An EFSUMB Introduction into Dynamic Contrast-Enhanced Ultrasound (DCE-US) for Quantification of Tumour Perfusion

Einführung des „Dynamic Contrast-Enhanced Ultrasound (DCE-US)“ zur Quantifizierung der Tumorperfusion, EFSUMB-Statement

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Key words
- Ultrasound contrast agents
- guidelines
- therapy monitoring
- perfusion quantification

Zusammenfassung

Dynamic Contrast Enhanced Ultrasound (DCE-US) ist eine Quantifizierungstechnik des kontrastverstärkten Ultraschalls. Die EFSUMB-Leitlinien 2004, 2008 und 2011 erläutern die Grundlagen für Ultraschallkontrastmitteltechniken, geben aber keine detaillierte Information zu den Anwendungsmöglichkeiten, Vorgehensweise und Besonderheiten von DCE-US. Ziel dieses EFSUMB-Dokuments ist es, notwendige Grundlagen, technischen Voraussetzungen für die Analyse von Zeit-Intensitäts-Kurven und den (standardisierten) Ablauf der Daten-Analyse und Empfehlung zur Interpretation zu geben.

Abstract

Dynamic Contrast Enhanced Ultrasound (DCE-US) is an imaging technique that utilizes microbubble contrast agents in diagnostic ultrasound. The EFSUMB guidelines published in 2004, updated in 2008 and 2011 focused on the use of DCE-US, including essential technical requirements, training, investigational procedures and steps, guidance on image interpretation, established and recommended clinical indications and safety considerations. However the quantification of images acquired with ultrasound contrast agents (UCAs) is not discussed in the guidelines. The purpose of this EFSUMB document is to provide some recommendations and descriptions of the quantification of ultrasound images, technical requirements for analysis of time-intensity curves (TICs), methodology for data analysis, and interpretation of the results.

received 6.6.2012
accepted 25.6.2012

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DOI http://dx.doi.org/10.1055/s-0032-1313026
Published online: July 27, 2012
Ultraschall in Med 2012; 33: 344–351 © Georg Thieme Verlag KG Stuttgart · New York · ISSN 0172-4614

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Introduction

UCA, in conjunction with contrast specific imaging modes, are increasingly accepted in clinical use for diagnostic imaging and pre- and post-interventional work-up [1]. Contrast-enhanced ultrasound (CEUS) has improved the detection and characterization of pathologies in comparison to conventional ultrasound. In addition, Dynamic Contrast Enhanced Ultrasound (DCE-US) overcomes subjective evaluation of the enhancement between normal and abnormal parenchyma, or between a focal lesion and the surrounding tissue. Furthermore, DCE-US offers the potential for a better understanding of the pathophysiology of angiogenesis of benign and malignant neoplasia. This article focuses on DCE-US for quantification of tumour perfusion; other applications, e. g., use in cardiology, or quantification of kidney and brain perfusion are just mentioned.

Accurate quantification of tissue perfusion with DCE-US should ideally be similar irrespective of the ultrasound equipment, data acquisition and analysis software. The parameters encountered in DCE-US quantification will be presented and explained in order to support the future work in this research field and to facilitate the standardization and recommendations of DCE-US technique following review of advantages and limitations of the different quantification approaches.

Why do we need quantification?

Quantification of DCE-US is needed to evaluate data objectively, to enable comparison of imaging techniques, to evaluate new UCA applications, to quantify tissue and tumour enhancement in order to characterize focal lesions, to evaluate therapeutic response, and to limit varia-

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bility in clinical diagnosis. An objective and quantitative diagnosis is of particular relevance in the follow up of cancer patients.
Current assessment of response to cancer treatment is mainly based on interval evaluation of the tumour size according to the Response Evaluation Criteria In Solid Tumours (RECIST) [2]. Unfortunately RECIST is limited as it reflects only tumour size changes (which are often delayed) and is unable to identify non-responders at an early time-point, when novel cytostatic biologic agents are employed [3]. A patient may be misclassified as non responder because the tumour size may remain unchanged, or may even increase in the early time due to hemorrhage, necrosis and edema, despite that the viable tumour portions are instead decreased.
To circumvent this problem new methods to assess tumour response at two or more months based on tumour perfusion have been introduced in the form of modified RECIST (mRECIST) criteria [4]. The advent of novel therapies targeting tumour angiogenesis and vascularity has highlighted the need for accurate and reproducible quantitative techniques to assess early changes in tumoral vascularity.

