



**HAL**  
open science

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

Stéphanie Pitre, Bénédicte Coiffier, Laurène Jourdain, Baya Benatsou, Ingrid Leguerney, Nathalie Lassau

### ► To cite this version:

Stéphanie Pitre, Bénédicte Coiffier, Laurène Jourdain, Baya Benatsou, Ingrid Leguerney, et al.. Toward a Standardization of Ultrasound Scanners for Dynamic Contrast-Enhanced Ultrasonography: Methodology and Phantoms. *Ultrasound in Medicine & Biology*, 2017, 43 (11), pp.2670 - 2677. 10.1016/j.ultrasmedbio.2017.06.032 . hal-03307576

**HAL Id: hal-03307576**

**<https://hal.science/hal-03307576>**

Submitted on 29 Jul 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

STÉPHANIE PITRE-CHAMPAGNAT,\* BÉNÉDICTE COIFFIER,\*<sup>Y</sup> LAURÈNE JOURDAIN,\* BAYA BENATSOU,\*<sup>Y</sup> INGRID LEGUERNEY,\*<sup>Y</sup> and NATHALIE LASSAU\*<sup>Y</sup>

\* University Paris-Sud CNRS, Université Paris-Saclay, Villejuif, France; and <sup>Y</sup>Gustave Roussy, Villejuif, France

(Received 25 August 2016; revised 28 June 2017; in final form 30 June 2017)

**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 5 0.15; CG 5 35 dB and 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](mailto: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.

Address correspondence to: Stéphanie Pitre-Champagnat, IR4 M UMR 8081- University Paris Sud, 114 rue Edouard Vaillant, 94805 Villejuif, France. E-mail: [stephanie.pitre@u-psud.fr](mailto:stephanie.pitre@u-psud.fr)

## 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 month with a cut-off of 40% of AUC to predict efficiency of treatments (Lassau et al. 2014).

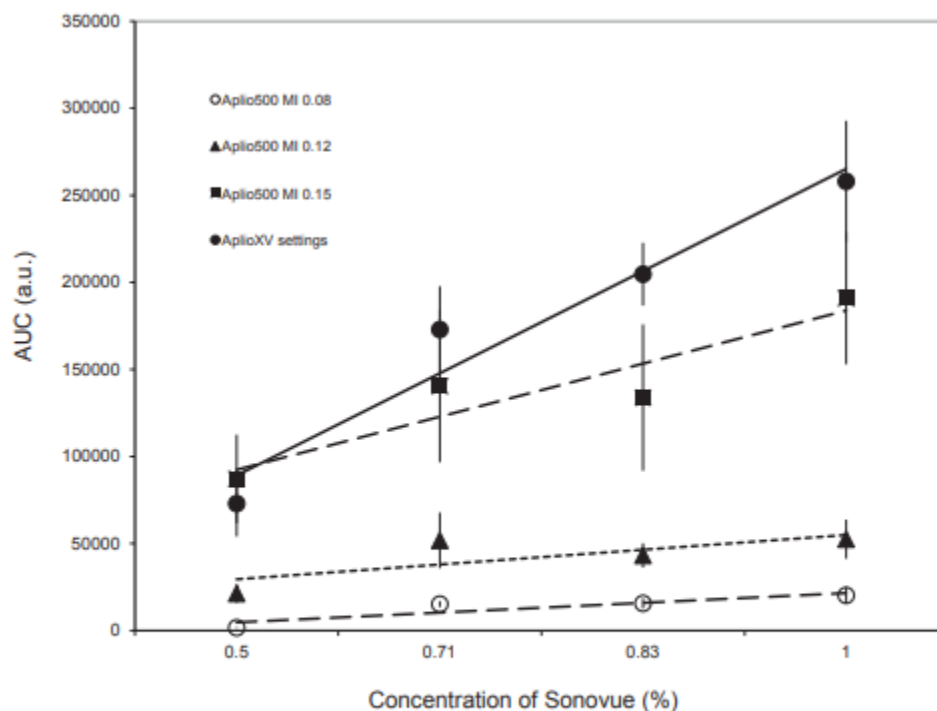


Fig. 2. Impact of varying concentration of contrast agents on AUC (arbitrary unit) at 3 MI (0.08, 0.12 and 0.15, respectively). The linear relationship obtained with the AplioXV (Toshiba Medical System, Tokyo, Japan) was also plotted. Measurements were performed with the abdominal curvilinear probe PVT-375 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 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 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 recurrently 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 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; Quiaia 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  $\leq 0.2$ . 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 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 reception harmonic 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:

