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Perfusion quantification using dynamic contrast-enhanced ultrasound: The impact of dynamic range and gain on time–intensity curves

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ABSTRACT

The objective of this study was to assess the impact of dynamic range and gain on perfusion quantification using linearized log-compressed data. An indicator-dilution experiment was developed with an in vitro flow phantom setup used with SonoVue contrast agent (Bracco SpA, Milan, Italy). Imaging was performed with a Philips iU22 scanner and a C5-1 curvilinear transducer using a contrast-specific nonlinear pulse sequence (power modulation) at 1.7 MHz. Clinical dynamic contrast-enhanced ultrasound image loops of liver tumors were also collected for preliminary validation of the in vitro findings. Time–intensity curves were extracted from image loops with two different approaches: from linearized log-compressed data and from linear (uncompressed) data. The error of time–intensity curve parameters derived from linearized log-compressed data (deviation from linear data) was found to be less than 2.1% and 5.4% for all studied parameters in the in vitro experiment and in the clinical study, respectively, when a high dynamic range setting (at least 50 dB on the iU22) is used. The gain must be carefully adjusted to ensure a high signal-to-noise ratio and to avoid signal saturation. From the time–intensity curve analysis it was also found that rise time of the bolus time–intensity curve is the least variable of all the studied time–intensity curve parameters.

1. Introduction

It is widely recognized that oncological, cardiovascular and inflammatory diseases are associated with altered regional and/or systemic perfusion, which if measured reproducibly may be important biomarkers for diagnostic and prognostic purposes. More recently there has been increasing interest in using dynamic contrast-enhanced ultrasound (DCE-US) to assess altered tissue perfusion. Ultrasound contrast agents, which consist of microbubbles, are routinely used clinically in Europe and Asia in the detection and characterization of focal liver tumors and in the monitoring of local ablative therapies. DCE-US is safe, portable, and produces images in real time [1,2]. The introduction of non-destructive low mechanical index (MI < 0.06) nonlinear imaging techniques, which take advantage of the highly nonlinear behavior of microbubbles, has allowed real-time imaging of tumor perfusion [3].

With the advent of novel therapies targeting tumor angiogenesis and vascularity over the last decade, the need for more reproducible quantitative techniques to assess more subtle tissue perfusion changes has emerged. Both computed tomography and magnetic resonance imaging studies can be enhanced with the injection of a contrast agent and be used to assess perfusion changes. Dynamic contrast-enhanced computed tomography (DCE-CT) and magnetic resonance imaging (DCE-MRI) have been applied to monitoring anti-vascular therapies in cancer patients [4,5]. One of the limitations of both modalities is that most contrast agents used leak freely into the interstitial space. As a consequence, quantitative analysis of DCE-CT and DCE-MRI perfusion studies cannot allow discrimination of flow and vascular permeability and neither of the two techniques has been applied into routine clinical practice to date. DCE-US may be more appropriately used in monitoring anti-angiogenic and anti-vascular therapies, as microbubbles are true intra-vascular agents, i.e. they do not leak into the interstitial space and should therefore enable true perfusion quantification. However very few methodologies and protocols for quantification of perfusion changes with DCE-US have been developed and validated to facilitate their implementation in clinical practice [6,7].

After a contrast bolus injection, time–intensity curves can be formed from DCE-US image loops. These curves may be fitted with mathematical models (usually from indicator-dilution theory)

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defined by a set of parameters related to tissue perfusion [8–11]. It is widely believed that user-adjustable scanner settings including MI, nonlinear pulse sequence, dynamic range, and gain may affect those parameters. However, in clinical practice, settings such as MI and nonlinear pulse sequence are usually left unchanged during patient follow-up, whilst dynamic range and gain may be changed, thereby limiting the effectiveness of any longitudinal quantitative DCE-US studies. There is also some controversy over the use of time–intensity curves derived from linear data versus linearized log-compressed data to calculate perfusion-related parameters [12–17]. With non-destructive low MI contrast imaging, the amplitude of backscattered signals from microbubbles is very low; clinical ultrasound scanners therefore operate at low dynamic range (typically between 10 and 30 dB) and compress the data logarithmically for better image presentation. However, if the log-compressed image data are to be quantified, such low dynamic range values may lead to signal saturation and hence prevent proper linearization of the log-compressed data.