Clinical Applications

Early clinical trials assessing tumour response in gastrointestinal stromal tumour (GIST) were based on subjective qualitative DCE-US. More recent studies assessing earlier response in renal cell carcinoma, hepatocellular carcinoma (HCC), and colorectal metastases used semi-quantitative techniques [5–9]. Lassau and colleagues demonstrated a correlation between blood volume parameters (AUC and AUWO) and Progression Free Survival (PFS) and Overall Survival (OS) in the assessment of early response in renal cell carcinomas and HCC [5, 7]. However, Williams and colleagues showed no significant correlation between any of the parameters extracted with DCE-US and Progression Free Survival assessed by the RECIST method [8].
The use of respiratory gated contrast enhanced ultrasound to assess response to cytotoxic and antiangiogenic treatment of patients with colorectal liver metastasis was also investigated in 7 patients [9]. The ratio of wash-in time of the lesion to that of the normal parenchyma (WITR) was used to compare the perfusion rate. In a reproducibility study, the average deviation of WITR was found to be as low as 9%. So far the main use of DCE-US quantification is for monitoring therapeutic response to drugs implying an effect on tumour vascularization. This brief overview of clinical studies highlights the interest in the field of DCE-US quantification and its future potential. Currently there are numerous clinical trials including more than 500 patients [10] evaluating the assessment of early response to anti-angiogenic drugs using DCE-US quantification demonstrating the potential of this technique in comparison to DCE-MRI. Whilst the main use of DCE-US quantification is for monitoring therapeutic response to drugs implying an effect on tumour vascularization, the diagnostic evaluation of inflammatory and other neoplastic diseases appear to represent additional applications.
However, there are different approaches and technical issues which may affect the reliability of the results and may explain contrasting results between studies, and may potentially limit or prevent the routine clinical application of the technique.

Agent administration methods

Available contrast agents

Four transpulmonary UCAs (SonoVue® [phospholipid/SF_6, Bracco], Luminity® [perflutren, octafluoropropane with a phospholipid shell, Lantheus], Optison® [octafluoropropane, perflutren with an albumin shell, GE Healthcare] and Levovist® [production has been discontinued]) are currently approved by the European Medicines Agency for use in European countries. Luminity® and Optison® have restricted indications and availability. Other UCAs are approved outside Europe and some are under investigation. This article will focus mainly on SonoVue® [1], as it is the agent widely used in Europe.

Dosage

The recommended dose for bolus injection of SonoVue® is 2.4 mL irrespective of the patient's weight, but this dose may vary between 1 mL and 4.8 mL depending on the sensitivity of the equipment, the imaging frequency, the degree of vascularity, and the depth of the target lesion. With more recent and sensitive equipment the lower doses are adequate and preferred. The dose may be reduced to 1 mL when scanning kidneys (and particularly in renal transplants), while it can be increased to 4.8 mL in the case of a superficial lesion using a high frequency linear array or endoscopic transducers [1, 11, 12]. For infusion studies up to 2 vials (9.6 mL) can be infused at a rate of about 1 mL/min (or less) depending on the enhancement level required [13].

Administration methods

DCE-US can be performed using two different administration methods:

1. Bolus injection of UCA with wash-in/wash-out analysis: Single plane at low mechanical index (MI) imaging is usually performed at 10–20 frames per second for the duration of the enhancement. The average intensity within a region of interest (ROI) is calculated in linear units and displayed as a function of time, i.e. a time–intensity curve which describes the wash-in and wash-out of the contrast agent in the ROI. Additional ROIs can be placed in a reference tissue for comparison purposes or in different areas of the lesion. The majority of clinical studies to date are based on this method.
2. Intravenous infusion of UCA with disruption-replenishment analysis: Scanning is in a single plane during a steady state level in blood of contrast agent concentration. The UCA is administered using a pump or drip (this applies only to Definity®) over 5 to 20 minutes. UCA is first imaged without being disrupted at low MI, then a few frames are acquired at high MI (often at the highest available) causing bubble disruption in the image plane. Immediately after, the MI is reverted to its low setting and the arrival of fresh microbubbles is imaged. A time intensity curve is formed from the above image sequence in order to measure the replenishment rate of the UCAs in the ROI. Various models describe the replenishment process, which can be utilized for the analysis of flow [14–17]. This method should only be performed with ultrasound scanners that support the above protocol.