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

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 with the 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  $A_n(x)$  corresponds to the non-linear attenuation from the contrast agents. Finally,  $G(x)$  depends on the imaging settings, including the system gain, beam and receive profiles and the electronic noise  $N$ .

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

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

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 SonoVue 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 original vial. Four concentrations of SonoVue (Bracco) were considered:  $C_0$ ;  $0.83 \times C_0$ ;  $0.71 \times C_0$ ; and  $0.5 \times C_0$ . The various concentrations of SonoVue (Bracco) necessary for the experiment were therefore prepared from the  $C_0$  concentration SonoVue (Bracco) vial to which physiologic 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 a good 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-agar gel 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  $1548.65 \text{ m}\cdot\text{s}^{-1}$  and an acoustic attenuation of  $0.560.01 \text{ dB}\cdot\text{cm}^{-1}\cdot\text{MHz}^{-1}$ .

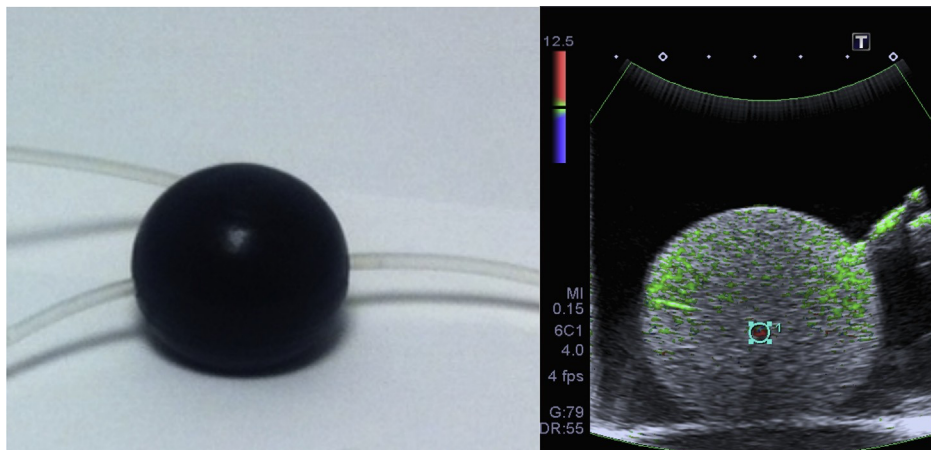


Fig. 1. Spherical phantom of 50-mm diameter with agar-agar gel and its contrast-enhanced ultrasound image obtained with a VRI-coded technique. VRI 5 vascular recognition imaging.

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 × 310 × 100 mm<sup>3</sup> with foam absorbent on the internal walls to limit ultrasound reflections to the tank interfaces. 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. The fluid 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 connected the pump to the phantom. This length is required to simulate the transit time of the TIC similar to that measured in the 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 raw linear data with the quantification software CHI-Q (Toshiba, Puteaux, France). Each acquisition involved a manual selection of the region of interest (ROI) selected in the core tube. TICs, corresponding to the mean US intensity's temporal evolution induced by the contrast uptake and expressed in arbitrary units, were extracted automatically 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 obtain the same  $S$  value as that measured from the AplioXV (Toshiba Medical System) scanner.

