Toward a Standardization of Ultrasound Scanners for Dynamic Contrast-Enhanced Ultrasonography: Methodology and Phantoms

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TOWARD A STANDARDIZATION OF ULTRASOUND SCANNERS FOR DYNAMICCONTRAST-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. Wetested 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 matchthe slopes of the AplioXV, resulting in the following settings on the Aplio500: at 3.5 MHz: MI 5 0.15; CG 5 35 dBand at 8 MHz: MI 5 0.10; CG 5 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.

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Introduction

Dynamic contrast-enhanced ultrasound (DCE-US) is a functional imaging modality dedicated to the quantitative assessment of tissue micro-vascularization in cardiologyand 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), thisimaging 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 month with a cut-off of 40% of AUC to predict efficiency of treatments (Lassau et al. 2014).

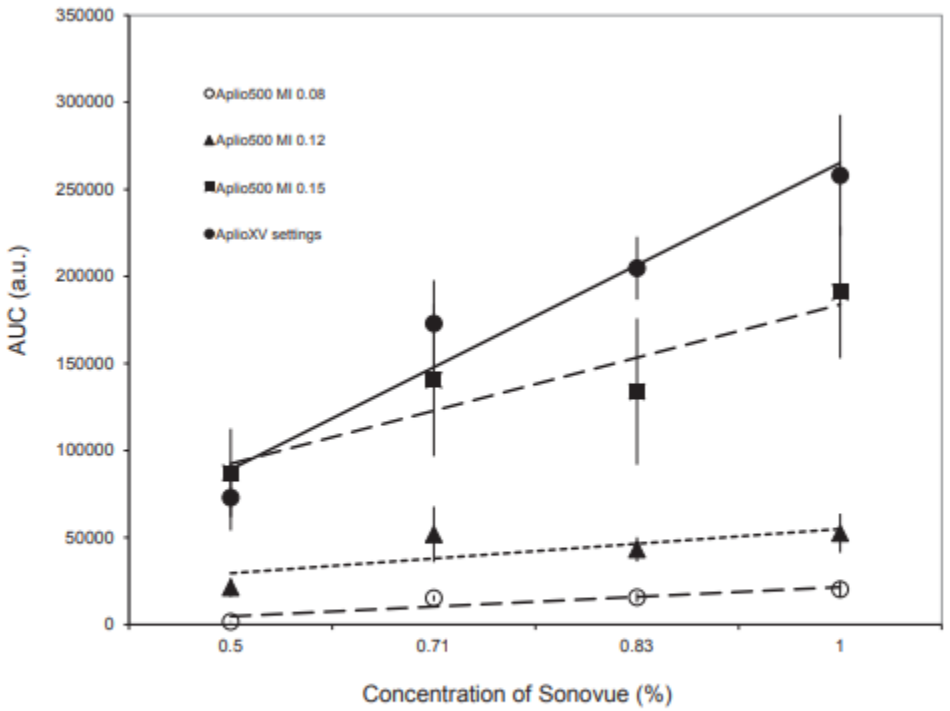

Fig. 2. Impact of varying concentration of contrast agents on AUC (arbitrary unit) at 3 MI (0.08, 0.12 and 0.15, respectively). The linear relationship obtained with the AplioXV (Toshiba Medical System, Tokyo, Japan) was also plotted. Measurements were performed with the abdominal curvilinear probe PVT-375 BT (3.5 MHz). AUC = area under the curve; MI = mechanical index.

One of the levers to the dissemination of the DCE- US method is the standardization of ultrasound scannersfor a homogeneous quantification of tumor perfusion. Inpractice, 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 mea-sure the same signal, making it difficult to transfer acquisition protocols of one type of ultrasound systemto 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 multicentricstudy. This constraint contributes to the limitation of thedissemination 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 toassess functional imaging biomarkers (Katabathina 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 arecurrently used in quantitative imaging positronemission 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, phan- toms are mainly used to evaluate methodologicaldevelopments. Indeed, many teams studied blood flow with a phantom based on a renal dialysis cartridge, described first by Hindle and Perkins (1994). This phan-tom with parallel tubes of 200 mm 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 forreproducibility studies because of its delicate implementation. Another category of phantom consists of a single tube, a design well adapted forrepeatability 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, thefirst step for standardization of DCE-US imaging.

