# Did You Know?
## APT CEST Imaging

### Contrast agents for MRI : limitations and concerns

Magnetic resonance (MR) imaging is well known for its noninvasiveness and abundance of image contrasts. Conventional MRI and perfusion MRI are developed and used for differential diagnosis. The imaging of brain tumors has significantly improved with the use of magnetic resonance techniques. Conventional MR imaging provides mainly anatomic or structural information about the brain. Still, conventional MR techniques continue to have important limitations for example, in distinguishing high-grade from low-grade tumors, determine exact limits of tumor extension, and discriminate between recurrent tumor and radiation necrosis.

The vascular abnormalities in brain tumors and altered flow dynamics lead to changes in blood volume and flow, which are exploited in MR perfusion imaging.

T2* dynamic susceptibility imaging is a very common perfusion technique used for brain tumor imaging. The T2* effects of gadolinium contrast agents (GBCAs) result in decreased signal intensity during the passage of gadolinium. This technique is widely used, rapid and has robust signal changes that gives a significant result in brain imaging.

No doubt Gadolinium contrast injections improve diagnostic accuracy in imaging. On the other hand, in recent years one of the biggest concerns in radiology was the safety of GBCAs used in MRI (see DYN N°13, April 2017). More and more radiologists are concerned about gadolinium deposition and possible effects of gadolinium toxicity and side effects. In July 2017, the European Medicines Agency (EMA) issued a final opinion that recommended restricting the use of some linear gadolinium-based contrast agents (GBCAs) and suspending the marketing authorizations of others, citing concerns about gadolinium deposition (Ref. 1).

The logical conclusion of this concern was the search for novel image contrasts in MR research community. Novel image contrasts have been developed by exploiting different aspects: physical or structural properties (diffusion-weighted imaging), MR elastography; functional properties (perfusion, BOLD, resting state fMRI, etc.); and chemical composition (MR spectroscopy, chemical exchange saturation transfer (CEST).

### CEST MRI: Principles and applications

CEST has emerged as a novel MRI contrast mechanism that is well suited for molecular imaging studies. This new mechanism can be used to detect small amounts of chemical species of interest through saturation of their labile protons, allowing a wide range of applications (Ref. 2). In CEST, magnetization is transferred from other molecules to water molecules, so that the saturation effect (i.e., signal reduction) that was originally on the targeted species can instead be observed on water. The requirement for this transfer to take place is that the chemical species must have in its structure a $_1$H proton that is exchangeable with those of water (Figure 1A).

As the chemical species is usually present in very limited quantities compared to water ($10^{-5}$ ~$10^{-6}$), no noticeable signal change would be observed if a single transfer took place (Figure 1B-C). The core feature of CEST is the continuous transfer of excited $_1$H protons, leading to a buildup of saturation in water (Figure 1D). Indeed, when exchanging a saturated proton with water, that proton will be replaced with an unsaturated $_1$H proton from water, which can in turn be saturated for another transfer. In this way, the concentration of the targeted species can be indirectly measured by the decrease of water signal, easily detected by the classic MR imaging sequences (Figure 1E). Clinically, most CEST applications focus on those metabolites that can be found in the human body or chemical substances that can be externally administrated.

**In this article we will talk about the most common type of CEST imaging Amide CEST that is known as amide proton transfer (APT).**

The last provides the most stable and sensitive detection compared to other diaCEST (classified by their chemical shifts as diamagnetic) imaging in vivo at 3 T. APT requires little power and has the benefit of a high concentration of total amide protons, allowing detection in vivo in animals and humans. The major known contributors to APT are the proteins and peptides of the tissue. The main applications reported for APT are the detection of cancer and ischemic stroke. The APT in tumors is positive, while an opposite effect is found in acute ischemia. In addition, APT has been demonstrated for tumor grading, differentiation of tumor from edema, and separation of tumor progression from radiation necrosis. APT imaging is advantageous for ischemic stroke and relies on pH level: reduced pH in the ischemic region leads to lowered APT exchange rate, and as a result, a decrease in CEST is observed. The advantage of APT imaging of ischemic stroke is detection in the acute stage due to its high sensitivity to pH changes.

