Towards robust glucose chemical exchange saturation transfer imaging in humans at 3 T: Arterial input function measurements and the effects of infusion time

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Funding information
National Institutes of Health, Grant/Award Number: RO1 EB019934; Regional Research Funding, Grant/Award Number: F2018/1490; Swedish Brain Foundation, Grant/Award Number: FO2017–0236; Swedish Cancer Society, Grant/Award Numbers: CAN 2018/550, CAN 2018/468, CAN 2015/251; Swedish Research Council, Grant/Award Numbers: 2019–01162, 2017–00995, 2015–04170; Johns Hopkins University; Lund University

Dynamic glucose-enhanced (DGE) magnetic resonance imaging (MRI) has shown potential for tumor imaging using D-glucose as a biodegradable contrast agent. The DGE signal change is small at 3 T (around 1%) and accurate detection is hampered by motion. The intravenous D-glucose injection is associated with transient side effects that can indirectly generate subject movements. In this study, the aim was to study DGE arterial input functions (AIFs) in healthy volunteers at 3 T for different scanning protocols, as a step towards making the glucose chemical exchange saturation transfer (glucoCEST) protocol more robust. Two different infusion durations (1.5 and 4.0 min) and saturation frequency offsets (1.2 and 2.0 ppm) were used. The effect of subject motion on the DGE signal was studied by using motion estimates retrieved from standard retrospective motion correction to create pseudo-DGE maps, where the apparent DGE signal changes were entirely caused by motion. Furthermore, the DGE AIFs were compared with venous blood glucose levels. A significant difference (p = 0.03) between arterial baseline and postinfusion DGE signal was found after D-glucose infusion. The results indicate that the measured DGE AIF signal change depends on both motion and blood glucose concentration change, emphasizing the need for sufficient motion correction in glucoCEST imaging. Finally, we conclude that a longer infusion duration (e.g. 3–4 min) should preferably be used in glucoCEST

Abbreviations used: AIF, arterial input function; AUC, area under curve; BGL, blood glucose level; CEST, chemical exchange saturation transfer; CSF, cerebrospinal fluid; DGE, dynamic glucose-enhanced; DSC, dynamic susceptibility contrast; MTR, magnetization transfer ratio; PVC, peripheral venous catheter; ROI, region of interest; WM, white matter.

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INTRODUCTION

Chemical exchange saturation transfer (CEST) MRI and chemical exchange sensitive spin lock (CESL) MRI, using D-glucose or glucose analogs as a contrast agent, have shown potential in tumor imaging. The CEST principle allows for a compound present in low concentrations to be detected through its chemical exchange with water after radio-frequency saturation of the exchanging protons. In a typical glucose CEST (glucoCEST) experiment, glucose is administered intravenously, followed by registration of the change in MR signal over time, an approach referred to as dynamic glucose-enhanced (DGE) MRI.

GlucoCEST has been proposed as a future alternative or complement to perfusion imaging using gadolinium because information about microvasculature, blood–brain barrier permeability, and D-glucose uptake can be obtained. Knutsson et al. showed that it is feasible to measure arterial input functions (AIFs) using glucoCEST data acquired in healthy humans at 7 T. The CEST effect size benefits from higher magnetic field strengths, such as 7 T, because T1 of tissue and blood water protons increases with magnetic field strength, allowing the saturation to remain for a longer period. Additionally, the chemical shift in Hertz increases with field strength, which enhances the separation of the D-glucose hydroxyl proton resonances and the water protons, thus reducing the interference from direct water saturation. At lower field strengths, the fast exchange between the hydroxyl protons in D-glucose and water protons leads to coalescence of the hydroxyl and water proton resonances, further reducing the signal change. Hence, while translation to lower clinical field strengths is ongoing and relevant, it is challenging due to the lower CEST effect.

The exchanging hydroxyl protons in D-glucose attenuate the water signal when saturation is applied to any of their resonance frequencies (from approximately 1 to 3 ppm relative to water). Subtraction of images acquired after D-glucose administration from the baseline images enables detection of the signal difference caused by the increase in D-glucose concentration. This approach will, in contrast to magnetization transfer ratio (MTR) asymmetry analysis, be enhanced by the D-glucose concentration-dependent increase in transverse relaxation rate, which is a favorable aspect of DGE imaging. Another advantage with this difference method is that only saturation at a single offset frequency is required, which will increase temporal resolution compared with dynamic collection of a full or even partial Z-spectrum.