Bolus Injection method

Bolus injection for quantitative DCE-US using SonoVue® should be performed with a short angio-catheter typically 20G (never smaller diameter than 22G), placed in an antecubital vein, without using any extension line. A 3-way stop valve may be used at

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the end of the catheter to allow controlled access. Studies have been performed with a 5 mL saline flush but others recommend its exclusion, to avoid its unpredictable contribution on contrast mixing and acceleration within the venous system and its influence in the time intensity curve profile. However, when no saline flush is used a short canula to limit the volume of UCA remaining in the angio-catheter and stop valve is required. The bolus injection should be quick in order to mimic a step function as described by the mathematical model used for the analysis of the data.

For other UCAs (Luminity® and Optison®) where the injection volume is much smaller than that of SonoVue® or when very small volumes of SonoVue® are utilized, an extension line and a saline flush are necessary.

Infusion delivery method

Slow infusion of SonoVue® requires either a pump that can be placed vertically or a specific rotating pump to continuously agitate the microbubbles [13]. Definity® can be used with a pump or drip bag. One to two vials can be mixed together in a large syringe (10 – 20 ml) and then placed on the pump for a slow infusion. Depending on the enhancement level required, SonoVue® is applied at a rate of 1 mL/min (or less) to reach a steady state delivery of bubbles.

Bolus versus infusion technique

Both infusion and bolus techniques provide estimation of parameters that relate to perfusion. For follow-up examinations, it is necessary to use the same quantification technique (including the UCA administration method) keeping all imaging settings identical. DCE-US using infusion and disruption-replenishment of the microbubbles is a little more complicated since it requires the use of a pump (that may rotate in order to avoid floating of the microbubbles), the use of a more complex scanning sequence that involves both low MI and high MI scanning (and may not be available with all scanners) and the infusion rate to reach steady state level reflecting that of the tissue of interest can be difficult to achieve. However the acquisition can be repeated few times during the course of an infusion, at different planes and possibly improve the accuracy of the measurements.

The choice between the two techniques also depends on the purpose of the study. Both techniques might vary due to the patient hemodynamic status. The dual blood supply of the liver is further complicating blood flow quantification. After a bolus injection, the arterial blood supply is responsible for the initial enhancement of the normal parenchyma and focal lesions, as the microbubbles arriving through the portal blood supply are delayed by 5 to 10 sec. On the other hand, with the infusion technique, the replenishment reflects a combination of arterial and portal flow inputs. So far the bolus technique is used more widely.

Mathematical models

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Indicator dilution techniques may be used for the quantification of macro- and microvascular blood flow in DCE-US [18, 19]. In contrast to SonoVue® and other contrast agents, which are strictly intravascular agents, CT and MRI contrast agents show extravascular distribution, limiting such methods in measuring blood flow using multi-compartmental models.

The use of these techniques allows for the estimation of blood flow parameters of tumours and organs. Although research is on going for extracting absolute measures of blood flow and volume with DCE-US, at present this technique is considered reliable to identify relative changes of these parameters only, and not absolute values. The quantification approach varies with the contrast agent administration method (bolus or infusion).

A summary of the various mathematical models that apply to the quantification of tumour and organ perfusion is described to encourage further study of the quoted references for more in-depth understanding.

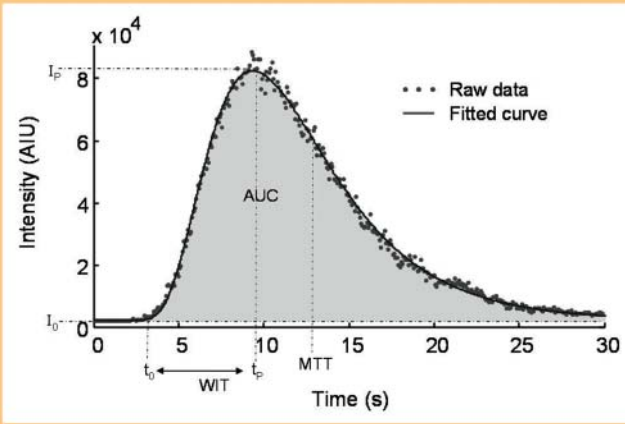

Abb. 1 Typical TIC for intravenous bolus injection of UCA and explanation of important parameters. Intensity is measured in absolute intensity units (AIU) and time in seconds (sec) (for explanation of the parameters described in the Figure see Table 1). All time and intensity values are calculated from the fitted curve and not on raw image data.