The aim of this study was to assess the impact of ultrasound scanner settings, such as dynamic range and gain, on perfusion quantification using linearized log-compressed data in both an in vitro experiment and a clinical study. The error of time–intensity curve parameters extracted from linearized log-compressed data was estimated from comparisons of those parameters when extracted from linear data.

2. Materials and methods

2.1. In vitro experiment

2.1.1. Indicator-dilution model

An indicator-dilution experimental setup was developed, inspired by that described by Lucidarme [18], and is displayed in Fig. 1. The renal dialysis cartridge (model FX60M, Fresenius Medical Care, Bad Homburg, Germany) comprised 25.5 cm long capillaries of internal diameter 185 μm and with total capillary volume 74 ml. The input of the cartridge was connected to a tube that was connected to a 1 l reservoir. The output of the cartridge was connected to a tube running through a peristaltic pump (SP vario/PD 5101, Heidolph, Germany) which was maintaining a constant flow rate of 130 ml/min. There was no recirculation in the flow phantom. Degassed and deionized water at ambient temperature (25 °C) was used as the fluid in the experiment.

2.1.2. Contrast agent

The contrast agent used was SonoVue (Bracco SpA, Milan, Italy) which consists of a phospholipid shell containing sulphur hexafluoride, an inert gas. SonoVue was used in the in vitro experiment at it is presently the most widely used and clinically approved contrast agent [2]. It was also the agent used in the clinical study of the present work. The agent was prepared immediately prior to the experiment by mixing 25 mg of the lyophilised powder with 5 ml of saline, according to the manufacturer directions. It was delivered as a 0.05 ml bolus by the same operator to ensure reproducibility of injections.

2.1.3. Image acquisition

The cartridge was imaged with a Philips C5-1 curvilinear transducer connected to a Philips iU22 ultrasound scanner (Philips Healthcare, Andover, MA). The cartridge was immersed in a degassed and deionized water bath at ambient temperature so that the distance between the transducer and the cartridge was 9 cm, and thus the cartridge was at a typical depth for imaging with a C5-1 transducer. The transducer was positioned so that the image plane was perpendicular to the direction of the capillaries (transverse plane).

A contrast-specific nonlinear pulse sequence (power modulation) was used with a 1.7 MHz center frequency, 37% fractional

