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● *Original Contribution*

REPRODUCIBLE COMPUTER-ASSISTED QUANTIFICATION OF MYOCARDIAL PERFUSION WITH CONTRAST-ENHANCED ULTRASOUND

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Abstract—Myocardial perfusion can be quantified by myocardial contrast echocardiography (MCE) and is used for the diagnosis of coronary artery disease (CAD). However, existing MCE quantification software is highly operator dependent and has poor reproducibility and ease of usage. The aim of this study was to develop robust and easy-to-use software that can perform MCE quantification accurately, reproducibly and rapidly. The developed software has the following features: (i) semi-automatic segmentation of the myocardium; (ii) automatic rejection of MCE data with poor image quality; (iii) automatic computation of perfusion parameters such as myocardial blood flow (MBF). MCE sequences of 18 individuals (9 normal, 9 with CAD) undergoing vasodilator stress with dipyridamole were analysed quantitatively using the software. When evaluated against coronary angiography, the software achieved a sensitivity of 71% and a specificity of 91% for hyperemic MBF. With the automatic rejection algorithm, the sensitivity and specificity further improved to 77% and 94%, respectively. For MBF reproducibility, the percentage agreement is 85% (κ = 0.65) for inter-observer variability and 88% (κ = 0.72) for intra-observer variability. The intra-class correlation coefficients are 0.94 (inter-observer) and 0.96 (intra-observer). The time taken to analyse one MCE sequence using the software is about 3 min on a PC. The software has exhibited good diagnostic performance and reproducibility for CAD detection and is rapid and user-friendly. **(E-mail: mengxing.tang@imperial.ac.uk)**

Key Words: **Myocardial contrast echocardiography, Myocardial perfusion, Computer-assisted quantification, Coronary artery disease, Reproducibility.**

INTRODUCTION

Myocardial contrast echocardiography (MCE), which utilises microbubbles, is clinically employed for the assessment of myocardial perfusion and the detection of coronary artery disease (CAD) (Kaul 1997, 2008; Senior et al. 2009a). Current MCE analyses performed in hospitals rely mainly on human visual assessment (Dwivedi et al. 2007; Janardhanan et al. 2003; Jeetley et al. 2004). Such qualitative assessment has poor reproducibility and is highly dependent on the experience level of the clinician (Ma et al. 2009; Yu et al. 2004). This has precluded widespread use of this technique. Hence, there is a need for more effective quantitative assessment of MCE data. Quantitative MCE is performed with the replenishment–destruction method first proposed by Wei et al. (1998). Time–intensity perfusion curves can then be derived and relevant perfusion parameters can be computed to quantify myocardial blood flow.

Accurate quantification is, however, hindered by the noise and high variability inherent in the MCE data (Tang et al. 2011). There is also a lack of robust computer software that allows clinicians to perform myocardial perfusion quantification accurately. In general, automatic and sophisticated image processing and quantitative tools designed specifically for MCE are lacking (Ma et al. 2009; Marwick et al. 1998). This results in the use of existing software to be time consuming, operator dependent and less reproducible. Current quantification studies are conducted by using either custom-designed research software (Peltier et al. 2004; Wei et al. 2001) or commercial software such as QLAB (Philips Ultrasound) (Hayat et al. 2008; Senior et al. 2005), HDI-Lab (Philips

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Ultrasound) (Ghanem et al. 2007; Shimoni et al. 2003) and ECHOPAC (GE Vingmed Ultrasound A/S) (Malm et al. 2006; Palmieri et al. 2004). These quantification software require the user to manually and arbitrarily select several regions of interest (ROIs) within the myocardium that the operator considers to be suitable for analysis and representative of each vascular territory (Palmieri et al. 2004; Peltier et al. 2004; Wei et al. 2001). This is highly subjective and different users tend to choose ROIs that vary significantly in size, shape and location. This, in turn, affects the fitting of the perfusion curve, and the extracted perfusion parameters can vary considerably with different ROI selections. This makes MCE quantification highly operator dependent, and accurate quantification requires significant user expertise or training (Wei et al. 2001). In addition, the ROI chosen for a particular time frame has to be adjusted manually for all the other frames in the sequence so as to account for motion artefact and avoid left ventricle cavities (Malm et al. 2006; Peltier et al. 2004). This is time consuming and further increases operator dependence. The aforementioned factors could be important contributors to the high variability reported for MCE quantification in several reproducibility studies conducted using the existing software (Ghanem et al. 2007; Palmieri et al. 2004).