According to simulations, the arterial DGE signal change is expected to be around 1% at 3 T, depending on saturation strength subject to B1 and frequency offset. Patient movement can induce signal changes of the same order of magnitude as the expected CEST signal at tissue boundaries, leading to a "pseudo-CEST effect". Motion correction and dynamic B0 correction are therefore important issues to be resolved for reliable DGE imaging.

D-glucose is promising as a biodegradable contrast agent, but an intravenous D-glucose injection does not come entirely without (transient) side effects. Both sensory effects and physiological responses have been reported. The sensory effects reported in previous glucoCEST studies include a sugary taste in the mouth, a warm or pulsating feeling at the injection site and in the head and crotch, as well as an urge to urinate. Physiological responses include vessel dilatation and volumetric changes of the ventricles. The sensory side effects are unpleasant for the subject and may, as a consequence, generate movements. The physiological changes can produce DGE signal changes that are not related to the CEST effect, which complicates the DGE MRI interpretation.

The typical D-glucose infusions used in previous glucoCEST/CESL experiments have ranged from around 30 s to 2 min in duration, using doses of either 50 mL of 50% w/v dextrose or 100 mL of 20% w/v dextrose. In a recent glucoCEST experiment, Kim et al. used a clamp infusion of 20% dextrose based on the method by DeFronzo et al. By adjusting individual D-glucose infusion rates, the blood glucose level (BGL) was raised to hyperglycemic levels and stabilized. This infusion method provides high stability of BGLs but is time consuming. The time required to reach the targeted plasma glucose level was up to 12 min. An earlier study on insulin response showed that a slower D-glucose infusion rate gives a reduced insulin response without affecting the maximum BGL. While a fast injection of contrast agent is often desired for kinetics assessment in bolus tracking studies, for example, dynamic susceptibility contrast (DSC) MRI, it is of interest to investigate whether a 4-min infusion duration could reduce unwanted injection-related effects, without deteriorating the DGE image quality, as a step towards an optimized glucoCEST protocol.

The aim of this study was to collect glucoCEST images using different scanning protocols at 3 T, including two different infusion durations (1.5 and 4.0 min) and saturation frequency offsets (1.2 and 2.0 ppm), and to compare the arterial DGE signal change with the change in venous blood glucose level (ΔBGL) in healthy volunteers.
2 | METHODS

2.1 | Subjects and MR image acquisition

All data acquisitions were performed at Skåne University Hospital, Lund, Sweden. The project was approved by the local ethics committee (The Regional Ethical Review Board in Lund, EPN 2017/673) and written informed consent was obtained from all subjects. Exclusion criteria were sensitivity for D-glucose (diabetes mellitus, sickle cell disease, and blood iron deficiency). Nine healthy volunteers (two males and seven females, aged 22–51 years) were scanned on a 3 T MAGNETOM Prisma (Siemens Healthcare, Erlangen, Germany) with a 20-channel head coil (Siemens). Morphologic images of each healthy volunteer (subject) were examined by an experienced neuroradiologist (PCS) to exclude pathology.

Seven subjects fasted for 4–6 h before the examination as recommended to stabilize the baseline blood glucose and insulin levels. Peripheral venous catheters (PVCs) were inserted in both arms and plastic tubes were connected to the PVCs. A baseline BGL was measured upon arrival to assure normal fasting BGLs between 3.9 and 7.5 mM (70–135 mg/dL). An intravenous infusion of 50 mL of D-glucose (50% dextrose) was performed in one arm over a period of 4.0 min using a power injector. The D-glucose infusion was followed by a saline flush of 30 mL, included in the total infusion duration to assure that all D-glucose entered the vessel at the same rate. Venous blood samples (~1–2 mL per sample) were collected in the contralateral arm before and 1.0, 1.5, 2.0, 3.0, 5.0, 7.0, 10, and 15 min after the start of the D-glucose infusion. Venous BGLs were measured using a blood gas analyzer (i-Stat, Abbot Scandinavia AB, Sweden). Venous blood glucose curves were not available for subject 7 due to problems with the blood sampling procedure. The subjects were asked to orally report their experiences of the D-glucose infusion after the scanning.