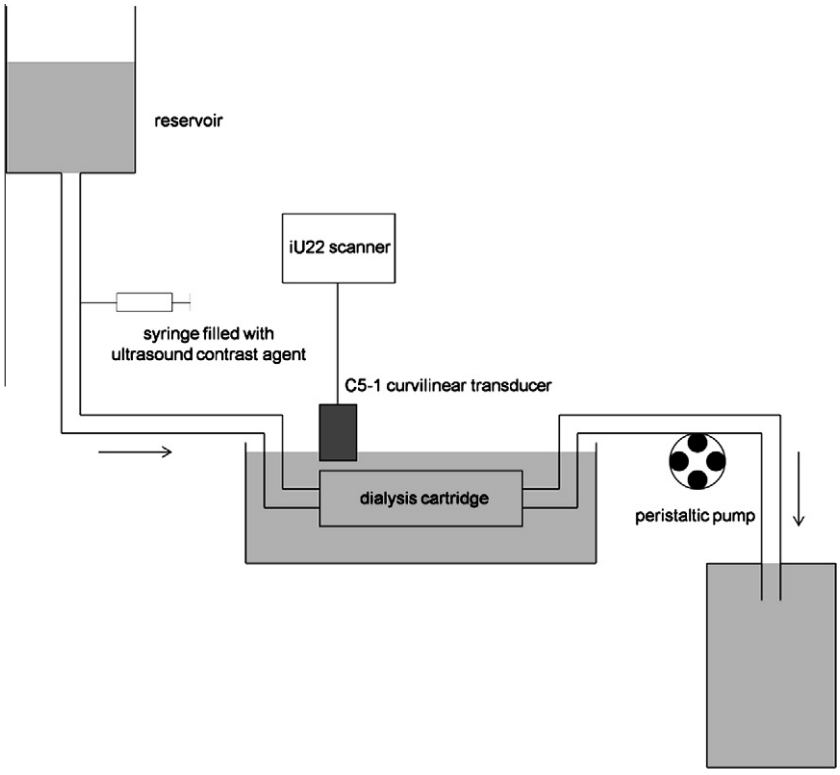

Fig. 1. In vitro experimental setup.

bandwidth acoustic pulse at an MI of 0.06. Gain values of 50, 55 (default value given the ultrasound scanner setup), 65, and 70 dB, and dynamic range values of 10, 20, and 30 dB, which corresponded, respectively, to the lowest, default, and highest dynamic range values, respectively, available to the user given the ultrasound scanner setup, were used. These dynamic range values corresponded to displayed compression values of 30, 40, and 50, respectively. In addition, a dynamic range value of 50 dB (not accessible to the user given the ultrasound scanner setup) was also used.

After a bolus injection, 1-min image loops were acquired as linear data (i.e. before logarithmic compression is applied in the ultrasound scanner). Each acquisition was repeated twice for averaging purposes. The capture tool provided by the manufacturer was run on a laptop computer connected to the ultrasound scanner via Ethernet connection. Log-compressed data were created offline by applying 10, 20, 30, and 50 dB dynamic range logarithmic compression to acquired linear data image loops. In the application of logarithmic compression some data are irreversibly discarded. This happens when the data lie outside the dynamic range used (this process is also referred to as "clipping"). Log-compressed data were then linearized by undoing the logarithmic compression to create linearized log-compressed data. The logarithmic compression law was provided by the manufacturer, and is expressed as $I_{\text{log-compressed}} = 10\log_{10}(\frac{I_{\text{linear}}}{I_{\text{ref}}})$, where I_{linear} is linear intensity, and I_{ref} is a reference linear intensity specific to the ultrasound scanner.

2.1.4. Image analysis

The image loops were transferred to a personal computer for further analysis. In all acquired image loops, a region of interest (ROI) was drawn so that it would encompass the cartridge cross-section.

Time–intensity curves were obtained by computing the mean intensity of pixels comprised within the ROI at each time point. Time–intensity curves were then fitted using a least square algorithm based on the Nelder–Mead method (Matlab fminsearch function, Matlab, The MathWorks, Natick, MA) with a local density random walk function described by [10,19]:

$$I(t) = AUC\frac{e^{\lambda}}{\mu}\sqrt{\frac{\mu}{(t-t_0)}\frac{\lambda}{2\pi}}\exp\left\{-\frac{1}{2}\lambda\left(\frac{\mu}{(t-t_0)}+\frac{(t-t_0)}{\mu}\right)\right\}+I_0$$

AUC is the area under the curve, λ^{-1} is the skewness of the curve, μ is the travel time between the entry and exit sites of the ROI at the carrier fluid velocity, t_0 is the bolus arrival time, and I_0 is the baseline intensity offset. Peak intensity (PI) was defined as max $\{I(t)\}$, rise time (RT) was defined as the time the intensity takes to increase from 5% of PI to 95% of PI, and mean transit time (MTT), which is defined as the average time the indicator takes to go from injection to detection site, was equal by definition to μ. For each tested combination of gain and dynamic range, the percent (%) error of estimated time–intensity curve parameters (using time–intensity curve parameter values computed with linear data as reference) was defined as follows (the error on RT for gain = 50 dB and dynamic range (DR) = 30 dB was used as an example):

$$\text{Error}_{\{\text{gain 50 dB, DR 30 dB}\}} = \frac{\left|RT_{\{\text{gain 50 dB, DR 30 dB}\}} - RT_{\{\text{gain 50 dB, linear data}\}}\right|}{RT_{\{\text{gain 50 dB, linear data}\}}}$$

