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Mini Review

Dynamic Contrast Enhancement MRI Studies Using Low-Dose Gadolinium-Based Contrast Agents

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The theory for the use of paramagnetic agents to measure tissue perfusion is based on two primary mechanisms of image contrast, relaxivity and susceptibility effects [1,2]. Relaxivity effects result from dipolar enhancement of T1 and T2 rates. Because tissue T1 relaxation rates are intrinsically smaller, the dominant effect is shortening of T1 relaxation times. The second mechanism of image contrast is the variation in tissue magnetic field produced by heterogeneous distribution of high magnetic susceptibility agents. Quantitation of tissue perfusion requires a detailed understanding of the relation between contrast agent concentration and associated MR signal changes. If this relationship is known, tracer kinetic modeling can be used to calculate regional cerebral blood flow (rCBF) and blood volume (rCBV).

Many workers have modeled the dynamic enhancement data that can be generated by repeated dynamic contrast enhanced (DCE) MR imaging of tissue after injection of Gd-labeled tracers. A set of T1-weighted (T1W) images is acquired, starting before a short (bolus) injection, and continued as uptake by the tissue and usually washout from the tissue are observed. The signal in a region of interest or pixel can give information about blood flow, capillary leakage, and related physiological parameters. A variety of quantities (some of them physiologic) have been estimated, e.g. fractional plasma volume (v_p), transfer constant (K^{trans}), and the fractional volume of extravascular extracellular space (*ve*) [3].

Gadolinium (Gd)-based paramagnetic contrast agents are relatively safe when used in clinically recommended doses. However, with the rapidly expanding body of literature linking Gd-based paramagnetic contrast agents and nephrogenic systemic fibrosis (NSF), awareness of the potential side effects and adverse reactions from Gd is now an important requirement for practicing radiologists [4]. In this new era with emerging clinical and experimental evidence of brain gadolinium deposition in those with repeated exposure, these safety assumptions are once again brought into question [5]. The common clinical dosage for GBCAs is 0.1 mmol per kilogram of body weight, which has a very high benefit-to-risk ratio [6]. A higher GBCA dose leads to better brain lesion detection [7], but a concern is the dose-dependent long-term retention of gadolinium in tissue, especially after injection of less thermodynamically stable (ie, linear) GBCAs [8]. Thus, medical agencies (the European Medical Agency, the Food and Drug Administration in the United States, the Pharmaceutical and Medical Devices Agency in Japan) have recommended limiting the injected dose [6].

Alternatives, manganese and iron oxide contrast agents can be used to replace GBCA in a number of MRI examinations, but gadolinium remains a strong candidate when properly indicated. Higher relaxivity is classically obtained by using a higher molecular weight of the molecule to reduce the tumbling rate of the gadolinium chelate. However, because of the larger molecular weight, the distribution volume of these compounds is reduced, and this leads to reduced accessibility to some pathology [6]. Gadopiclenol at 0.05 mmol/kg yielded comparable change in contrast-to-noise ratio and morphologic characterization of brain tumors compared with gadobenate, gadoterate, or gadobutrol at 0.1 mmol/kg [9]. Since both kidney risk, e.g. NSF, and long term Gd deposition are dose-

dependent, to limit the volume of administered GBCA was highly recommended. Thereafter, we are reviewing those studies where lower dose GBCA was used clinically for the DCE-MRI.

Hacklander, et al. employed one eighth of standard dose, i.e. 1 mmol of gadopentetate dimeglumine diluted in 10 ml saline for mapping relative cerebral blood volume, rCBV, in two patients. The results agree with those obtained by nuclear medicine techniques [10,11]. In another study, single-slice brain and neck images were rapidly acquired during the passage of a small (1/10th of normal dose) bolus of contrast. Parametric images, absolute CBF, CBV and time to peak (TTP) were constructed from the MR data by extracting the bolus transit curve for the brain and the peak arterial input curve from the carotid vessels in the neck. 24 patients with Acute stroke were studied. Results showed that the technique provided a reproducible measure of relative CBF, CBV, and TTP [12].