Dynamic acquisition of glucoCEST images was accomplished at a temporal resolution of 36 or 42 s, depending on the imaging parameters described in Table 1, and with a total scan time of around 15 min. After collecting a number of baseline images (Table 1), D-glucose was administered intravenously and the DGE response was evaluated for selected protocols, all employing a prototype CEST sequence with turbo spin echo readout and a turbo factor of 64. Subjects were imaged using a 3D encoding consisting of eight or 10 partitions with a field of view of 212 × 185 mm², matrix size 64 × 56, in-plane resolution of 3.3 × 3.3 mm², partition thickness of 4 mm, and TR/TE = 3000/9.0 ms. Saturation was achieved using 10 Gaussian-shaped pulses, either $B_1 = 0.60 \, \mu T$ or $B_1 = 1.6 \, \mu T$, of 100-ms duration and 10-ms interpulse delay at a single saturation offset of 1.2 or 2.0 ppm from the water resonance frequency, respectively. These offsets are expected to give comparable effects, with 2.0 ppm being less affected by the steep direct saturation curve and therefore less sensitive to $B_0$ variations (e.g. due to motion). Two non-saturated $S_0$ images were acquired by saturating at +1500 ppm at the beginning of the CEST image acquisition before infusion. An overview of the parameters for the different participants is provided in Table 1.

Two of the subjects (denoted A and B) were scanned without D-glucose infusion but with corresponding imaging protocols (Table 1). These subjects did not therefore have PVCs inserted and the venous BGL was not measured. Subject A was scanned twice, with both the 1.2 ppm/0.6 $\mu T$ and 2.0 ppm/1.6 $\mu T$ protocols, referred to as A1 and A2, respectively. Subject B was scanned with saturation at 2.0 ppm.

In addition to the seven infusion cases scanned according to the description above, eight subjects were infused and scanned using the same pulse sequence but with a single-slice approach instead. As it was not possible to perform a proper retrospective motion correction for these 2D images, the DGE MRI results from these data were omitted. However, four of these subjects had a shorter D-glucose infusion duration of 1.5 min, and the venous BGLs and reports of side effects of the infusion are included in the results.

Anatomical T1 MPRAGE images (1.0 × 1.0 × 1.0 mm³ isotropic resolution, $T_1/TE/TR = 900/2.54/1900$ ms) were acquired for all subjects. An additional experiment was performed to evaluate possible volumetric changes of the lateral ventricles after D-glucose administration: T1 MPRAGE images were collected in one subject (27-year-old male) before and after a 4.0-min D-glucose infusion (50 mL, 50% dextrose). In total, six image volumes were collected in a total time of 40 min. Blood samples were collected at the start of each MPRAGE, and venous BGLs were measured using the same methods as in the glucoCEST experiment described above.

| TABLE 1 | Overview of glucoCEST acquisition parameters for healthy volunteers with ($n = 7$) and without ($n = 2$) D-glucose infusion |
|----------|-----------------------------------------------|
| Subject  | Temporal resolution (s) | Number of slices | Saturation offset/B₁ (ppm/μT) | Number of dynamics | Baseline: duration (min) | Infusion duration (min) |
| 1–4      | 42               | 10            | 1.2/0.60                         | 25               | 4               | 4.0               |
| 5        | 42               | 10            | 2.0/1.6                          | 25               | 4               | 4.0               |
| 6–7      | 36               | 8             | 2.0/1.6                          | 28               | 6               | 4.0               |
| A1⁺      | 36               | 8             | 1.2/0.60                         | 25               | 3               | -                 |
| A2⁺      | 36               | 8             | 2.0/1.6                          | 25               | 3               | -                 |
| B        | 36               | 8             | 2.0/1.6                          | 18               | 3               | -                 |

*A1 and A2 respectively denote two infusions with two different saturation offsets, 1.2 and 2.0 ppm. In addition, Subject 1 (A1) and 2 (A2) were scanned without D-glucose infusion but with corresponding imaging protocols (Table 1)*.
2.2 Postprocessing, data analysis, and statistics

All data were converted to NIfTI format and analyzed using Matlab R2019a (MathWorks, Natick, MA, USA). The first unsaturated ($S_0$) image and the first saturated image were discarded to assure proper steady state. Retrospective motion correction was performed using the Elastix\textsuperscript{22} rigid body transform, giving six motion parameters (translation and rotation in each of the three dimensions). A parameter file similar to the one used by Herz et al.\textsuperscript{25} but with the “Number Of Spatial Samples” set to 2000, was employed. The $S_0$ image and all the saturated images were registered to the first retained glucoCEST preinfusion image.