Wash-in/wash-out analysis with bolus injection

After an intravenous bolus injection of contrast microbubbles, a time-intensity curve (TIC) is formed, which displays the average intensity in a region of interest as a function of time, reflecting the transit of the UCA. The TIC describes the wash-in and wash-out of the contrast microbubbles in the ROI (**Fig. 1**).

Time intensity curve parameters in detail

Several derived TIC parameters are purely descriptive/empirical. Since it is assumed that the signal intensity in DCE-US is proportional to the amount of microbubbles, and the microbubbles remain strictly intravasal, the TIC parameters are related to the vascularisation of the analysed region. Some parameters (peak intensity, area under the curve) are more correlated to the local blood volume of the region (~ mL) while others reflect more blood flow (TTP, WIT). All time and intensity values are calculated from the fitted curve and not from raw image data.

Time parameters [sec]

Time zero offset (t_0)

Time from the UCA injection to the first appearance of microbubbles in the ROI, corresponding to the point on the abscissa, where the TIC curve starts the uprise. The enhancement value at time zero offset is utilized as baseline and subtracted from the following contrast enhanced measurements. It is not a relevant parameter related to perfusion, but is listed here for the sake of completeness.

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Time to peak (t_p)
It is the time from zero intensity (right before the contrast arrives in the ROI) to maximum intensity. This parameter is calculated from the fitted mathematical model and often is supplied in a closed form analytical expression.

Wash-in time (WIT)
It is time from 5 % intensity to 95 % intensity. It is proportional to the time to peak but it is sometimes used with mathematical models that do not have closed form analytical expressions of t_p.

Wash-out time (WOT)
It is the time from the peak of the TIC curve to the zero value again. The latter time point (zero enhancement) is rarely seen in the raw data as it may take a long time for the ROI to become completely black again. It is easily calculated from the fitted mathematical model (curve).

Mean transit time (MTT)
This parameter describes the mean time taken by the bubbles (from the time of first arrival in the ROI) to pass through the ROI. Mathematically it is the first moment of the TIC curve. This parameter is easily calculated from the fitted mathematical model and often is given in a closed form analytical expression.

Full width half max (FWHM)
Full-width at half-maximum is the time between the half amplitude values in each side of the maximum. It is an empirical parameter and it should not be confused with the mean transit time.

Peak intensity (I_p)
Peak intensity is the maximum intensity in the TIC curve. For cases where the TIC curve does not start from zero and it has a small offset, the peak intensity is the difference between the maximum and minimum intensity. It is preferred to subtract the offset from the curve so that the TIC starts from zero level.

Area under the curve (AUC)
As the name denotes, it is the area under the TIC curve above baseline [shaded area in **Fig. 1**] and it is calculated numerically between the time t_0 and a predefined time t_{end}. This parameter is related to blood volume (as shown in the analysis below). It is important to fix the start and end time point when calculating the AUCs in therapy monitoring trial with repeated DCE-US exams.

Physical interpretation of TIC parameters derived from indicator dilution
If the amount of an indicator (in our case contrast microbubbles) is measured in a ROI, then the volumetric flow rate and blood volume can be deduced with the Stewart-Hamilton relationships [20] as

$$Q = \frac{X}{\int_0^\infty c(t)dt}, \qquad V = Q \times MTT,$$

where Q is the flow rate, X is the amount of the indicator, c is the concentration, V is the volume and t is time. The mean transit time is found from the following equation:

$$MTT = \frac{\int_0^\infty tc(t)dt}{\int_0^\infty c(t)dt}.$$

In ultrasound we measure image signal intensity of backscattered ultrasound from microbubbles, $I(t)$, and not concentration, $c(t)$. However, it has already been established that the intensity I is linearly proportional to concentration c at low microbubble concentration,

$$I(t) = \alpha \times c(t),$$

where a is a proportionality constant [21]. Thus, by measuring the average intensity in a ROI, and calculating the various parameters of **Table 1** we are able to deduce relative measures of blood flow in a ROI.