2.2. Clinical study

The study protocol was approved by the local Research Ethics Committee. Informed consent was obtained from all subjects. Three subjects with biopsy proven colorectal cancer liver metastasis were enrolled. A DCE-US scan was performed with the subject in the supine position using a C5-1 transducer connected to an iU22 scanner. The same contrast-specific nonlinear pulse sequence and acoustic pulse as in the in vitro experiment were used. Gain was set at default value of 55 dB. Two-minute linear data image loops were acquired and transferred to a personal computer for further analysis. Log-compressed and linearized log-compressed data were created offline as described above for the in vitro experiment. Image analysis was identical to that performed in the vitro experiment, with the ROI drawn around the lesion of interest. For each dynamic range applied, mean and standard deviation of percent error of estimated time–intensity curve parameters over the three clinical cases were calculated.

3. Results

3.1. In vitro experiment

Results are displayed in Table 1. The effect of dynamic range on time–intensity curves at fixed gain of 55 dB is illustrated in Fig. 2. At fixed gain, the percent error of all studied time–intensity curve parameters increased when dynamic range decreased. At fixed dynamic range, the percent error of RT was minimal with a gain of 65 dB, while that of MTT, PI, and AUC was minimal with a gain of 55 dB. For all combinations of dynamic range and gain, the maximum percent error for rise time, mean transit time, peak intensity, and area under the curve was 4.7%, 6.2%, 95%, and 94%, respectively.

3.2. Clinical study

Results are displayed in Table 2. The effect of dynamic range on time–intensity curves at fixed gain of 55 dB is illustrated in Fig. 3. As in the in vitro experiment, the percent error of all studied time–intensity curve parameters increased when dynamic range decreased. The maximum mean percent error for rise time, mean transit time, peak intensity, and area under the curve was 6.2%, 16%, 97%, and 95%, respectively.

4. Discussion

In comparing linearized log-compressed data with linear data, the use of a dynamic range of 50 dB resulted in a minimum number of pixels with intensities outside the dynamic range (signal saturation) and reduces the error on all time–intensity curve parameters.

Table 1
[In vitro experiment] Percent error (mean ± standard deviation) of estimated time–intensity curve parameters (rise time (RT), mean transit time (MTT), peak intensity (PI), and area under the curve (AUC)) for various combinations of gain and dynamic range (DR).

Gain (dB)	DR (dB)	RT	MTT	PI	AUC
50	10	3.9 ± 0.2	6.2 ± 1.8	90 ± 12	89 ± 13
55	10	4.7 ± 3.7	1.7 ± 1.9	90 ± 16	88 ± 17
65	10	2.3 ± 0.4	5.8 ± 2.2	92 ± 14	91 ± 15
70	10	2.9 ± 1.4	6.2 ± 1.5	95 ± 21	94 ± 21
50	20	2.4 ± 0.1	3.7 ± 1.0	66 ± 13	65 ± 14
55	20	2.7 ± 1.1	1.7 ± 0.2	62 ± 17	61 ± 13
65	20	1.2 ± 1.0	3.6 ± 1.6	70 ± 14	69 ± 17
70	20	1.9 ± 0.9	3.7 ± 0.9	79 ± 20	78 ± 31
50	30	1.8 ± 0.1	2.4 ± 0.6	46 ± 23	44 ± 15
55	30	4.5 ± 3.9	1.2 ± 0.1	38 ± 15	36 ± 13
65	30	0.8 ± 0.4	2.4 ± 1.2	49 ± 16	48 ± 19
70	30	1.3 ± 0.9	2.4 ± 0.5	63 ± 20	63 ± 21
50	50	0.9 ± 0.4	1.2 ± 0.3	16 ± 12	15 ± 14
55	50	2.1 ± 1.7	0.6 ± 0.1	2.1 ± 2.0	1.0 ± 1.6
65	50	0.4 ± 0.5	1.2 ± 0.6	17 ± 9.1	16 ± 7.3
70	50	0.6 ± 0.1	1.2 ± 0.2	39 ± 19	38 ± 16

