DCE Measurement

Practicalities of performing Dynamic Contrast Enhanced MRI in clinical trials.

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This presentation is directed towards those individuals responsible for developing, implementing and evaluating DCE-MRI protocols in an early stage clinical trial setting. Particular emphasis is given to the challenges arising from implementing DCE-MRI protocols in the body.

Dynamic Contrast Enhanced MRI (DCE-MRI) is method used to probe the vascular properties of tissues. It is widely used in the assessment of novel cancer therapeutics which target specific tumour growth factors, in particular therapeutics designed to inhibit vascular endothelial growth factors (1,,2) or promote vascular disruption (3). Novel therapeutics may be administered as single agents or in combination with conventional treatments. An early image based indication that the novel therapeutic/combination are demonstrating activity is vital for the patient and for the development cycle of the drug (4). In oncology, early stage clinical trials patient numbers are small and it is therefore vital that any methodology employed to evaluate patient data in this setting is robust, sensitive and reproducible (5). Several of the key data acquisition processes required to enable DCE-MRI to meet these demands are developed below.

The following challenges in the implementation of DCE-MRI protocols in body are well recognised: patient motion, coverage, temporal sampling, pharmacokinetic model selection, arterial input function estimation, instrumental quality and stability. Although this list is not exhaustive, these are the major challenges and several approaches will be outlined that provide methods for addressing them.

Acquisition methodology

A DCE-MRI acquisition repeatedly samples, over a fixed period of time, the same tissue volume before, during and after the administration of a bolus of gadolinium contrast medium. Following data acquisition, signal changes induced by changes in T1 relaxation following the contrast bolus are firstly converted into changes in time varying Gd concentrations and subsequently, through the use pharmacokinetics models, into quantitative microvasular properties (6, 7). The DCE-MRI acquisition is in practice determined by several, sometimes conflicting, requirements, including the trade off between the volume coverage and the rate of temporal sampling required to provide data with sufficient support for pharmacokinetic modelling. In addition to dynamic data, pre-contrast (and or post- contrast) reference data (8, 9,) are required to enable the estimation of the initial tissue T1 relaxation time, which then permits

the conversion of the DCE-MRI signal intensities into Gd concentrations. The choice of acquisition technique is largely dependent of factors such as coverage required, temporal sampling rate, single or multi-centre trial sites and magnetic field strength. Currently 3D spoiled gradient echo sequences are the recommended method of choice for DCE-MRI as these are readily available on all clinical scanners (5, 10).

Estimation of an arterial input function (AIF).

A core requirement for the pharmacokinetic modelling of DCE-MRI data is an accurate arterial input function (AIF) ideally derived from the same DCE-MRI data. In practices, this is often a challenge as a result either of the location of the target lesion or the measurement method used to acquire the AIF. Acquisition-related factors leading to poor AIF estimates include poor temporal resolution (>3s) per data sample, flow sensitivity of the method of acquisition and poor excitation. As a result of these challenges, alternative methods have been employed, among them the use of a population-derived AIF (11) or additional acquisition strategies employing a measurement of a pre-bolus using higher temporal sampling (12).

Tackling Motion

Various forms of patient motion occur (respiration, peristalsis, swallowing) during the DCE-MRI acquisition which can corrupt the data unless techniques are employed to mitigate their effects. In practice, it is not possible to select fixed lesions particularly in the case of liver or lung disease. DCE-MRI acquisitions acquired during respiration will inevitably suffer from both mis-registration and blurring, which impact on post processing and pharmacokinetic modelling. Coronal or sagittal acquisitions are favourable acquisition planes in DCE-MRI studies in the body as motion occurs predominately in-plane and this aids subsequent post-processing. Image registration of DCE-MRI data is still an area of development, with software tools for registration of DCE-MRI data still not widely available or validated (13, 14). An alternative strategy is to acquire DCE-MRI data in multiple sequential breath-holding in expiration (15). This acquisition strategy eliminates blurring of the acquired data and reduces the challenge of aligning the DCE-MRI data volumes prior to pharmacokinetic modelling (16).

Quality Assurance

A number of factors may adversely impact on the quality of DCE-MRI derived data; these may be scanner dependent and may involve lack of consistency in patient set up, difficulty in matching anatomical locations over sequential studies and challenges in defining the regions of interest for analysis. All of these factors require both assessment and control procedures. Quality assurance is an essential element of the preparation and development of DCE-MRI protocols. It is vital that protocols are tested on both test objects and volunteers as part of a validation process which has to be completed before the commencement of the trial. Follow-up quality assurance during the trial is also a vital part of the clinical trial. Test objects should be able to

provide information on the stability of the MR scanner over the duration of the DCE-MRI protocol, the accuracy of the T1 estimates (derived from the static and dynamic data), geometric distortion over large field of view, and the excitation slice profile (5, 10). At field strengths above 1.5T B1 variation can be problematic for T1 estimation methods based on variable flip approaches. As a consequence of BI variations encountered at higher static fields >3.0T most clinical trials are conducted at 1.5T. For studies conducted at 3.0T it may be necessary to correct for B1 variations (17).

In summary several, of the major challenges in implementing DCE-MRI protocols in the body in particular those associated with scanner qualification, motion and AIF estimation can be overcome in routine practices, provided appropriate steps are taken and staff are appropriately trained to recognise the problems that can occur.

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