The aim of our study is to validate a robust method toestablish the calibration in contrast mode of two differentultrasound scanners using settings initially defined for a French multicenter study. To this purpose, the calibration method was based on variations of the enhanced signal in- tensity 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 havingsimilar performance between the two echographs was performed with three probes: the abdominal curvilinear probe PVT-375 BT (3.5 MHz) for both ultrasound scan-ners, 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 param-eters 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 thegain 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 proto-col. 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 valueof CG, and then determination of the optimum CG with the value of the fixed MI. The acoustic power (AP) was determined in the function of MI, to as low a level as possible.

Table 1. Ultrasound scanners settings

Setting parameters	Settings of AplioXV*		Settings of Aplio500*	
	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 5 dynamic range; MI 5 mechanical index; AP 5 acoustic power; CG 5 color gain; PRF 5 pulse repetition frequency; VRh 5 vascular receptionharmonic frequency (in Hertz); VRI 5 vascular recognition imaging.

* Toshiba Medical System, Tokyo, Japan.

Method of the variation of concentrations

This method was based on the ultrasonography (US) intensity linearly linked to the number of microbubbles (Correas et al. 2000; Lampaskis and Averkiou 2010). A mathematical description of the formation of ultrasound echoes in DCE-US imaging was proposed by Tang et al. (2008). In the case of the pulse inversion mode,the contrast agent echoes E_{CA} can be defined as follows:

$$E_{CA} = 2C(x)kH_1^2 A_1^2(x)A_2(x)A_n^2(x)G(x) - G(x)N \quad (1)$$

Here, C(x) is the concentration of the contrast agents, H_1 is the amplitude of the initial pulse at the frequency f_0, k is an arbitrary constant in relation with the non-linear scattering at the harmonic signal with frequency of 2 f_0. The contrast agent echo is varied withthe attenuation A in the medium: linear attenuation due to the tissue $A_1(x)$ and $A_2(x)$ at fundamental and second harmonic frequency, respectively, whereas $A_n(x)$ corre- sponds to the non-linear attenuation from the contrast agents. Finally, G(x) depends on the imaging settings, including the system gain, beam and receive profilesand the electronic noise N.

When no microbubbles exist between the probe andthe target, $A_n(x)$ will be assumed as unity. Moreover, thenoise N is considered to have a Gaussian distribution witha mean of 0 and a variance of V. In the case of a target thatis fixed within a phantom, the mathematical description of the echo will be treated as independent of depth, and eqn 1 becomes:

$$E_{CA} = SH_i^2 C; \quad (2)$$

where S is a parameter proportional to the linear attenuation at a fixed depth and the imaging settings of the ultra-sound system. The calibration method considered eqn 2 and was based on the variation of the concentration of contrast agents C.

The contrast agent used was 0.1 mL of SonoVue (Bracco, Milan, Italy) injected into a circuit of water of 90 mL. This volume was associated with the ratio routinely used for clinical examinations (4.8 mL of Sono-Vue for 5 L of blood). After conditioning SonoVue(Bracco) with 5-mL sodium chloride, the obtained solution corresponds with the concentration, namely C_0 in the experiments. For the calibration methodology, the concentration values were determined depending on the feasibility of dilution, because the SonoVue (Bracco) is kept under pressure, which implied a dilution in its orig-inal vial. Four concentrations of SonoVue (Bracco) wereconsidered: C_0; 0.83 xC_0; 0.71 xC_0; and 0.5 xC_0. The various concentrations of SonoVue (Bracco) necessary for the experiment were therefore prepared from the C_0 concentration SonoVue (Bracco) vial to which physio- logic saline was added. Thus, for the 0.83 C_0, 0.71 C_0 and 0.5 C_0 concentrations, saline volumes of 1 mL, 2 mL and 5 mL were added, respectively. The concentration was only varied by a maximum factor of 2 to ensure agood linear relationship with backscattered intensity (Lampaskis and Averkiou 2010).

