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Dynamic contrast enhanced ultrasound for therapy monitoring

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ABSTRACT

Quantitative imaging is a crucial component of the assessment of therapies that target the vasculature of angiogenic or inflamed tissue. Dynamic contrast-enhanced ultrasound (DCE-US) using microbubble contrast offers the advantages of being sensitive to perfusion, non-invasive, cost effective and well suited to repeated use at the bedside. Uniquely, it employs an agent that is truly intravascular. This papers reviews the principles and methodology of DCE-US, especially as applied to anti-angiogenic cancer therapies. Reproducibility is an important attribute of such a monitoring method: results are discussed. More recent technical advances in parametric and 3D DCE-US imaging are also summarised and illustrated.

1. Introduction

The advent of a new generation of targeted or 'biological' therapeutic agents for cancer and a spectrum of other diseases has highlighted the need for noninvasive assessment of their effect. In many cases, anatomic imaging alone is inadequate and functional assessment is required [1]. Specifically, the imaging of blood flow and other microvascular parameters has a special role to play as the vasculature is often either the main or indirect target of these therapies. While for such interventions as thermal ablation, the question might simply be, 'Is there flow or not?', for anti-angiogenic and anti-inflammatory therapy the incremental effect on vascularisation needs to be measured. This is achieved by the quantification of tracer kinetics and is often known as Dynamic Contrast-Enhanced (DCE) imaging. The use of microbubbles to create DCE-US images has some obvious attractions: the procedure uses neither ionising radiation nor nephrotoxic contrast agents; microbubbles are a pure intravascular contrast agent and report exclusively on the vascular space; ultrasound imaging provides high framerates that can be used to tackle tissue motion problems; the method is cost-effective and suitable for repeated use; it is portable and can be used at the bedside of sick patients.

DCE-US continues to grow in its applications but is already showing itself to be a useful tool for monitoring the vascular effects of therapeutic agents. This review focuses on the methodology and its challenges, and the recent use of DCE-US to monitor changes induced by anti-angiogenic and anti-inflammatory therapies, both as a potential biomarker of response and as a tool to enable dose optimization of therapy in individual patients [2].

2. Methods of DCE-US imaging

Therapy monitoring with DCE-US is typically performed by measuring longitudinal changes in a given patient relative to a pre-treatment baseline evaluation. Parameters derived from these measurements which are sensitive to changes induced by vascular therapeutics are potential candidate imaging biomarkers of response. A burgeoning number of clinical trials have examined such candidate measurements [3–5] and produced an array of perfusion-related parameters.

These parameters can roughly be categorized as predominantly haemodynamic (e.g., perfusion, flow velocity) or predominantly morphological (e.g., blood volume, vascular heterogeneity, fraction of volume perfused), or a combination of the two (see Table 1). There has been considerable effort among investigators to identify which of these parameters are the most relevant for the purpose of monitoring therapy. While DCE-US can be implemented a bolus transit method similar to that employed X-ray CT or MRI, the unique ability of ultrasound to disrupt bubbles gives rise to a

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Table 1
Some measurable DCE-US parameters.

Haemodynamics	Vascular morphology	Combined
Peak enhancement	Vascular volume	Mean transit time
Flow velocity	Spatial heterogeneity	Transit-time distribution
Wash-in time/rate	Percent volume perfused	Parametric histograms
Wash-out time/rate		
Area under the bolus curve		
Perfusion		

second technique, referred to as the disruption-replenishment method. These two methods differ in technique and yield different measurements.

3. Bolus-transit method

Blood flow in tissue can be assessed within the image plane following the passage of a bolus injection of contrast agent, commonly administered into a peripheral vein. The characteristic wash-in and wash-out of the contrast enhancement is determined by the flow rates and volume of the vascular compartments that lie between the site of injection and the location of imaging (Fig. 1a). It is important to note that when a volume of tissue is imaged, the enhancement is also dependent on the vascular geometry in addition to the ultrasound machine settings and local beam characteristics [6,33]; these can be confounding factors when comparing patients and when comparing cancerous to normal tissue. Subsequently, a time-intensity signal is extracted from within a region of interest, often using commercially available software that ensures an image map linearly relating signal intensity to microbubble concentration [8]. Quantitative parameters are derived from the scan by fitting the time-intensity data with a number of available indicator-dilution models [7]. Characteristics of the curve including the peak intensity, wash-in/wash-out time, mean transit time (MTT) and area under the curve (AUC) are commonly used to describe the state of the tissue microvasculature and monitor its change with time and therapeutic intervention (Fig. 2a). Limitations of the bolus method include the uncertainty of the input function of bubble concentration to the region of interest caused by the spreading of the bolus during its transit to the measurement site and by variation in rate of injection if administered manually. Methods to deconvolve the arterial input function from the true tissue enhancement have been investigated [9,10]. In practice, the ultrasound imaging plane must remain in a single position for the entire study, so that studies employing a single bolus are also limited to a single plane. However, the single bolus method remains a widely used technique owing to its general simplicity of implementation, high contrast signal to noise ratio in most tissues of interest and its relative success as a therapy monitoring tool [11].