All motion-corrected saturated images were normalized to the motion-corrected $S_0$ acquired before infusion and the preinfusion images were averaged to represent a baseline image. ΔDGE maps were generated by subtracting each dynamic glucoCEST image, $S(t)$, from the baseline image, $S_{base}$, so that a positive ΔDGE signal can be interpreted as an increased D-glucose concentration in the voxel\textsuperscript{2}:

$$\Delta\text{DGE}(t) \; (\%) = \frac{S_{base} - S(t)}{S_0} \times 100\%.$$

Averaged area under curve (AUC\textsubscript{mean}) maps were created as following:

$$\text{AUC}_{\text{mean}} \; (\%) = \frac{\sum_{t=1}^{N} \Delta\text{DGE}(t)}{N},$$

where $N$ is the number of images over a selected time interval $\Delta t = t_2 - t_1$. The division by $N$ was performed to achieve comparable normalized signal magnitudes regardless of temporal resolution. AUC\textsubscript{mean} maps were calculated for each subject over four 2-min time intervals. The first interval (referred to as baseline) corresponded to the initial 2 min of the period before D-glucose infusion. The second, third, and fourth intervals represented postinfusion intervals, starting 2, 4, and 6 min after the start of the D-glucose infusion, respectively. The AUC\textsubscript{mean} time intervals are schematically illustrated in Figure 1. A baseline of 3 min was assumed in the AUC\textsubscript{mean} calculations for the subjects without infusion, and four 2-min AUC periods were analyzed, similar to the actual infusions.

Anatomical MPRAGE images were resliced to correspond to the glucoCEST images in terms of spatial resolution and slice positioning, using SPM12.\textsuperscript{33} ΔDGE time curves were measured in regions of interest (ROIs) of a cerebral artery, in white matter (WM), and in cerebrospinal fluid (CSF) in the lateral ventricles, identified in the resliced anatomical images. The ΔDGE time curves were temporally smoothed using a three-point moving mean (Matlab function \texttt{movmean}). The AUC\textsubscript{mean} values for the four 2-min intervals described above were calculated for the ROIs in artery, WM, and CSF. All subjects that received D-glucose infusion ($n = 7$) were grouped together and the ΔDGE AUC signal in the arterial ROIs after D-glucose infusion in the second to fourth interval, compared with the baseline, was evaluated using two-sided Wilcoxon signed-rank tests.

To further evaluate the effect of motion on the ΔDGE signal, rigid body motion estimates (three degrees of translations and rotations for each volume in time) were applied to the first retained glucoCEST preinfusion image to simulate an artificial time series. This procedure was executed in Matlab with the \texttt{imwarp} function using a rigid body 3D transformation. A pseudo-DGE time series, where the ΔDGE signal was entirely caused by movements, was then calculated using Equation 1. The average ΔDGE signal in the imaged volume over time was calculated for each subject before and after motion correction as well as in the pseudo-DGE maps. The outer two slices were excluded from the analysis, leaving six or eight slices depending on the protocol. This exclusion was necessary to avoid erroneous signal contributions caused by the motion correction in the outermost slices.

![FIGURE 1](https://example.com/figure1.png)  
Schematic illustration showing the different intervals of dynamic glucose-enhanced (DGE) data acquisition and analysis. Each image series started with two $S_0$ images, followed by a baseline period of varying duration, infusion, and postinfusion periods. For the AUC data analysis, 2-min segments were used, one representing the first 2 min of the baseline and three representing postinfusion intervals, starting 2, 4, and 6 min after the start of the D-glucose infusion.
For the analysis of the ventricle volume, the lateral ventricles were segmented out using FSL FAST segmentation followed by manual delineation, and the volume of the lateral ventricles was calculated at each time point. The two volume measurements before D-glucose infusion were averaged to represent a baseline value. The change in ventricular volume was plotted as a function of time together with venous BGLs. To evaluate the quality of the ventricular volume estimation, an additional scan of the same subject, but without D-glucose infusion, was performed in a separate session 3 weeks before the glucose infusion scan. Three MPRAGE volumes were collected and the volume of the lateral ventricles was calculated in each of these image volumes as described above.

A two-sample t-test was used to compare the maximum change in BGL between the 1.5- and 4.0-min infusion groups, including subjects from both the single-slice and the 3D acquisitions. The baseline venous BGL was subtracted to obtain the change in BGL. The relationship between DGE AIFs and venous BGLs was evaluated using a linear regression analysis.

An additional analysis of B0 shifts and their effect on the DGE signal for 1.2 ppm/0.6 μT and 2.0 ppm/1.6 μT was performed, and is described in detail in the supporting information.