To study settings with the 2 different ultrasound probes, we developed 2 corresponding phantoms with a material mimicking the acoustic properties of tissue (Fig. 1). For the settings with the abdominal probe, a spherical phantom of 50-mm diameter with agar-agargel was developed to obtain maximum peak intensities (PIs) from the TICs similar to those measured on 539 patients included in the French multicentric study (mean PI 5 611 a.u. and range: 0–18920 a.u.). The gel used is 82.6% distilled water, 6% glycerol, 3% of graphite and 0.4% preservative (Culjat et al. 2010; Madsen et al.1998). Acoustic properties are a velocity of 1548 6 5 m.s^{21} and an acoustic attenuation of 0.5 6 0.01 dB cm^{21} MHz^{21}.

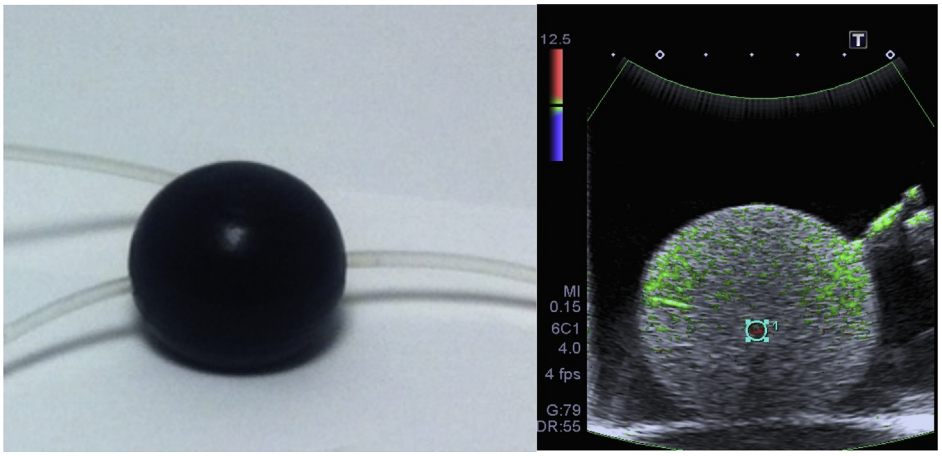

Fig. 1. Spherical phantom of 50-mm diameter with agar-agar gel and its contrast-enhanced ultrasound image obtained with a VRI-coded technique. VRI 5 vascular recognition imaging.

A straight silicone tube of 2-mm inner diameter traversed this phantom. It was placed in a Polymethyl Methacrylate tank filled with water to facilitate the propagation of ultrasound to the probe,itself immersed in the tank opposite the phantom.The external dimensions of the tank were 275 3 105 3 100 mm^3 with foam absorbent on the internal walls to limit ultrasound reflections to the tank inter-faces. In the case of the linear probe, the ultrasonic attenuation at 7 MHz is too high in tissues and limits the use of agar-agar gel. Thus, the phantom was simplified to a silicone tube through the tank.

We designed a simple open-circuit flow model. Thefluid was non-degassed water at 20°C and was driven by a peristaltic pump (PumpDrive PD5101, Heidolph Instruments, Schwabach, Germany), providing a continuous non-pulsatile flow at 42.5 mL/min. A tube with an inner diameter of 2 mm and with a length of 1 m connectedthe pump to the phantom. This length is required to simulate the transit time of the TIC similar to that measured inthe study of 539 patients (mean transit time 5 20 s and range: 0–180 s). The first step was to determine the reference dynamics of the AplioXV (Toshiba). Because these experiments have 12% of variability from the injection (Gauthier et al. 2012a), 8 acquisitions were performed for each of the 4 concentrations of SonoVue (Bracco) and for each parameter setting (MI and CG). For each acquisition, a 2-min perfusion curve was recorded following the SonoVue (Bracco) injection. This step was carried out for curvilinear and linear probes.