Main models
Various mathematical and empirical models have been developed from indicator dilution principles that model the flow of contrast microbubbles in the vasculature. The DCE-US TIC curves are fitted to these models in order to remove noise in the data, isolate the primary pass, and extract more reliably and reproducibly the hemodynamic parameters described in **Table 1**. In addition, with the mathematical models we are able to have closed form analytical solutions for MTT and t_p. A review of these models

parameter name	parameter symbol	units	explanation
time zero offset	t_0	(sec)	time from the UCA injection to the first appearance of any UCA signal within the ROI, corresponding to the point on the abscissa, where the TIC curve starts the uprise
time to peak	t_p	t_p (sec)	time from zero intensity to maximum intensity
wash-in time	WIT	(sec)	time from 5 % intensity to 95 % intensity
wash-out time	WOT	(sec)	time from maximum intensity to zero intensity during the wash-out phase
mean transit time	MTT	(sec)	the mean time taken by the bubbles to pass through the ROI. Mathematically it is the first moment of the fitted curve
time for full width half max	FWHM	(sec)	full-width at half-maximum (time between the half amplitude values in each side of the maximum or in other words time from the point of 50 % intensity in the upslope to 50 % in the downslope of the curve)
peak intensity	I_p	AIU	maximum value of the intensity in arbitrary units
area under the curve	AUC	AIU×sec	the area under the TIC curve

Table 1 A list of main bolus injection wash-in/wash-out parameter names, symbols, units, and explanations. Some of these same parameters are also shown in Fig. 1. In the literature more parameters may be found but they are finally all related to the ones listed below.

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and the underlying assumption for their applicability in DCE-US may be found in literature [22]. A short description of the main models is presented here.

Lognormal

Microbubbles traverse a ROI at different times, because they are dispersed through branching vessels, or due to laminar flow, or turbulence. A time-intensity curve is interpreted as the probability density function of transit time in a ROI. It specifies the amount of indicator particles that traverse through a ROI during a time interval. For a network of vessels with a large number of generations the flow distribution is a lognormal function. The Lognormal model for bolus injection of UCA is the most widely used at the present.

Diffusion with drift models (Local density random walk model – LDRW)

This model is the solution of the one dimensional diffusion with convection partial differential equation in the case of no special boundary conditions at the outlet. The movement of the indicator particles (UCA) is regarded as a longitudinal diffusion superimposed on a linear convection. This model produces very similar curves with the Lognormal model.

Gamma Variate

This model is obtained assuming constant blood flow and unidirectional tracer motion. The flow is modelled as series of homogeneous mixing compartments of equal volume. The simplicity of the Gamma Variate function has motivated various groups to employ it for fitting DCE-US TIC curves.

Lagged Normal Function

This model is based on the assumption that there are two compartments: a large vessel characterized by a Gaussian dispersion of the tracer transit times and a microvascular bed which is a homogeneous mixing compartment represented by a single exponential function.

The models described above produce very similar results and in fact it is often difficult to distinguish between them (**Fig. 2**, where the Lognormal, LDRW, and Gamma Variate models are fitted to DCE-US data).

Other models to obtain TIC curves were derived empirically, for instance using the least-square approach (Patent: WO/2008/053 268 entitled "Method and system for quantification of tumoral vascularization).

Disruption-replenishment analysis with infusion of UCA

With this technique, UCA is administered as a continuous infusion and a disruption-replenishment analysis is applied (**Fig. 3**). In essence, this technique relies on the application of a negative bolus and the quantification of the replenishment rate which is related to the regional flow rate. The initial rate and steady state of replenishment are related to flow and vascular (blood) volume, respectively. Models have been developed to describe the echo-signal dynamics during the replenishment phase, which account for the vessel network morphology and ultrasound beam characteristics.