A dual temporal resolution (DTR) DCE-MRI were proposed comprising a low-dose prebolus for estimating the AIF, and a separate standard dose bolus for the TRF, DTR approaches were used to improve the quality of AIF and perfusion measurements [13]. Canet, et al. (1995) used a peripheral intravenous (i.v.) injection of a gadolinium (Gd) chelate to obtain a well-characterized LV time-intensity curve. The results showed that with high temporal resolution T1-weighted MR imaging and a low dose of Gd chelate, i.e., one-tenth of the standard dose, is sufficient given the cardio-vascular input function. In addition, the low-dose DCE MRI series better preserved the linear relationship between dose and tissue enhancement and free of truncation of the bolus peak of MR signal due to contrast saturation [14, 15].

Interestingly, the low dose high temporal resolution (LDHT) prebolus DCE-MRI itself can potentially be used solely for kinetic parametric mapping. Baxter, et al. (2009) used it as a means to improve the likelihood of capturing MR images during the optimal phases of liver enhancement [16]. The authors routinely perform a timing bolus sequence using a low-dose, i.e. a small bolus of 0.02 mmol of intravenous gadolinium contrast to determine appropriate scan delays for the subsequent full-dose gadolinium enhanced acquisitions. Liver perfusion images, including arterial fraction, arterial flow, portal flow, distribution volume and mean transit-time, were calculated from patients with Cirrhosis and compared with controls. The results showed that it is feasible to obtain potentially useful hepatic perfusion parameters from prebolus DCE MR images.

A high temporal resolution (time per frame is 1.0 s) sequence with a low dose (LDHT) prebolus (0.02 mmol/kg) DCE MRI was acquired to allow calculation of pharmacokinetic parametric parameters in a patients with type 2 neurofibromatosis. Results showed that biomarkers from DCE-MRI, e.g. K^{trans} etc. of vestibular schwannomas, were predictive of tumor volume response to inhibition of vascular endothelial growth factor inhibition. [17]. With the use of the LDHT, a new method based on the microsphere principle, for estimation of absolute CBF using a low-dose high temporal T1W DCE MRI acquisition was developed [18]. In vivo application of this method showed that the CBF maps displayed excellent GM-WM flow contrast using a much smaller dose of GBCA (0.02 mmol/kg). The typical test–retest coefficient of variation observed in this study suggests that the T1W DCE MRI measured CBF has sufficient reproducibility to be used in longitudinal studies, especially if large changes due to therapeutic intervention are expected.

Most of the LDHT DCE was acquired with high temporal but low spatial resolution. A DCE-MRI technique that can provide both high spatio-temporal resolution and whole-brain coverage for quantitative microvascular analysis is highly desirable but currently challenging to achieve. Efforts have been made seeking to develop a novel DTR DCE-MRI- based methodology for deriving accurate, whole-brain high-spatial resolution microvascular parameters [19]. Dual injection DTR DCE-MRI was performed and composite high-temporal and high-spatial resolution tissue gadolinium-based-contrast agent (GBCA) concentration curves were constructed. The high-temporal but low-spatial resolution first-pass GBCA concentration curves were then reconstructed to higher spatial resolution using a process called LEGATOS. The accuracy of kinetic parameters (K^{trans}, v_p, and v_e) derived using LEGATOS was evaluated in 17 patients with vestibular schwannoma (VS) and 13 patients with glioblastoma. Tissue from 15 tumors (VS) was examined with markers for microvessels (CD31) and cell density (hematoxylin and eosin [H&E]). The results showed that LEGATOS derived parameter maps offered superior spatial resolution and improved parameter accuracy compared to the use of high-temporal resolution data alone and other high-spatial resolution approaches, and correlated with tissue markers of vascularity and cell density ($P \leq 0.006$). The LEGATOS method was stated capable of generating accurate, high-spatial resolution microvascular parameter estimates from DCE-MRI.

Gong, et al. (2018) proposed a deep learning method. Results showed that the gadolinium reduced 10-fold while preserving contrast information and avoiding significant image quality degradation. The issuance of U.S. Patent has been announced very recently [21]. We may look forward to seeing that the low-dose DCE-MRIs enhanced by such AI driven technique can be used to generate high temporal resolution perfusion-permeability parametric images with an accuracy equivalent to those from other state-of-arts techniques, such as the LEGATOS [19] etc.

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