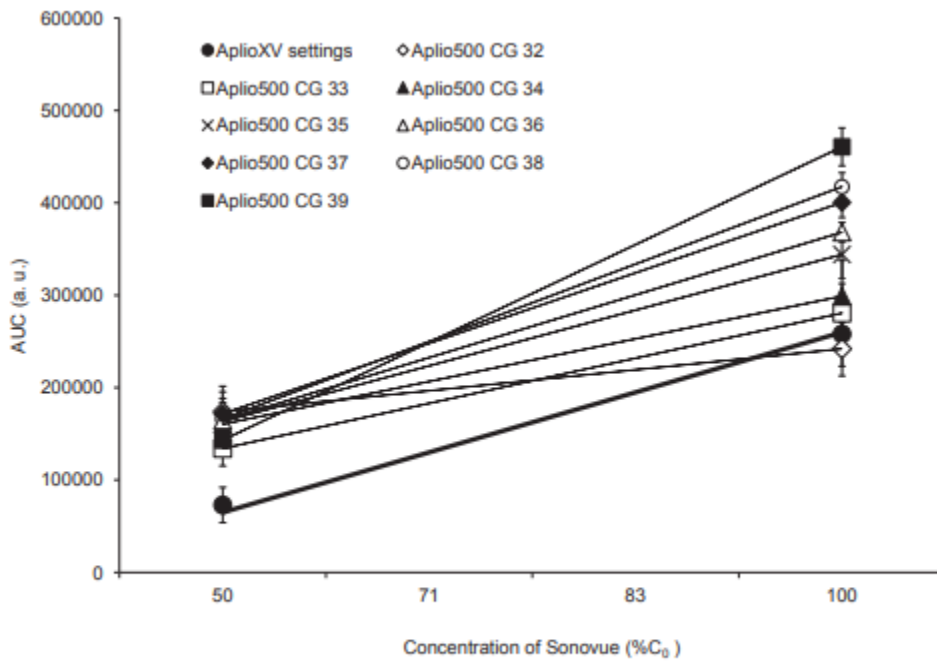


Fig. 3. AUC (a.u.) versus concentration of contrast agents curve at 8 CG (32–39 dB). The linear relationship obtained with the AplioXV (Toshiba Medical System, Tokyo, Japan) was also plotted. Measures were performed with the abdominal curvilinear probe PVT-375 BT (3.5 MHz). AUC = area under the curve;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

A calibration method for DCE-US ● S. PITRE-CHAMPAGNAT *et al.*

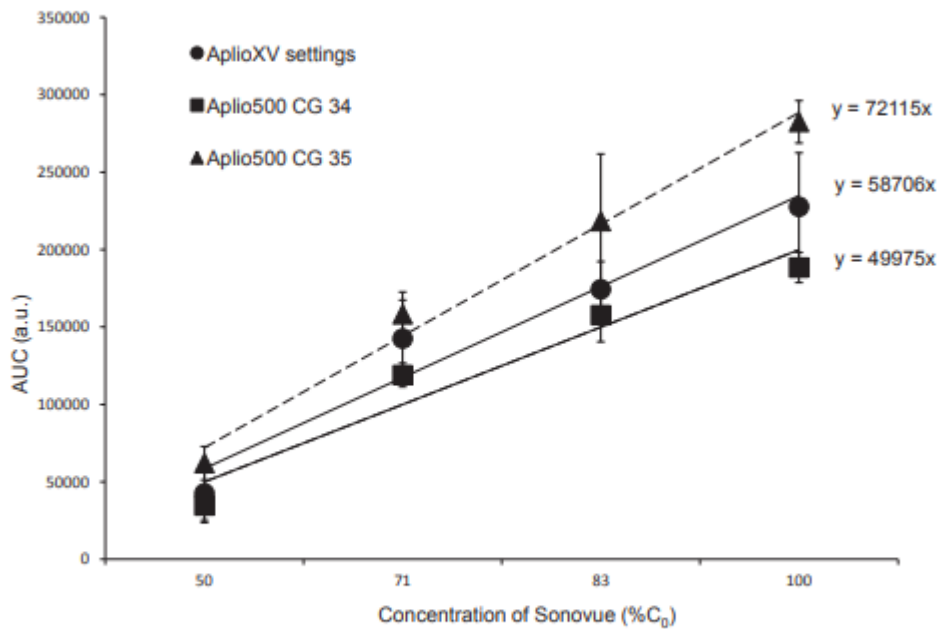


Fig. 4. AUC (a.u.) versus concentration of contrast agents versus curve at 2 CG (34 and 35 dB, respectively). The linear function relationship obtained with the AplioXV (Toshiba Medical System, Tokyo, Japan) was also plotted. Measurements were performed with the abdominal curvilinear probe PVT-375 BT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