Wei's mono-exponential model

In 1998, Wei et al. [18] were the first to introduce the method of disruption-replenishment and the development of the mono-exponential model,

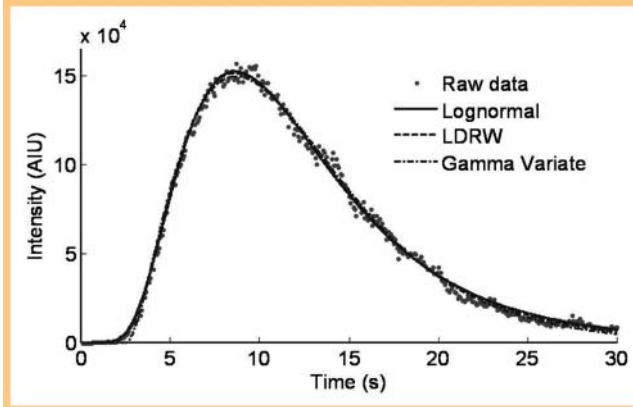

Abb. 2 Example of curve fitting of the Lognormal, LDRW, and Gamma Variate models on DCE-US data.

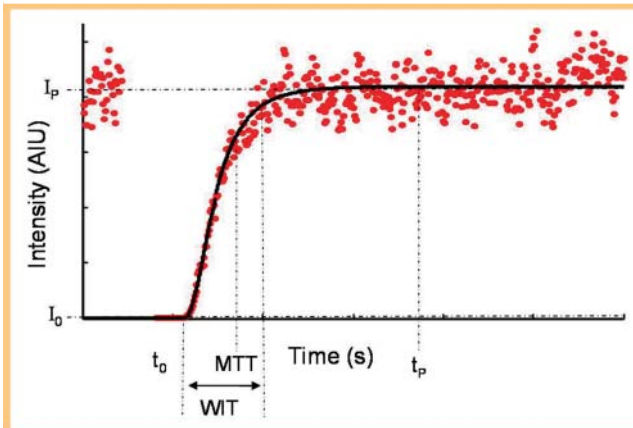

Abb. 3 Typical TIC for intravenous infusion of UCA with disruption-replenishment protocol and explanation of important parameters.

$$I(t) = A[1-\exp(-B\times t],$$

where $I(t)$ is the intensity of the signal in the ROI, the constant B is interpreted as flow velocity, A as relative blood volume, and $A\times B$ is an estimate of the flow rate. This mono-exponential model has been used extensively for myocardial perfusion quantification and to a very lesser degree in abdominal oncology applications. The main criticism of this model is that it does not account for the beam characteristics (neither destruction nor imaging) and thus it does not correctly model the wash-in of the agent in the ROI after destruction and instead of a sigmoid curve it predicts a sharp rising mono-exponential.

Krix's multi-vessel model

Krix et al. [16, 23, 24] used a similar approach as Wei, however, the modified formulas were no longer based on empiric assumptions and based on a multi-vessel model and it incorporated differences in the acoustic field properties when using high and low-MI imaging. This model was found to be at least equivalent to the mono-exponential model but it is nevertheless much less known.

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Arditi's-Hudson's perfusion model

An improvement to the Wei model was Arditi's model [14] which later on was further improved by Hudson et al. [15]. This model has 3 components that were not present in Wei's model: accounts for tissue perfusion through realistic microvascular geometry (Lognormal perfusion model), considers the ultrasound field properties of the destruction beam, and also considers the ultrasound imaging field. With the Arditi-Hudson model it is possible to calculate relative mean flow rate as

$$Q_r = A \times \bar{v},$$

where $\bar{v}$ is the mean flow velocity of a vascular network with a Lognormal distribution of velocities.

Equipment settings and patient based factors

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Equipment settings

The imaging parameters and specific settings greatly influence the quantification outcomes. All DCE-US examinations should be performed on systems with nonlinear imaging modes designed specifically for this purpose. The nonlinear imaging modes suppress most tissue echoes while detecting microbubbles echoes. Most systems have presets with all important imaging parameters set as defaults. However, the most important imaging parameters for quantification purposes are presented and discussed below.

Non-linear pulsing scheme

Various pulsing schemes exist that are designed specifically for suppressing tissue while detecting bubble echoes [25, 26]. Those are Pulse Inversion, Power Modulation, Power Modulated Pulse Inversion (also known as Cadence Pulse Sequencing), as well as some non-linear matched filtering schemes (such as FM chirps). The choice of the specific method belongs to the equipment manufacturer as it relies on many hardware issues normally not known to the clinician.