**FIGURE 2**  
(A) ΔDGE AUC$_{mean}$ maps of two representative subjects at 2-min intervals taken before and after D-glucose infusion (cf. Figure 1). The third subject, subject B, was imaged without D-glucose infusion. (B) ΔDGE signal in artery, white matter, and cerebrospinal fluid (CSF) together with the change in venous blood glucose level (ΔBGL) as a function of time for each subject. The regions of interest (ROIs) in which the ΔDGE signals were measured are indicated in the anatomical images in each plot. The time zero represents the start of the D-glucose infusion and the shaded areas in the graphs represent the infusion duration. (C) Scatter plot of arterial ΔDGE signal in one slice, at all time points when blood glucose was measured, and the corresponding change in venous BGL for all subjects who underwent D-glucose infusion as well as successful blood glucose sampling (1.2 ppm, n = 4; 2.0 ppm, n = 2)
3 | RESULTS

Motion-corrected DGE \( \text{AUC}_{\text{mean}} \) maps of one slice for three representative subjects are shown in Figure 2A. Four \( \text{AUC}_{\text{mean}} \) time intervals of 2 min each are shown. A signal change after D-glucose infusion was seen in all subjects, mainly manifested as hypointensities. Motion artifacts (residual uncorrected motion, seen as dark-bright patterns) appeared at tissue interfaces in some subjects, most prominently around the ventricles and in outer parts of the brain. One subject (subject B) without infusion is also included in Figure 2 and a signal change can be seen, especially near the edges of the brain and in the later \( \text{AUC}_{\text{mean}} \) intervals. When compared visually, the overall signal change was smaller for the subjects without infusion than in the D-glucose infusion group. Figure 2B includes dynamic curves for ROIs in an artery, WM, and CSF presented together with the \( \Delta \text{BGL} \). An increase in the arterial \( \Delta \text{DGE} \) signal of approximately 1%–4% following the D-glucose infusion was observed in all subjects. The \( \Delta \text{DGE} \) signal in WM was small in most subjects, compared with the arterial signal, and in many cases it was negative. The \( \Delta \text{DGE} \) signal in CSF was in some cases large (2%–4% in subjects 1, 4, and 6), but positive or negative. In the group without infusion, the \( \Delta \text{DGE} \) signal was close to zero in all tissues, except for subject A1, where a fluctuating \( \Delta \text{DGE} \) signal of ±1% could be seen in artery and CSF. A scatter plot between the DGE AIFs and the corresponding \( \Delta \text{BGL} \) for all subjects that had D-glucose infusion, except for subject 7, is presented in Figure 2C. A significant correlation of \( r = 0.65 \) was achieved.

Table 2 shows the maximum displacement (translation and rotation) retrieved from the rigid body motion estimates for each subject. Subjects 1, 4, and 6 had remarkably higher motion estimates than the other subjects, corresponding to translations of 1.7–2.1 mm and rotations of 0.8–1.9 degrees. Individual correlation coefficients between the \( \Delta \text{BGL} \) and the corresponding arterial \( \Delta \text{DGE} \) signal for subjects that had D-glucose infusion are presented in Table 2. The correlations were all positive, but only two out of six were significant. Correlation coefficients between \( \Delta \text{BGL} \) and \( \Delta \text{DGE} \) signal in WM are also included in Table 2. Negative significant correlations were found in three subjects.

In Figure 3, the \( \Delta \text{DGE} \) signal in the selected regions in artery, WM, and CSF of all subjects, grouped according to the following: 1.2 ppm/0.6 μT with infusion \((n = 4)\) and without infusion \((n = 1)\), as well as 2.0 ppm/1.6 μT with infusion \((n = 3)\) and without infusion \((n = 2)\). The last two rows of Figure 3 show the same data but instead grouped into one group with infusion \((n = 7)\) and one group without infusion \((n = 3)\). All \( \Delta \text{DGE} \) data points in each time interval are included for each subject. When grouping the subjects with infusion together \((n = 7)\), a significant signal increase in \( \Delta \text{DGE} \) signal in arteries compared with baseline was found in all postinfusion time intervals \((p = 0.03\) for all intervals\). In Figure 4, pseudo-DGE maps \((\text{DGE}_{\text{Pseudo}})\) are shown together with real noncorrected DGE \((\text{DGE}_{\text{NonCo}})\) and motion-corrected DGE \((\text{DGE}_{\text{MoCo}})\) maps for all subjects, using the \( \text{AUC}_{\text{mean}} \) for the 2–4 min period postinfusion \((\text{AUC}_{2-4\ \text{min}})\). The \( \text{DGE}_{\text{Pseudo}} \) maps and \( \text{DGE}_{\text{NonCo}} \) maps were similar but not identical when compared visually. Figure 5 shows the \( \Delta \text{DGE} \) averaged over the imaged volume (outer slices excluded) as a function of time, together with the motion estimates (translations and rotations) for five subjects. The averaged \( \Delta \text{DGE} \) signal was in some cases altered after motion correction, as seen in subjects 1 and 6.