APT-MRI is also showing potential for imaging cancer through an increase in cellular protein/peptide content of malignant cells with respect to normal tissue. It can be applied not only in brain tumors but also in the breast and prostate cancer detection. So that APT imaging offers a new imaging modality for MRI studies of diseases.

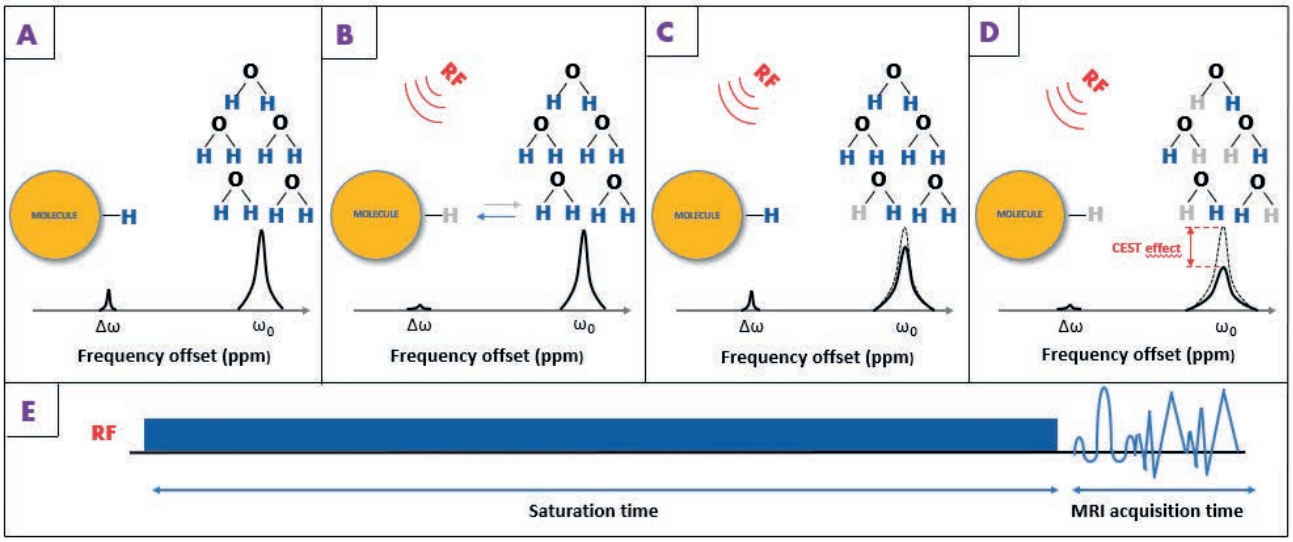


**Figure 1** CEST effect and imaging acquisition sequence. Image adapted from Prof. Xavier Golay, ECR 2017.

## In Olea Sphere®

Olea Medical® is one of the partners of the Horizon 2020 GLINT project (GlucoCEST Imaging in Neuroplastic Tumors), aiming at developing new CEST-based tools for more accurate and reliable cancer diagnosis tools (http://www.glint-project.eu/). One of the aims of Olea Medical® in the project is to develop a CEST Application in Olea Sphere® - using its dedicated Software Development Kit (SDK) – able to process and compare the clinical/preclinical data of different partners, based on different CEST methodologies and protocols. With this idea in mind and considering what is feasible in the clinical field, Olea Medical® is implementing different methodologies and alternative metrics that can improve as much as possible the quality of CEST signal, especially on 3T devices.

One of the dedicated plug-ins of Olea CEST Application aims at processing APT data.

The figure below shows a processed clinical example (Figure 2). APT-weighted image (left) and gadolinium-enhanced T1-weighted image (right) of a patient with an anaplastic Grade 3 astrocytoma, IDH mutant with ATRX loss, and retained 1p/19q.

The images were acquired by Sotirios Bisdas and his Clinical Scientists team (University College London) using a 3T MRI Scanner and were processed using Olea Sphere® CEST Application.

