated in a matching sequence, which was formed by the first image of each subsequence. Each subsequence and TICs were compensated by displacements at each respiratory phase. Finally, PPIs of four perfusion parameters were formed from the TICs after rMoCo.

2. Methods and experiments

2.1. In-vivo *experiments*

The performance of our proposed method was illustrated by the *in-vivo* liver ($n = 8$) DCEUS sequences of three healthy rabbits; and it was further verified by a damaged spleen ($n = 1$) DCEUS sequence of a human patient in this study. The experiments used a diagnostic ultrasound platform (DC-8 EXP, Mindray, Shenzhen, China) (Zhou et al., 2016) equipped with a linear array transducer (Mechanical index of 0.05) in the liver; and equipped with a convex array transducer (Mechanical index of 0.21) in the spleen. The frame rate was 15 Hz and the dynamic range was 40 dB. All DCEUS sequences had two modes, namely, fundamental (B mode) and contrast modal sequences. Additional information about DC-8 EXP was indicated in the website of Mindray (www.mindraynorthamerica.com/).

The rabbits were anaesthetized with 3% pentobarbital sodium. A bolus of 0.5 mL microbubble dilution of phospholipid stabilized sulfur hexafluoride (SonoVue, Bracco, Milan, Italy) was injected through an ear vein to the rabbits. A bolus of 2.5 mL microbubble dilution was intravenously injected to the patient. The microbubble concentration was 2×10^8 bubbles/mL. The venous indwelling needles were flushed with saline (9%, NaCl) immediately after microbubble injection. To ensure the consistency between the different examinations, the microbubble concentration and injection dose were the same; the patient was required to breathe freely; and the scanner was held in a fixed position to ensure that the imaging plane wasn't changed in the different perfusion experiments. The DCEUS sequence of the patient was provided by a hospital. The experimental protocol was approved by the Local Research Ethics Committee and the informed consent of the patient was obtained before the examination. All experiments were performed at room temperature.

2.1.1. Estimation respiratory kinetics using NMF

The flow chart of abdominal DCEUS-based PPI with non-negative rMoCo is shown in Fig. 1. The fundamental modal DCEUS sequence was selected in NMF due to its discovered advantages in respiratory kinetics estimation (Mulé et al., 2011; Wu et al., 2015). The contrast modal DCEUS sequence was then corrected to extract TICs and to form PPI. The NMF algorithm is listed in Table 1. The dynamic kinetic model assumed that the activity of each element in the fundamental modal sequence $V_{k\times m}$ was a linear combination of kinetic factors $P_{r\times m}$ with the factor coefficients $Q_{k\times r}$(Wu et al., 2015). According to this assumption, the matrix $V_{k\times m}$ could be written as:

$$V_{k\times m} \approx Q_{k\times r} P_{r\times m} \quad s.t \quad Q, P \geq 0 \tag{1}$$

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