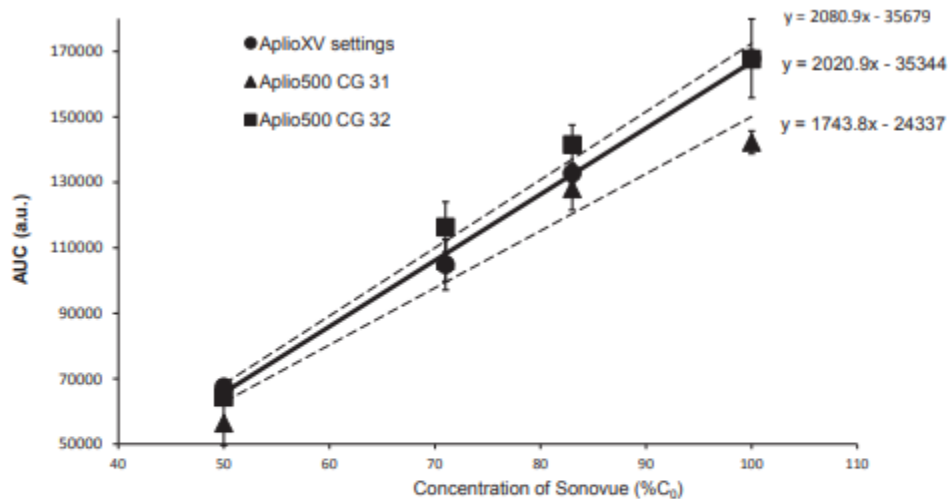


Fig. 5. AUC (a.u.) versus concentration of contrast agents curve at 2 CG (31 and 32 dB, respectively). With CG = 32, the point at 50% $C_0$  coincides with the 1 obtained with the AplioXV (Toshiba Medical System, Tokyo, Japan), also plotted. Measurements were performed with the linear probe PVT-805 AT (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 shown in Figure 2 with 3 mechanical indexes: 0.08, 0.12 and 0.15. AUC varies linearly with the concentration of SonoVue (Bracco), as expected, if one assumes proportionality between the number of microbubbles and the intensity of the detected ultrasonic signal. Furthermore, the increase of the MI is accompanied by an accentuation of the slopes of the linear regressions. Indeed, a high MI promotes the increase of the amplitude of the ultrasonic signal. In accordance with Figure 2, the measurements with the MI 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 results 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  $C_0$  and  $0.5 \times C_0$ ). 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 34 dB and CG 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 System) that gave the same signal variations as the AplioXV (Toshiba Medical System), the reference scanner used for the clinical protocol, were: MI 0.15; AP 0.75%; CG 35 dB.

This approach was also conducted with the linear probe. The results obtained and summarized in Figure 5 indicate a setting of MI 0.10; AP 1%; CG 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 performed in multicentric studies because no methodology has been developed to standardize the various machines from various companies. Quantitative approaches used to assist guided therapeutic procedures remain limited because of the difficulty of standardizing the scanners in the contrast-enhanced mode. The Quantitative Imaging Biomarkers Alliance (QIBA, Oak Brook, IL, USA) focuses 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 settings, the calibration method successfully determined the 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 protocol 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. In particular, we did not vary the dynamic range, which also impacts on perfusion quantification only from compressed data (Gauthier et al. 2011b).