Data analysis

The quantitative analysis was performed on the rawlinear data with the quantification software CHI-Q (Toshiba, Puteaux, France). Each acquisition involved a manual selection of the region of interest (ROI) selectedin the core tube. TICs, corresponding to the mean US intensity's temporal evolution induced by the contrast up- take and expressed in arbitrary units, were extractedautomatically from the quantification software (CHI-Q quantification software, Toshiba Medical System, Tokyo, Japan). The TICs were then modeled using a mathematical model (date of issue: May 2008; name of company: Institut Gustave Roussy (Igr); Names of Inventors: N. Elie, N. Lassau, P. Peronneau, V. Rouffiac; French patent number: WO 2008053268 A1) to obtain the semi- quantitative perfusion parameter, area under the curve (AUC), which is recognized as the least variable (Gauthier et al. 2011a) and the most reliable for monitoring therapeutic efficacy on the patient (Lassau et al. 2014; O'Connor et al. 2017). In our study, the calibration of ultrasound scanners was obtained from the slope S of the plot of concentration of SonoVue (Bracco) versus the AUC line. The aim was to obtainthe same S value as that measured from the AplioXV (Toshiba Medical System) scanner.

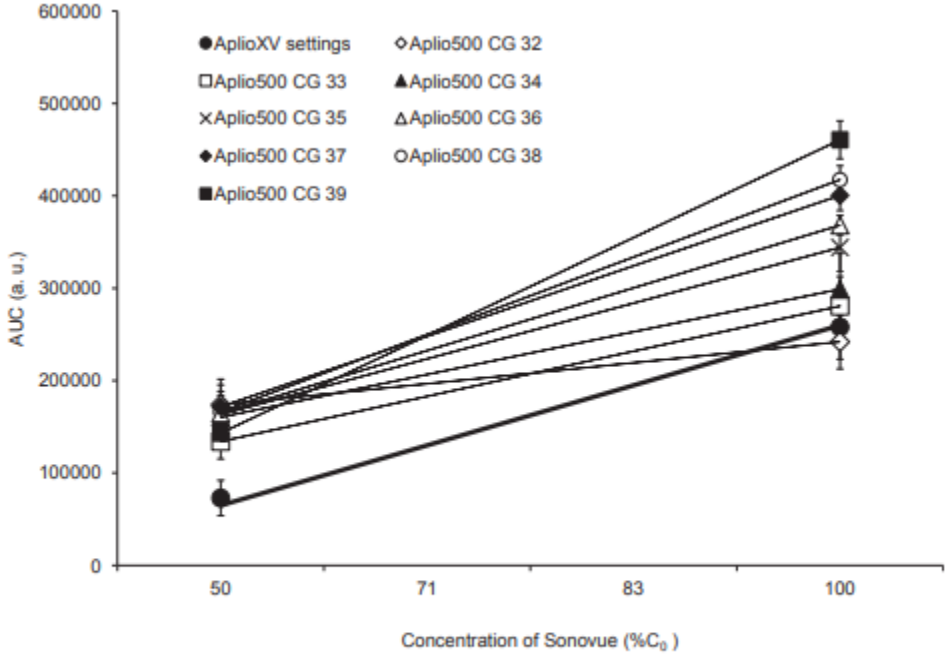

Fig. 3. AUC (a.u.) versus concentration of contrast agents curve at 8 CG (32–39 dB). The linear relationship obtained with the AplioXV (Toshiba Medical System, Tokyo, Japan) was also plotted. Measures were performed with the abdominal curvilinear probe PVT-375 BT (3.5 MHz). AUC = area under the curve; CG = color gain.