In this study, we developed a myocardial perfusion quantification software for MCE with the following main advantages. (i) A software and graphical user interface was developed for easy and fast semi-automatic segmentation and motion tracking of the myocardium. (ii) An algorithm was developed to automatically exclude from the analysis those myocardial segments with poor image quality. (iii) MCE quantification using the software is likely to be reproducible and less operator dependent compared with existing software and qualitative visual assessment. The diagnostic performance of the MCE quantification software in detecting CAD was evaluated on clinical patients and compared with that of qualitative MCE and single-photon emission computed tomography (SPECT), using coronary angiography as the gold standard.

METHODS

Study population and coronary angiography

From a cohort of 95 patients who had previously participated in a trial in which patients underwent simultaneous MCE and SPECT after dipyridamole infusion, 18 patients were selected (Senior et al. 2013) for this exploratory study. The demographic characteristics of the patients are summarized in Table 1. The patients underwent rest MCE and SPECT on the same day. These patients also underwent coronary angiography within 1 month of the imaging study on clinical grounds. Patients with CAD were defined as those with ≥70% luminal diameter stenosis of any major epicardial artery or major branch by qualitative coronary angiography. Among the recruited individuals, 9 did not exhibit CAD, 4 had single-vessel disease and 5 had multivessel disease. In total, there were 9 left anterior descending (LAD), 1 left circumflex (LCX), 4 right coronary artery (RCA) and 2 diagonal (DIAG) coronary artery cases of stenosis. The results from coronary angiography are used as the standard for the evaluation of diagnostic performance of the MCE quantification software. The study was approved by the institutional review board, and all patients gave informed consent.

Table 1. Demographic characteristics of patients, n = 18

Mean age	63 ± 17 y*
Male sex	11 (61%)
Previous myocardial infarction	5 (28%)
Diabetes	5 (28%)
Hypertension	10 (56%)
Smoker	2 (11%)

* Mean ± standard deviation.

Myocardial contrast echocardiography

Myocardial contrast echocardiography was performed using a commercial ultrasound machine iE33 (Philips Medical Systems, Best, Netherlands) and SonoVue (Bracco Research, Geneva, Switzerland) as the contrast agent. Triggered images were recorded within 3–4 min in the three apical views (apical four-chamber, apical two-chamber and apical three-chamber) using low-power MCE (power modulation technique) at a mechanical index of 0.1. The focus was set at the mitral valve level. SonoVue was initially started at 60 mL/h using an infusion syringe pump VueJect (BR-INF 100, Bracco Research), which gently rotates and maintains the contrast agent in homogenous opacification of the myocardium. Thereafter, the rate was set between 48 and 60 mL/h to allow homogenous opacification of the myocardium. Once optimised, the machine settings were held constant throughout each study. Flash-impulse imaging at a high mechanical index (1.0) was performed to achieve complete myocardial bubble destruction, after which end-systolic frames were recorded digitally. All the frames occur at the end-systolic phase of the cardiac cycle (end of T-wave on the electrocardiogram). One MCE sequence typically consists of several end-systolic frames (around 10 frames) which spans the same number of cardiac cycles. Once the resting images were acquired, dipyridamole was infused at 0.56 mg/kg over a 4-min period. After a 2-min interval, peak-stress images were subsequently recorded within 3–4 min of the same procedure.