Dual image display format

The use of a dual image display format is essential in contrast studies and it is strongly recommended. In this display format, a tissue image (conventional fundamental) and a bubble-only contrast image (non-linear pulsing scheme) are displayed side-by-side. The need arises from the fact that before contrast administration the nonlinear image is totally black and it is impossible to keep the lesion of interest in the image plane. For quantitative studies, it is critical to maintain the transducer at the same place and avoid motion.

Frequency

The selection of the appropriate frequency depends on the type of transducer, the organ vascularity and the depth of the target. The optimal choice results from a compromise between sensitivity in the microbubble detection and resolution. As SonoVue® resonance frequency of microbubbles is around 1 – 2 MHz, the lowest transducer frequency provides the best acoustic response.

Acoustic power

Mechanical Index (MI)

The MI is chosen such that the maximum non-linear signal is produced while there is no (or very minimal) microbubble destruction. For most systems and most applications typically MI < 0.1 must be used. The fact that different manufacturers measure the MI with slightly different methods and use different non-linear pulsing scheme, introduces differences in the absolute value of the MI at which minimal microbubble destruction is observed. It is recommended that the clinicians are familiar with their own systems and verify the specific value of the MI for non-destructive imaging. A simple way of estimating whether there is microbubble destruction or not is to scan new image planes and if the perfused parenchyma "flashes" when first imaged, then it is recommended to reduce the MI until this phenomenon is eliminated. Some manufacturers report the acoustic power as a percentage of the maximum acoustic power emitted from the system. While scanning, it is mandatory to avoid attenuating structures such as bone or cartilage (particularly during intercostal scanning) that can reduce the local acoustic energy. The effect can be almost nonvisible when working on conventional B-mode imaging, due to the high acoustic energy, but the use of a very weak acoustic field for DCE-US will increase the effect of any additional attenuating structure.

Number and position of focal zones

Since the non-linear pulsing schemes use multiple firings to form a line (2 – 4 pulses) and the frame rate of contrast specific clinical presets is greatly compromised, only a single focal zone should be used. In addition, the focal zone should be placed deep in the image (at no closer than the level of the lesion or roughly at 2/3 of the image depth) as this would result in a more uniform acoustic field and hence uniform excitation of the bubbles everywhere in the scanning plane. However, some researchers have utilized a more superficial focal zone, just in front of the center of the lesion and no formal comparison of the results with different positions has been carried out.

Depth

The image depth is selected according to the clinical application to cover the organ of interest. In most cases a slightly longer than needed depth is advised to ensure that the focal zone is also at a deeper location for a uniform acoustic field. In addition, in cases where post-processing algorithm for respiratory gating is to be applied, deep structures such as the diaphragm in liver scanning are required to be included in the image.

Receive Gain

Since a very low MI imaging is used to avoid bubble destruction, the receive gain should be set to a high value to ensure the detection of the low amplitude microbubble signals. The receive gain is a combination of two machine controls: the 2 D gain knob and the TGCs (time gain compensation). The overall gain should be such that a "hint of noise" is uniformly observed throughout the image depth. The TGC setting should be set at the same (usually central) position if not otherwise stated. The same gain settings should be reproduced in every investigation in each lesion over time.

Dynamic Range (compression)

The dynamic range (referred to as compression in some systems) should be set to a relatively high value to avoid signal saturation which introduces errors in the quantification of various parameters. Ideally a value of about 40 dB (or greater) is recommended [21]. However, often in commercial systems the denoted value is not the actual one. Thus, selecting a high value of dynamic range (compression) from the available ones on the user interface of the

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scanner is a good idea. The high dynamic range may make the images look a little "flat" (low variations of grey) but nevertheless it is recommended for quantification.

Persistence

Since persistence involves varying degrees of temporal averaging of the image data it should be turned off for quantification. The TIC analysis involves the evaluation of the intensity at a specific time point. Thus, temporal averaging would introduce inaccuracies in the intensity values. By turning persistence off, a small degradation of the image aesthetics is observed. However, since the objective of quantification study is the accurate estimation of various hemodynamic related parameters, the small image degradation is acceptable.