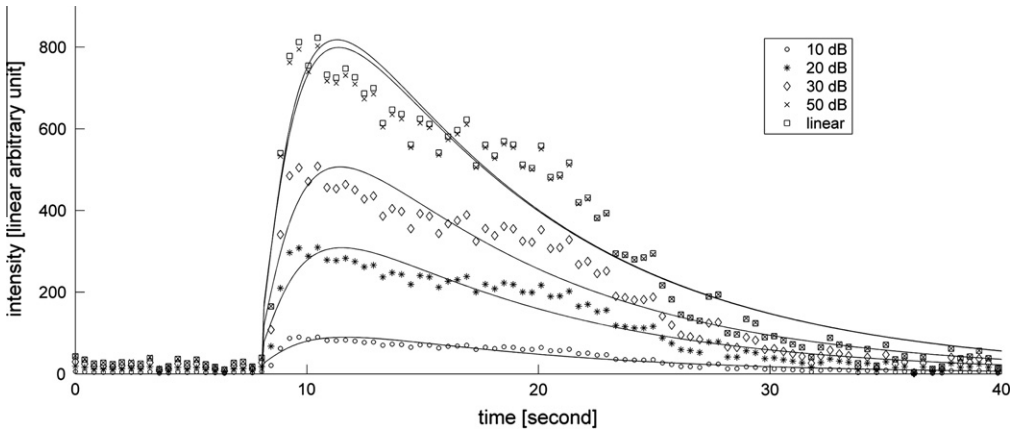

Fig. 2. [In vitro experiment] Effect of dynamic range on time–intensity curves at fixed gain of 55 dB.

Table 2
[clinical case studies] Percent error (mean ± standard deviation) of estimated time–intensity curve parameters (rise time (*RT*), mean transit time (MTT), peak intensity (PI), and area under the curve (AUC)) for various combinations of gain and dynamic range.

Gain (dB)	DR (dB)	*RT*	MTT	PI	AUC
55	10	6.2 ± 3.5	16 ± 5.4	97 ± 19	95 ± 18
55	20	4.2 ± 1.3	10 ± 4.2	81 ± 23	78 ± 29
55	30	2.4 ± 1.7	8.9 ± 4.5	45 ± 18	39 ± 16
55	50	1.4 ± 1.8	2.8 ± 3.1	5.4 ± 6.1	4.6 ± 5.3

As expected, the lower dynamic ranges result in more signal saturation. With a dynamic range of 50 dB and a gain of 55 dB, percent error for all studied parameters in the in vitro experiment was less than 2.1%. In the clinical study, a dynamic range of 50 dB (with the gain fixed at default value of 55 dB) led to lowest maximum percent error for all studied parameters of 5.4%. Such combinations of dynamic range and gain were best at preventing saturation while providing a sufficient signal-to-noise ratio. However given the ultrasound scanner setup, the maximum dynamic range setting accessible to the user was 30 dB. When using a dynamic range of 30 dB and a gain of 55 dB in the in vitro experiment, percent error for *RT* and MTT were still low (4.5 ± 3.9% and 1.2 ± 0.1%, respectively) whereas it increased substantially for PI and AUC (38 ± 15% and 36 ± 13%, respectively) due to the increased signal saturation in the logarithmic compression process. Similarly in the clinical study, a dynamic range of 30 dB (with the gain fixed at default value of 55 dB) led to low percent error for *RT* and MTT (2.4 ± 1.7% and 8.9 ± 4.5%, respectively) and much increased percent error for PI and AUC (45 ± 18% and 39 ± 16%, respectively).