Figure 6 shows \( \text{DGE}_{\text{NonCo}}, \text{DGE}_{\text{Pseudo}}, \) and \( \text{DGE}_{\text{MoCo}} \) time series of a center slice for the subject scanned without D-glucose infusion using both saturation offset protocols (1.2 ppm/0.6 μT and 2.0 ppm/1.6 μT, referred to as subjects A1 and A2, respectively). The 2.0-ppm images have a smoother appearance after motion correction than the 1.2-ppm images.

### Table 2

Maximum movements (translation and rotation) retrieved from the motion correction, and correlation coefficients \((r)\) and \( p \)-values \((p)\) between \( \Delta \text{DGE} \) in artery and change in venous blood glucose level \((\Delta \text{BGL})\), and between \( \Delta \text{DGE} \) in white matter (WM) and \( \Delta \text{BGL} \) for all subjects

| Maximum displacement | Correlation venous BGL – artery | Correlation venous BGL – WM |
|----------------------|---------------------------------|-----------------------------|
|                      | \( r \) | \( p \) | \( r \) | \( p \) |
| translation (mm)     | rotation (degrees)               |                             |                             |
| 1                    | 2.1  | 1.9  | 0.48 | 0.3  | –0.83 | * |
| 2                    | 0.9  | 0.9  | 0.52 | 0.2  | –0.72 | * |
| 3                    | 0.5  | 0.5  | 0.57 | 0.1  | –0.32 | 0.4 |
| 4                    | 1.7  | 1.8  | 0.97 | *   | –0.46 | 0.3 |
| 5                    | 0.6  | 0.3  | 0.54 | 0.2  | 0.20  | 0.7 |
| 6                    | 1.7  | 0.8  | 0.81 | *   | –0.86 | * |
| 7                    | 0.6  | 0.3  | N/A  | N/A  | N/A   | N/A |
| A1#                  | 0.4  | 0.4  | N/A  | N/A  | N/A   | N/A |
| A2#                  | 0.3  | 0.3  | N/A  | N/A  | N/A   | N/A |
| B                    | 0.1  | 0.6  | N/A  | N/A  | N/A   | N/A |

Venous blood D-glucose levels were not available for one subject due to blood sampling failure (subject 7). The asterisk (*) indicates \( p < 0.05\). N/A = not available. Shading is used to help distinguish between the different protocols; subjects 1–4 (1.2 ppm, 4.0-min infusion), subjects 5–7 (2.0 ppm, 4.0-min infusion), and subjects A–B (no infusion). #Subject A was scanned twice, first with 1.2-ppm offset and then with 2.0-ppm offset.
FIGURE 3  Box-and-whisker plots showing ΔDGE signal in arterial, white matter (WM), and ventricular regions of interest grouped into four different 2-min intervals. The time intervals were as follows: baseline, representing the initial 2 min of imaging, and three postinfusion intervals starting 2, 4, and 6 min, respectively, after the start of D-glucose infusion. The red line represents the median value, the upper and lower borders of the blue box represent the upper and lower quartile, respectively, and the end points of the whiskers represent the maximum and minimum ΔDGE value in each group. The bottom two rows show the results obtained when grouping the data for both frequency offsets. CSF, cerebrospinal fluid.
As stated in the Methods section, DGE data from the single-slice acquisitions were not included. The results from the D-glucose infusion in these subjects are, however, included in the following section. The average baseline BGL ± SD was 4.9 ± 0.9 mM and the averages of the maximum change in BGLs were 8.6 ± 2.3 and 8.7 ± 1.8 mM for the 1.5- and 4.0-min infusion groups, respectively. No significant difference in maximum change in BGL was found between the 1.5-min (n = 4) and the 4.0-min (n = 12) infusion groups (p = 0.96). The verbally reported D-glucose side effects of the 1.5-min infusion (n = 4) were a warm or cold feeling or tension at the injection site (100%, all subjects), a warm or pulsating sensation in the head and/or crotch (75%, three subjects), transient headache (75%, three subjects), experiencing an urge to urinate (50%, two subjects), and tension in the shoulder (25%, one subject). The reported side effects in the 4.0-min infusion group (n = 12, including the ventricle scan) were a warm or cold feeling or tension at the injection site (67%, eight subjects) and a warm or pulsating sensation in the head and/or crotch (25%, three subjects). The rest of the subjects (33%, four subjects) did not experience any side effects. One subject in the short infusion group reported a thrombophlebitis close to the site of injection (the basilic vein) a few days after the examination. Evaluation of the morphological images did not reveal any brain pathology in any of the examined subjects.