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

## CONCLUSION

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

*Acknowledgments*—The authors thank Stephen Randall Thomas of the IR4 M laboratory (University of Paris-Sud, Orsay, France) for valuable comments and suggestions. This study was supported by a grant from the

research program in physics, mathematics and engineering sciences applied to cancer research, of the French Plan Cancer 2013.

## REFERENCES

- Boellaard R, Rausch I, Beyer T, Delso G, Yaqub M, Quick HH, Sattler B. Quality control for quantitative multicenter whole-body PET/MR studies: A NEMA image quality phantom study with three current PET/MR systems. *Med Phys* 2015;42:5961–5969.
- Bruce M, Averkiou M, Tiemann K, Lohmaier S, Powers J, Beach K. Vascular flow and perfusion imaging with ultrasound contrast agents. *Ultrasound Med Biol* 2004;30:735–743.
- Casciaro S, Conversano F, Musio S, Casciaro E, Demitri C, Sannino A. Full experimental modelling of a liver tissue mimicking phantom for medical ultrasound studies employing different hydrogels. *J Mater Sci Mater Med* 2009;20:983–989.
- Claassen L, Seidel G, Algermissen C. Quantification of flow rates using harmonic grey-scale imaging and an ultrasound contrast agent: An in vitro and in vivo study. *Ultrasound Med Biol* 2001;27:83–88.
- Claudon M, Dietrich CF, Choi BI, Cosgrove DO, Kudo M, Nolsoe CP, Piscaglia F, Wilson SR, Barr RG, Chammas MC, Chaubal NG, Chen MH, Clevert DA, Correas JM, Ding H, Forsberg F, Fowlkes JB, Gibson RN, Goldberg BB, Lassau N, Leen EL, Mattrey RF, Moriyasu F, Solbiati L, Weskott HP, Xu HX, World Federation for Ultrasound in Medicine, European Federation of Societies for Ultrasound. Guidelines and good clinical practice recommendations for Contrast Enhanced Ultrasound (CEUS) in the liver—Update 2012: A WFUMB-EFSUMB initiative in cooperation with representatives of AFSUMB, AIUM, ASUM, FLAUS and ICUS. *Ultrasound Med Biol* 2013;39:187–210.
- Correas JM, Burns PN, Lai X, Qi X. Infusion versus bolus of an ultrasound contrast agent: in vivo dose-response measurements of BR1. *Invest Radiol* 2000;35:72–79.
- Culjat MO, Goldenberg D, Tewari P, Singh RS. A review of tissue substitutes for ultrasound imaging. *Ultrasound Med Biol* 2010;36:861–873.
- Dietrich CF, Averkiou MA, Correas JM, Lassau N, Leen E, Piscaglia F. An EFSUMB introduction into Dynamic Contrast-Enhanced Ultrasound (DCE-US) for quantification of tumour perfusion. *Ultraschall Med* 2012;33:344–351.
- Gauthier M, Leguerney I, Thalmens J, Chebil M, Parisot S, Peronneau P, Roche A, Lassau N. Estimation of intra-operator variability in perfusion parameter measurements using DCE-US. *World J Radiol* 2011a;3:70–81.
- Gauthier M, Pitre-Champagnat S, Tabarout F, Leguerney I, Polrot M, Lassau N. Impact of the arterial input function on microvascularization parameter measurements using dynamic contrast-enhanced ultrasonography. *World J Radiol* 2012a;4:291–301.
- Gauthier M, Tabarout F, Leguerney I, Polrot M, Pitre S, Peronneau P, Lassau N. Assessment of quantitative perfusion parameters by dynamic contrast-enhanced sonography using a deconvolution method: An in vitro and in vivo study. *J Ultrasound Med* 2012b; 31:595–608.
- Gauthier TP, Averkiou MA, Leen EL. Perfusion quantification using dynamic contrast-enhanced ultrasound: The impact of dynamic range and gain on time-intensity curves. *Ultrasonics* 2011b;51:102–106.
- Gauthier TP, Chebil M, Peronneau P, Lassau N. In vitro evaluation of the impact of ultrasound scanner settings and contrast bolus volume on time-intensity curves. *Ultrasonics* 2012c;52:12–19.
- Hindle AJ, Perkins AC. A perfusion phantom for the evaluation of ultrasound contrast agents. *Ultrasound Med Biol* 1994;20:309–314.
- Hudson JM, Williams R, Tremblay-Darveau C, Sheeran PS, Milot L, Bjarnason GA, Burns PN. Dynamic contrast enhanced ultrasound for therapy monitoring. *Eur J Radiol* 2015;84:1650–1657.
- Katabathina VS, Lassau N, Pedrosa I, Ng CS, Prasad SR. Evaluation of treatment response in patients with metastatic renal cell carcinoma: Role of state-of-the-art cross-sectional imaging. *Curr Urol Rep* 2012;13:70–81.
- Kier C, Meyer-Wiethe K, Seidel G, Mertins A. Improved modelling of ultrasound contrast agent diminution for blood perfusion analysis. *Med Image Comput Assist Interv* 2009;12:935–942.
- Lampaskis M, Averkiou M. Investigation of the relationship of nonlinear backscattered ultrasound intensity with microbubble concentration at low MI. *Ultrasound Med Biol* 2010;36:306–312.