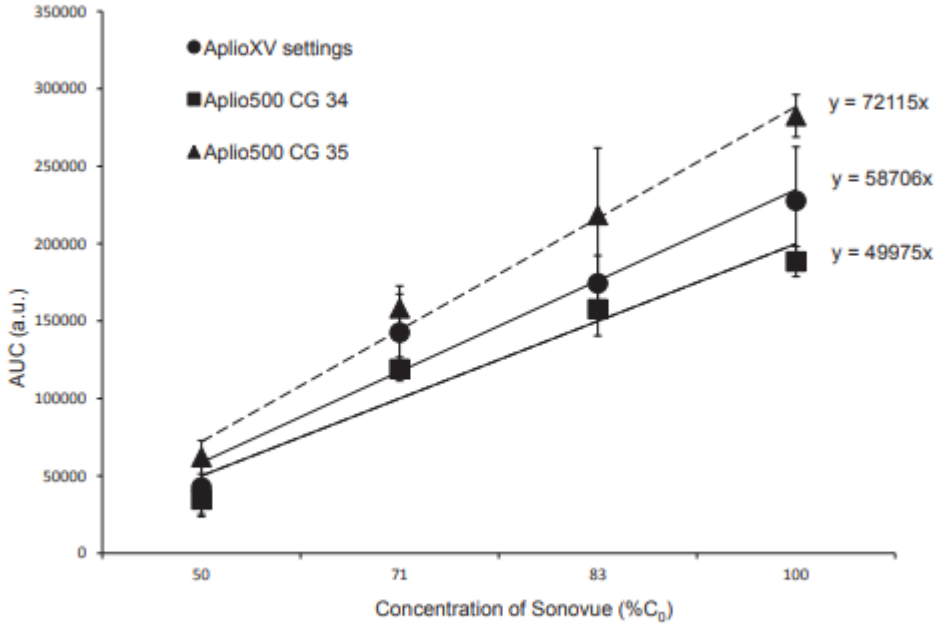

Fig. 4. AUC (a.u.) versus concentration of contrast agents versus curve at 2 CG (34 and 35 dB, respectively). The linear function relationship obtained with the AplioXV (Toshiba Medical System, Tokyo, Japan) was also plotted. Measurements were performed with the abdominal curvilinear probe PVT-375 BT (3.5 MHz). AUC = area under the curve; CG = color gain.

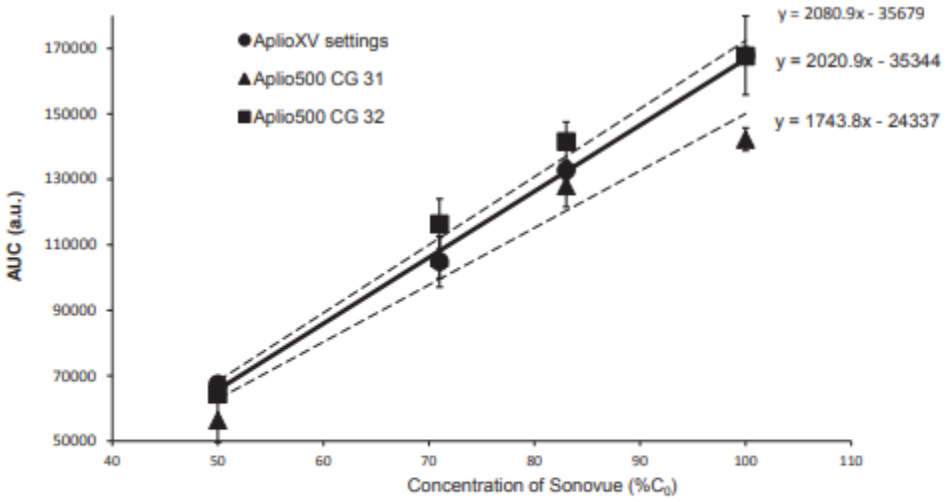

Fig. 5. AUC (a.u.) versus concentration of contrast agents curve at 2 CG (31 and 32 dB, respectively). With CG = 32, the point at 50%C_0 coincides with the 1 obtained with the AplioXV (Toshiba Medical System, Tokyo, Japan), also plotted. Measurements were performed with the linear probe PVT-805 AT (8 MHz) for the AplioXV (Toshiba Medical System), and the probe PLT-1005 BT (10 MHz) for the Aplio500 (Toshiba Medical System). AUC = area under the curve; CG = color gain.

RESULTS

The results obtained with the abdominal probe for the 2 Aplio devices (Toshiba Medical System) are shownin Figure 2 with 3 mechanical indexes: 0.08, 0.12 and 0.15. AUC varies linearly with the concentration of Sono-Vue (Bracco), as expected, if one assumes proportionality between the number of microbubbles and the intensity ofthe detected ultrasonic signal. Furthermore, the increase of the MI is accompanied by an accentuation of the slopesof the linear regressions. Indeed, a high MI promotes theincrease of the amplitude of the ultrasonic signal. In accordance with Figure 2, the measurements with theMI 5 0.15 with the Aplio500 (Toshiba Medical System)appeared closest to those obtained with the AplioXV (Toshiba Medical System). Once fixed, MI studies have focused on the variation of the CG parameter and the re-sults are presented in Figure 3. In the first approach, a wide range of CG values were tested for each of the 2 extreme concentrations of SonoVue ([Bracco] at C0 and 0.5 xC0). The closest match of the slope S as obtained with the Aplio500 (Toshiba Medical System) was achieved with a CG of 34 dB on the AplioXV (Toshiba Medical System).

