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● *Original Contribution*

TOWARD A STANDARDIZATION OF ULTRASOUND SCANNERS FOR DYNAMIC CONTRAST-ENHANCED ULTRASONOGRAPHY: METHODOLOGY AND PHANTOMS

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Abstract—The standardization of ultrasound scanners for dynamic contrast-enhanced ultrasonography (DCE-US) is mandatory for evaluation of clinical multicenter studies. We propose a robust method using a phantom for measuring the variation of the harmonic signal intensity obtained from the area under the time-intensity curve versus various contrast-agent concentrations. The slope of this measured curve is the calibration parameter. We tested our method on two devices from the same manufacturer (AplioXV and Aplio500, Toshiba, Tokyo, Japan) using the same settings as defined for a French multicenter study. The Aplio500's settings were adjusted to match the slopes of the AplioXV, resulting in the following settings on the Aplio500: at 3.5 MHz: MI = 0.15; CG = 35 dB and at 8 MHz: MI = 0.10; CG = 32 dB. This calibration method is very important for future DCE-US multicenter studies. (E-mail: stephanie.pitre@u-psud.fr) **© 2017 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Dynamic contrast-enhanced ultrasound (DCE-US), Methodologies of ultrasound calibration, Flow phantom.**

INTRODUCTION

Dynamic contrast-enhanced ultrasound (DCE-US) is a functional imaging modality dedicated to the quantitative assessment of tissue micro-vascularization in cardiology and oncology. In oncology, the quantitative approach is essential to evaluate therapeutic efficiency with monitoring of the progression of tumor vascularization. Despite several guidelines and many published clinical studies (Claudon et al. 2013; Dietrich et al. 2012; Lassau et al. 2010, 2011; Piscaglia et al. 2012), this imaging technique is still rarely used for the assessment of tumor responses, which require the quantification of ultrasound images with rigorous methodology to analyze the time-intensity curves (TICs). A French multi-centric study (2007–2010), which included 539 patients with solid tumors who were treated with antiangiogenic drugs, was performed with a standardized procedure of both acquisition and DCE-US quantification (Lassau et al. 2012). A DCE-US perfusion parameter, the area under the curve (AUC) was validated as a biomarker at 1 mo with a cut-off of 40% of AUC to predict efficiency of treatments (Lassau et al. 2014).

One of the levers to the dissemination of the DCE-US method is the standardization of ultrasound scanners for a homogeneous quantification of tumor perfusion. In practice, each type of ultrasound scanner has its own settings and yet no common standard exists. The same settings on two different ultrasound systems do not measure the same signal, making it difficult to transfer acquisition protocols of one type of ultrasound system to another. So, when predictive values of tumor vasculature are identified by a clinical study, these can only be exploited by imaging departments that have the same model of ultrasound scanner, the same probes and the same settings, as was the case in the French multicentric study. This constraint contributes to the limitation of the dissemination of the DCE-US imaging method. The challenge now is to take into account the diversity of ultrasound and instrumental developments while maintaining the predictive values of therapeutic response established through clinical studies. Radiologists have indicated the need to standardize DCE-techniques to assess functional imaging biomarkers (Katabathina

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et al. 2012; O'Connor et al. 2017; Sullivan et al. 2015). The standardization of ultrasound scanners in contrast mode must be performed by *in vitro* studies with dedicated test objects or phantoms. These are currently used in quantitative imaging positron emission tomography/computed tomography (PET/CT) and PET/magnetic resonance (PET/MR) systems (Boellaard et al. 2015) to evaluate and control the performance of the devices. In the field of DCE-US, phantoms are mainly used to evaluate methodological developments. Indeed, many teams studied blood flow with a phantom based on a renal dialysis cartridge, described first by Hindle and Perkins (1994). This phantom with parallel tubes of 200 μm with cellulose walls, reproduced the physiologic conditions of the microvasculature with laminar flow. This phantom was used in particular to assess quantification methods (Claassen et al. 2001; Gauthier et al. 2011a, 2012b; Kier et al. 2009; Li et al. 2002; Lohmaier et al. 2004; Lucidarme et al. 2003; Quaia et al. 2009; Ugolini et al. 2000; Veltmann et al. 2002) and to characterize novel ultrasound contrast agents (Casciaro, et al. 2009; Lavisse et al. 2008; Radhakrishnan et al. 2012). This type of phantom is still difficult to use for reproducibility studies because of its delicate implementation. Another category of phantom consists of a single tube, a design well adapted for repeatability studies (Gauthier et al. 2011a), and also used to assess new contrast agents (Lavisse et al. 2008; Radhakrishnan et al. 2012) or new quantification methods (Bruce et al. 2004; Gauthier et al. 2012a,b; Lampaskis and Averkiou 2010). Finally, a versatile liver machine perfusion system was developed for *ex vivo* DCE-US assessment. However, to date, we find neither *in vitro* phantom nor methodology that is dedicated to calibrate ultrasound scanners, the first step for standardization of DCE-US imaging.

The aim of our study is to validate a robust method to establish the calibration in contrast mode of two different ultrasound scanners using settings initially defined for a French multicenter study. To this purpose, the calibration method was based on variations of the enhanced signal intensity with a range of concentrations of contrast agent.

MATERIALS AND METHODS

Ultrasound scanners

Two ultrasound scanners were studied. The first was the ultrasonograph used for the clinical validation of DCE-US in predicting outcomes of antiangiogenic therapy for solid tumors (Lassau et al. 2014): AplioXV (Toshiba Medical System, Tokyo, Japan). The other was the latest ultrasound scanner Aplio500 (Toshiba Medical System) In our study, the search for settings having similar performance between the two echographs was performed with three probes: the abdominal curvilinear probe PVT-375 BT (3.5 MHz) for both ultrasound scanners, and the linear probe PVT-805 AT (8 MHz) for the AplioXV, compared with the new dedicated probe PLT-1005 BT (10 MHz) for the Aplio500. Two setting parameters can adjust the DCE-US response: mechanical index (MI) and color gain (CG). To avoid destruction of the microbubbles, MI must be strictly <0.2. We chose to avoid exceeding an MI of 0.15. The parameter CG modifies the gain of an analogue amplifier of the probe and acts both on the collected signal and on the noise. In separate experiments, we varied the MI and the CG to change the dynamics of Aplio500 to obtain the same dynamics as the AplioXV, the reference in the French multicentric protocol. All settings are summarized in Table 1. Therefore, we determined the settings of the Aplio500 in two steps: determination of the optimum MI with an arbitrary value of CG, and then determination of the optimum CG with the value of the fixed MI. The acoustic power (AP) was

Table 1. Ultrasound scanners settings

	Settings of AplioXV*		Settings of Aplio500*	
Setting parameters	Curvilinear probe PVT-375 BT	Linear probe PVT-805 AT	Curvilinear probe PVT-375 BT	Linear probe PLT-1005 BT
Frequency (MHz)	4	12	4	12
DR (dB)	55	55	55	55
MI	0,1	0,1	To be determined	To be determined
AP (%)	0,8	0,8	Varying with MI	Varying with MI
CG (dB)	32	37	To be determined	To be determined
PRF	3,9	8,8	3,9	8,8
VRh (MHz)	3	5	3	5
filter	2	2	2	2
Focal VRI (%)	50	50	50	50
Depth (cm)	12	4	12	4

DR = dynamic range; MI = mechanical index; AP = acoustic power; CG = color gain; PRF = pulse repetition frequency; VRh = vascular reception harmonic frequency (in Hertz); VRI = vascular recognition imaging.

* Toshiba Medical System, Tokyo, Japan.