Lassau N, Bonastre J, Kind M, Vilgrain V, Lacroix J, Cuinet M, Taieb S, Aziza R, Sarran A, Labbe-Devilliers C, Gallix B, Lucidarme O, Ptak Y, Rocher L, Caquot LM, Chagnon S, Marion D, Luciani A, Feutray S, Uzan-Augui J, Coiffier B, Benastou B, Koscielny S. Validation of dynamic contrast-enhanced ultrasound in predicting outcomes of antiangiogenic therapy for solid tumors: The French multicenter support for innovative and expensive techniques study. *Invest Radiol* 2014;49:794–800.

Lassau N, Chapotot L, Benatsou B, Vilgrain V, Kind M, Lacroix J, Cuinet M, Taieb S, Aziza R, Sarran A, Labbe C, Gallix B, Lucidarme O, Ptak Y, Rocher L, Caquot LM, Chagnon S, Marion D, Luciani A, Uzan-Augui J, Koscielny S. Standardization of dynamic contrast-enhanced ultrasound for the evaluation of anti-angiogenic therapies: The French multicenter Support for Innovative and Expensive Techniques Study. *Invest Radiol* 2012;47:711–716.

Lassau N, Koscielny S, Albiges L, Chami L, Benatsou B, Chebil M, Roche A, Escudier BJ. Metastatic renal cell carcinoma treated with sunitinib: Early evaluation of treatment response using dynamic contrast-enhanced ultrasonography. *Clin Cancer Res* 2010; 16:1216–1225.

Lassau N, Koscielny S, Chami L, Chebil M, Benatsou B, Roche A, Ducreux M, Malka D, Boige V. Advanced hepatocellular carcinoma: Early evaluation of response to bevacizumab therapy at dynamic contrast-enhanced US with quantification—Preliminary results. *Radiology* 2011;258:291–300.

Lavisse S, Peronneau P, Rouffiac V, Paci A, Vigouroux J, Opolon P, Roche A, Lassau N. Acoustic characterization of a new trisacryl contrast agent. Part II: Flow phantom study and in vivo quantification. *Ultrasonics* 2008;48:26–34.

Li PC, Yeh CK, Wang SW. Time-intensity-based volumetric flow measurements: An in vitro study. *Ultrasound Med Biol* 2002;28: 349–358.

Lohmaier S, Ghanem A, Veltmann C, Sommer T, Bruce M, Tiemann K. In vitro and in vivo studies on continuous echo-contrast application strategies using SonoVue in a newly developed rotating pump setup. *Ultrasound Med Biol* 2004;30:1145–1151.

Lucidarme O, Kono Y, Corbeil J, Choi SH, Mattrey RF. Validation of ultrasound contrast destruction imaging for flow quantification. *Ultrasound Med Biol* 2003;29:1697–1704.