For a quantification approach to be accepted in routine clinical practice, the derived parameters related to microvascular blood flow and volume must be robust to varying acquisition settings. Currently most clinical DCE-US exams are performed using low dynamic range settings (set as default by the manufacturer and typically between 10 and 30 dB) for display purposes. In addition, most clinical users also do not have access to linear data. Based on the above results, parameters such as peak intensity and area under the curve will be more prone to error caused by signal saturation. On the other hand, rise time and mean transit time are less influenced by dynamic range and will be less prone to error. These observations may be explained by the fact that both rise time and mean transit time are time-related parameters, i.e. they reflect temporal features of bolus kinetics, which are less correlated with the amount of contrast agent injected than amplitude-related parameters (peak intensity and area under the curve) are. Therefore time-related parameters are less impacted by signal saturation due to log-compression. The correlation of rise time and/or mean transit time with microvascular blood flow and volume is outside the scope of the present work and will be addressed in the future.

The selection of a high dynamic range (at least 50 dB) with clinical scanners that produce linearized log-compressed data for quantification purposes is suggested, since all parameters considered in this work had minimal deviations from those extracted from linear data when the highest dynamic range considered was applied. It is also important to realize that in order to properly lin-

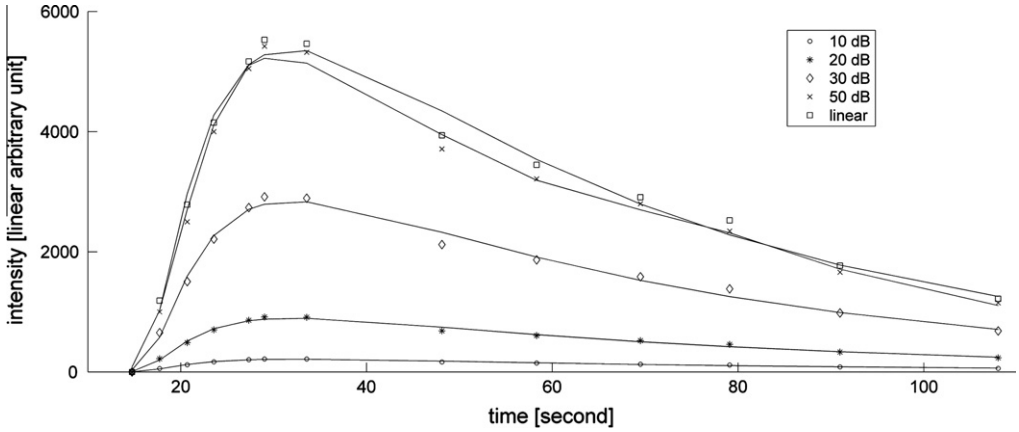

Fig. 3. [clinical study] Effect of dynamic range on time–intensity curves at fixed gain of 55 dB.

earize log-compressed data, one may use quantification software produced by ultrasound scanner manufacturers (e.g. Philips's QLAB, Toshiba's CHI-Q) which have access to how the logarithmic compression was applied. Another approach is to experimentally derive the linearization scheme with measurements from tissue phantoms.

While DCE-US image loops interpretation is used clinically for the detection and characterization of focal liver tumors, this study was intended to investigate the impact of ultrasound scanner settings on microvascular blood flow quantification with DCE-US. The clinical study was performed to confirm our in vitro experiment findings on dynamic range and gain settings suitable for quantification studies. Tumor perfusion quantification with DCE-US may be used to monitor therapeutic response to anti-angiogenic and anti-vascular therapies in cancer patients [6,7].

5. Conclusion

Linearized log-compressed data may be used for perfusion quantification as they are very close to linear data when a high dynamic range (at least 50 dB) is used and provided that the gain is set to limit saturation while a high signal-to-noise ratio is maintained. With current clinical ultrasound scanners operating at low dynamic range for better image presentation, rise time is the least variable of all the studied parameters.

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