Segmentation of the lateral ventricles, without D-glucose infusion, resulted in a volume of 22.9 mL. The difference between the first and second image volume and between the first and third image volume was less than 0.1%. Results of the measurement with D-glucose infusion on the same subject are presented in Figure 7. The averaged baseline volume was 22.3 mL and the average volume after infusion was 22.5 mL, which corresponds to an average change of about 1%. This subject did not experience any side effects of the D-glucose infusion.

Results of the analysis of $B_0$ shifts and their effect on the DGE signal are provided in the supporting information.
Signal changes were seen in all DGE AUC<sub>mean</sub> maps after D-glucose injection. Of the nine subjects, five were scanned using saturation at 1.2 ppm, a frequency often utilized at higher field strengths (i.e. 7 T and above), because three of the D-glucose hydroxyl protons are resonating at around 1.2 ppm. However, these three protons have an exchange rate of thousands of Hz, and are coalesced with the water proton resonance at 3 T, leading to a steep slope in the Z-spectrum at this frequency. Previously, based on simulations, it was therefore recommended to use a saturation frequency at 2.0 ppm because the sensitivity to B<sub>0</sub> inhomogeneities decreases when saturating farther from the water resonance frequency. As shown by Zaiss et al., B<sub>0</sub>-induced frequency shifts caused by subject motion or field drift can manifest themselves as global hypointensities or hyperintensities in DGE maps. No dynamic B<sub>0</sub> correction was performed in this study, because a high temporal resolution was prioritized over multiple frequencies to enable measuring AIFs, which was accomplished by using a single saturation frequency offset. Subject A was scanned without D-glucose infusion using both saturation protocols, and the motion estimates were of comparable magnitude. The 1.2-ppm ΔDGE maps showed more signal fluctuations than the 2.0-ppm ΔDGE maps, as seen in Figure 6. This illustrates that the 1.2-ppm images are more affected by motion-induced B<sub>0</sub> artefacts. The effect of B<sub>0</sub> shifts on the DGE signal for 1.2 ppm/0.6 μT and 2.0 ppm/1.6 μT was investigated further (see the supporting information). As reported by others, this effect can be substantial. For instance, our analysis revealed that a typical shift of 1 Hz at 3 T can change the absolute size of the AIF by as much as 0.2 percentage points. In WM, this would be around 0.2%/Hz for 1.2 ppm/0.6 μT and around 0.1%/Hz for 2.0 ppm/1.6 μT. These results indicate that single saturation offset acquisition of glucoCEST images can be problematic, especially at saturation offsets closer to the water resonance. Hence, it appears that the use of single frequencies for DGE acquisition should be replaced by acquisition of the Z-spectrum, at least including a region around 0 ppm to estimate and correct for the field shifts due to motion or drift.
Hypointense areas over the whole brain were present in the AUCmean maps (Figure 2) for both the 1.2 ppm/0.6 μT and 2.0 ppm/1.6 μT groups. In general, the AUCmean in WM was slightly negative for all the postinfusion intervals (Figure 3). This observation is consistent with earlier results showing a reduced D-glucose effect in WM for a prolonged period of 10–20 min, but it has not been entirely explained. According to Equation 1, a positive ΔDGE signal would be expected in regions where the D-glucose concentration has increased compared with baseline. There is no physiological explanation to why the tissue glucose concentration should decrease directly after D-glucose injection, so the source behind the negative ΔDGE signal seen in some regions and subjects must be an MR-related phenomenon (i.e. water signal related). Due to the consistency of the reduction, it seems unlikely to be caused by B₀ shifts due to motion. Another possible source could be B₀ drift caused by gradient heating. However, the negative signal in WM tends to recover towards the end of the ΔDGE time series, as seen in the time curves in Figure 2, which suggests that it is related to the change in blood glucose concentration. A significant negative correlation between ΔDGE signal in WM and venous BGL was found in 50% of the subjects (Table 2). Possible causes for this decrease may be a susceptibility-based frequency shift or a tissue water signal change due to osmolarity differences between blood and tissue that is larger than the glucoCEST effect at 3 T, but smaller
than the corresponding effect at 7 T. As seen in Figure 3, the ΔDGE signal in WM was typically close to zero or positive in the subjects without D-glucose infusion. Additionally, the averaged ΔDGE signal over the imaged volume, shown in Figure 6, is typically close to zero for DGE\textsubscript{pseudo}, which is expected because motion-induced signal changes are likely to cancel out. This behavior is not observed in the DGE\textsubscript{MoCo}, showing that motion is not the dominating signal contributor in the motion-corrected DGE maps. Even although the cases without infusion are few, they are important as a reference and illustrate the difficulties in DGE imaging, and that careful postprocessing and analysis are needed to distinguish true ΔDGE signal from ΔDGE signal caused by motion.