The CEST acquisitions were B0 and B1 corrected. Finally, one of the enhanced metrics proposed in Olea Sphere® CEST Application was applied to generate the APT-weighted image (left). The higher CEST signal intensity is given by the proteins and peptides of the brain astrocytoma on the left temporal lobe (green color). Noteworthy, the conventional MRI findings did suggest a low malignancy tumor but the CEST acts complementary and clearly indicates metabolic activity consistent with higher grade astrocytoma.

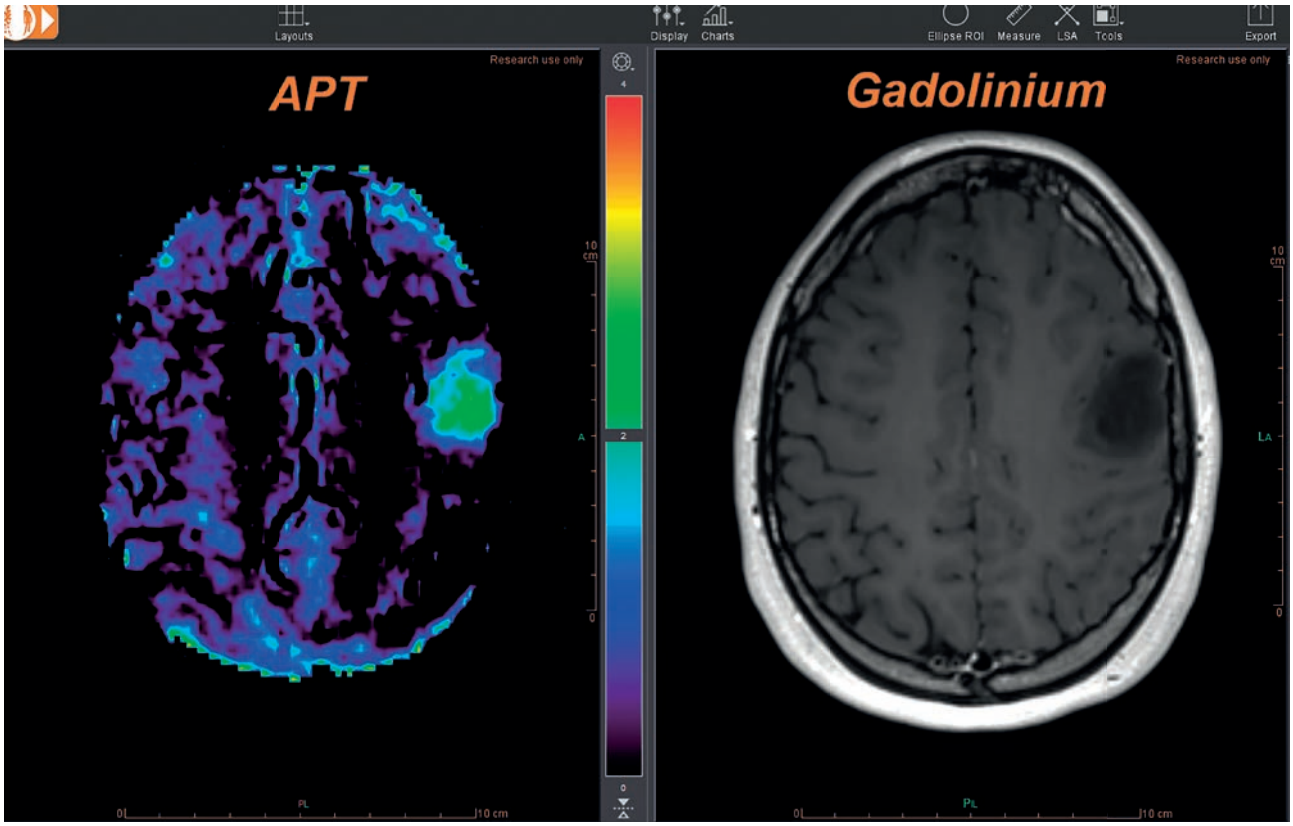


**Figure 2** APT vs Gadolinium at 3T. Images acquried by Sotirios Bisdas at his Clinical Scientific Team (UCL) and processed using Olea Sphere® CEST Application.


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## References


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