4. Constant infusion with disruption-replenishment

An alternative DCE-US method introduces the contrast agent into the venous circulation as a continuous, diluted infusion. With this technique, the systemic concentration of contrast agent will stabilize after approximately 1–2 min and will remain constant for the length of the investigation, typically 10–15 min. Perfusion and other vascular parameters are then assessed by a novel implementation of DCE-US, first described by Wei *et al.*,by disrupting the contrast agent in the plane of interest with a brief burst of high mechanical index ultrasound and metering the subsequent microbubble replenishment with time [12] (Fig. 1b). With replenishment times for most tissues typically requiring up to 10 s, flow measurements can be repeated in quick succession and multiple imaging planes can be quantified during a single dose examination [13]. Because the input function to this indicator dilution model is defined not by a bolus but by a brief disruption event in the tissue of interest, transit of the agent through the cardiopulmonary system no longer influences the results. Curve fitting models for the disruption-replenishment technique have evolved from a mono-exponential (which makes the incorrect assumption that the vascular network is a perfect mixing chamber) to models that account for fractal microvascular geometries [14,15], ultrasound field effects [16] and finally to comprehensive models that incorporate microvascular structure and ultrasound beam geometries throughout the scan field [17,18,29], with each development leading to improved measurement reproducibility [19] (Fig. 2b). In addition to measuring blood flow and blood volume, more recent models introduce a parameter that relates the shape of the

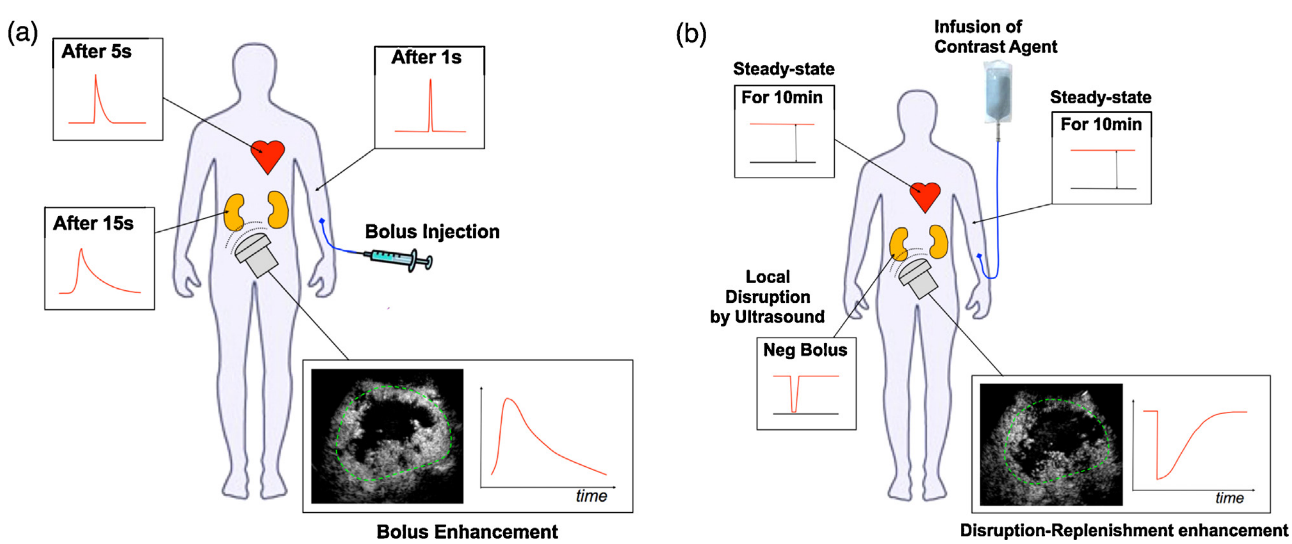

Fig. 1. DCE-US. Schematic representation of: (a) bolus injection of a microbubble contrast agent; and (b) infusion with disruption-replenishment. The injected bolus (a) undergoes spreading as it passes through the circulation from the injection site, creating a complex and generally unknown input function at the tumour, which must be imaged for 2–3 min to capture its passage. The disruption-replenishment technique (b) enables the creation of a spatially localised 'negative' bolus within the tumour itself. Because a steady state is established, repeated measurements on the same or adjacent tissue planes can be performed in rapid succession, with each measurement requiring less than 30 s.