Madsen EL, Frank GR, Dong F. Liquid or solid ultrasonically tissue-mimicking materials with very low scatter. *Ultrasound Med Biol* 1998;24:535–542.

O'Connor JP, Aboagye EO, Adams JE, Aerts HJ, Barrington SF, Beer AJ, Boellaard R, Bohndiek SE, Brady M, Brown G, Buckley DL, Chenevert TL, Clarke LP, Collette S, Cook GJ, deSouza NM, Dickson JC, Dive C, Evelhoch JL, Faivre-Finn C,

Gallagher FA, Gilbert FJ, Gillies RJ, Goh V, Griffiths JR, Groves AM, Halligan S, Harris AL, Hawkes DJ, Hoekstra OS, Huang EP, Hutton BF, Jackson EF, Jayson GC, Jones A, Koh DM, Lacombe D, Lambin P, Lassau N, Leach MO, Lee TY, Leen EL, Lewis JS, Liu Y, Lythgoe MF, Manoharan P, Maxwell RJ, Miles KA, Morgan B, Morris S, Ng T, Padhani AR, Parker GJ, Partridge M, Pathak AP, Peet AC, Punwani S, Reynolds AR, Robinson SP, Shankar LK, Sharma RA, Soloviev D, Stroobants S, Sullivan DC, Taylor SA, Tofts PS, Tozer GM, van Herk M, Walker-Samuel S, Wason J, Williams KJ, Workman P, Yankeelov TE, Brindle KM, McShane LM, Jackson A, Waterton JC. Imaging biomarker roadmap for cancer studies. *Nat Rev Clin Oncol* 2017;14:169–186.

Piscaglia F, Nolsoe C, Dietrich CF, Cosgrove DO, Gilja OH, Bachmann Nielsen M, Albrecht T, Barozzi L, Bertolotto M, Catalano O, Claudon M, Clevert DA, Correas JM, D'Onofrio M, Drudi FM, Eyding J, Giovannini M, Hocke M, Ignee A, Jung EM, Klausner AS, Lassau N, Leen E, Mathis G, Saftoiu A, Seidel G, Sidhu PS, ter Haar G, Timmerman D, Weskott HP. The EFSUMB Guidelines and Recommendations on the Clinical Practice of Contrast Enhanced Ultrasound (CEUS): Update 2011 on non-hepatic applications. *Ultraschall Med* 2012;33:33–59.

Quaia E, Nocentini A, Torelli L. Assessment of a new mathematical model for the computation of numerical parameters related to renal cortical blood flow and fractional blood volume by contrast-enhanced ultrasound. *Ultrasound Med Biol* 2009;35:616–627.

Radhakrishnan K, Haworth KJ, Huang SL, Klegerman ME, McPherson DD, Holland CK. Stability of echogenic liposomes as a blood pool ultrasound contrast agent in a physiologic flow phantom. *Ultrasound Med Biol* 2012;38:1970–1981.

Sullivan DC, Obuchowski NA, Kessler LG, Raunig DL, Gatsonis C, Huang EP, Kondratovich M, McShane LM, Reeves AP, Barboriak DP, Guimaraes AR, Wahl RL, Group R-QMW. Metrology standards for quantitative imaging biomarkers. *Radiology* 2015;277:813–825.

Tang MX, Mari JM, Wells PN, Eckersley RJ. Attenuation correction in ultrasound contrast agent imaging: Elementary theory and preliminary experimental evaluation. *Ultrasound Med Biol* 2008;34: 1998–2008.

Ugolini P, Delouche A, Herment A, Diebold B. In vitro flow quantification with contrast power Doppler imaging. *Ultrasound Med Biol* 2000;26:113–120.

Veltmann C, Lohmaier S, Schlosser T, Shai S, Ehlgren A, Pohl C, Becher H, Tiemann K. On the design of a capillary flow phantom for the evaluation of ultrasound contrast agents at very low flow velocities. *Ultrasound Med Biol* 2002;28:625–634.