Subsequently, the study was conducted on a small number of CG close to the value 34 dB and with the 4 concentrations of SonoVue (Fig. 4). S (from eqn 2) were 49975 a.u. and 72115 a.u. for CG 5 34 dB and CG 5 35 dB, respectively. When the S was determined from the AplioXV (Toshiba Medical System), the value was at 58706 a.u. The greatest value of CG was chosen, because it optimizes the dynamics and thus limits a loss of information for the quantification of contrast agents. Thus, the settings of the Aplio500 (Toshiba Medical Sys-tem) that gave the same signal variations as the AplioXV(Toshiba Medical System), the reference scanner used forthe clinical protocol, were: MI 5 0.15; AP 5 0.75%;
CG 5 35 dB.

This approach was also conducted with the linear probe. The results obtained and summarized in Figure 5 indicate a setting of MI 5 0.10; AP 5 1%; CG 5 32 dB.

DISCUSSION

DCE-US applications are increasing in oncology (Hudson et al. 2015). The acceptance of this technique has increased around the world with the recent approval of SonoVue (Bracco) in the United States for abdominal applications. In all functional imaging techniques, the key word is the standardization of the methodology (O'Connor et al. 2017; Sullivan et al. 2015) in order to perform multicentric studies for the validation of biomarkers. Currently, the results of imaging biomarkers are very heterogeneous in monocentric studies in MRI, and no validation has been performedin multicentric studies because no methodology has been developed to standardize the various machines from various companies. Quantitative approaches usedto assist guided therapeutic procedures remain limited because of the difficulty of standardizing the scannersin the contrast-enhanced mode. The Quantitative ImagingBiomarkers Alliance (QIBA, Oak Brook, IL, USA) fo- cuses task forces on standardization in order to propose clinical validations from multicentric studies conducted with various medical devices for each imaging modality.

In the field of quantitative tumoral perfusion, few multi-centric trials have been completed and none with multiple manufacturers. Moreover, device upgrades by manufacturers lead to difficulties in monitoring patients. In this context, our study provides a method for the calibration of an ultrasound scanner set-up based on the variations of contrast agent concentration. The first step, reported here, was to calibrate two devices from the same manufacturer.

Thus, without knowing the internal processing set- tings, the calibration method successfully determinedthe equivalent setting of another ultrasound system, the Aplio500 (Toshiba Medical System), to provide the same dynamic range of ultrasound intensity of AplioXV(Toshiba Medical System). The settings obtained with the curvilinear probe were MI 5 0.15 and CG 5 35 dB, and
with the linear probes: MI 5 0.10 and CG 5 32 dB.
Furthermore, the concentration method had a variability of 12%. This calibration method has proven to be easily feasible with simple phantoms, manual injections of contrast agents and without de-gassed water. It should enable rapid reproduction of the French multicentric pro-tocol across the medical community.

Finally, this calibration phantom appears to be a promising tool toward the standardization of ultrasound scanners. However, this new method also needs to be tested with other scanners from various manufacturers and using various contrast agents. Additionally, in our study, we chose to determine the settings according to two acquisition parameters (MI and CG). However, we could have expanded to several more parameters. Inparticular, we did not vary the dynamic range, which also impacts on perfusion quantification only from com-pressed data (Gauthier et al. 2011b).

This method could be also used with other DCE-US quantification methods with a validated microvasculari- zation parameter.

CONCLUSION

In this study, we proposed a robust method to mea- sure the dynamic of signal for calibration of the Aplio ul-trasound scanners (Toshiba Medical System). The next new challenge is therefore to take into account the diver-sity of ultrasound scanners, with their various technolo- gies, to extend the use of DCE-US while maintaining predictive values of therapeutic response established from clinical studies.

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