Patient based factors

Posture, resting time, heart rate, blood pressure and other cardiac functions, body and ambient temperature as well as metabolic and other factors and environmental conditions may influence the kinetics of the contrast agents in a patient. In general, the supine posture and fasting for > 6 hours are usually recommended together with normal comfortable room temperature, despite the fact that no study had addressed specifically their role in DCE-US quantification. However other parameters such as blood pressure and heart rate are out of the operators' control. Clearly examinations will have variability in case of elevated body temperature or cardiac rate or output changes over different DCE-US sessions. It may be useful to keep detailed record of patient based settings and surrounding factors. This may help explain discrepancies in unexpected findings taken at different sessions during follow-up with an identical standardized approach. Most importantly the same plane has to be used in follow-up exams (acoustic window, probe position) to avoid evaluation of different parts of the lesion which is well-recognised to be inhomogenous in vascularity.

Image loops properties

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Linearized image data

Data for quantitative studies can be taken at various stages of the image processing chain. The use of digitized video data is possible, but suffers limitations and thus not recommended. The best way is to work directly on raw linear data [27], however, this option is not always available. Some ultrasound scanners offer the opportunity to save the DICOM data in a "native" format that allows accurate removal of the logarithmic compression; some others offer an approximate linearization algorithm. It is necessary to work with linearized data due to the linear relationship between the microbubble concentration and the signal intensity and also to be able combine the data with the models (which are not in logarithmic scale). It is important to keep all imaging (machine) parameters unchanged after the baseline scan to enable the comparison of the effects of therapy in subsequent scans.

Recording (length of loops)

A digital video-clip (in DICOM format) should be stored for review, documentation, and quantification to cover the wash-in and wash-out. In studies with bolus injections of UCA 30 sec to 3 min loops should be saved, depending on the specific application (2 – 3 min for liver, 30 sec – 1 min for kidney, 1 min for breast, etc.). Most studies focussing on AUC and the wash-out recorded 3 minutes [10]. In studies using infusion of UCA and desruption-replenishment protocol a shorter loop of the replenishment of the lesion or organ is sufficient (15 – 60 sec).

Motion compensation and respiratory gating

Respiratory motion is a major source of error in the quantification of DCE-US [9]. Ideally, the target should remain within the imaging plane during the whole acquisition. This is possible if the transducer is held in a stable position imaging a non-moving organ, such as prostate, breast, subcutaneous lesion. For the thyroid, the patient should avoid swallowing and maintain a superficial respiration. For abdominal organs like kidney and liver, the issue is more complex.

Motion compensation algorithms for 2 D imaging only work when there is no out of plane motion. When out of plane motion occurs, the utilization of motion compensation techniques may result in flawed quantification results. One implementation of respiratory gating suggests a post processing scheme which is performed by selecting a reference position for the diaphragm (on the tissue side image in systems that have dual imaging capabilities) and rejecting (manually or with a programmed algorithm) all frames where the diaphragm deviated [9, 28]. Respiratory gating offers a good solution for situations where out-of-plane motion has occurred. The use of a limited number of frames (taken when the target area is in-plane) instead of the whole clip, was shown to provide acceptable results working on video data only for some, but not all quantification parameters [29].

Available quantification software packages

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There are several different software packages available for DCE-US quantification. Some of them are implemented into ultrasound machines and some are accessible as stand alone software for workstation use. Among them there are differences concerning curve fitting algorithms, specific names of perfusion parameters, type of image data, and quantification machine settings. Almost all manufacturers offer their own solution; some software packages have more solid and extensively published works, whereas for others the published evidence is limited or even lacking.

Reproducibility

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Reproducibility of DCE-US clinically is clearly important as it will determine whether the technique can be applied into routine practice. At present published data suggest the variability associated with DCE-US is acceptable for future practices [7 – 9, 30]. Future clinical studies should always incorporate reproducibility data of the technique used.

Concluding remarks

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The DCE-US technique is cost effective, mobile, safe and repeatable. Results of recent clinical trials suggest that quantitative DCE-US may be useful in the assessment of response to vascular targeted therapies. The current article provides general information about the technique and parameters utilized in DCE-US quantification and recommendations on its use providing a standardised approach which may improve clinical management.

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