Negative and positive signal changes were found in CSF, as exemplified here in the lateral ventricles. The DGE\textsubscript{pseudo} maps (Figure 4) reveal that motion can cause hypointensity or hyperintensity in and around the lateral ventricles. No consistent trend is seen for CSF in Figure 3, indicating that at least part of the signal change in CSF can be attributed to motion. A complementary explanation is volumetric changes of the ventricles after D-glucose injection, causing a water signal decrease due to partial volume effects, with neighboring tissues interpreted as an apparent decrease in D-glucose concentration. This can also explain why the signal change in the ventricular region is smaller after rigid motion correction in the cases without infusion than in the D-glucose infusion group, because the former only includes rigid motion, while the latter also consists of nonrigid motion due to ventricular swelling or shrinking. A volumetric change of up to 2% was measured in our experiment performed on one volunteer, as seen in Figure 7. When looking at the results, there are three points with a volume change of 1%–2%, but one with a negative change, reducing the average. The cause for this deviating data point is probably motion related, as this fourth image was, by visual inspection, blurrier at tissue interfaces than the others. Even although this would be an unbiased criterion for not including it, we felt it was appropriate to show all data. In support of the overall results, a previous study conducted by Puri et al. observed a similar volume increase of the lateral ventricles of 2.4% ± 0.4% after raising the BGL in healthy volunteers from 4.8 ± 0.2 to 8.4 ± 0.4 mM using oral administration of D-glucose.

### 4.2 Relationship between arterial DGE signal and BGLs

DGE AIFs have previously been measured in healthy volunteers at 7 T\textsuperscript{13} and in patients at 3 T.\textsuperscript{20} In this study at 3 T, a significant increase in the averaged arterial ΔDGE signal was found in the group with D-glucose infusion (n = 7), and we thus conclude that it is possible to measure arterial ΔDGE signal at 3 T. One limitation of this study is the small number of subjects that were investigated, and this limitation is only partially overcome by grouping all the infusion subjects with different acquisition conditions. The magnitude and shape of the arterial ΔDGE curve varied between individuals. The magnitude differences can most likely be explained at least in part by partial volume effects with surrounding tissue. A reasonable explanation for the finding of different magnitude combined with different shape of the DGE AIFs between subjects is the individual response to the D-glucose in terms of insulin response and metabolism, which will influence the curve shape, as discussed by Knutsson et al.\textsuperscript{13}

The subjects scanned using saturation at 1.2 ppm generally showed more fluctuations in the ΔDGE curves, probably because this is more sensitive to frequency shifts caused by changes in B\textsubscript{0}, as discussed in the previous section.

### 4.3 D-glucose infusion duration, venous BGLs, and D-glucose side effects

The blood glucose sampling procedure is challenging. Long plastic (polycarbonate) tubing is needed to avoid the nurses leaning into the magnet bore when collecting the blood samples. Tubing of 100-cm length was used in our previous glucoCEST experiments to facilitate the blood sampling process, but this was changed to a length of 25 cm. For one of the subjects, subject 7, it was not possible to retrieve blood through the tubing and the samples were thus limited to one sample before and one sample taken at the arm after the scanning. Saline flushes are necessary to aid the blood sampling process, but this was changed to a length of 25 cm. For one of the subjects, subject 7, it was not possible to retrieve blood through the tubing when collecting the blood samples. Tubing of 100-cm length was used in our previous glucoCEST experiments to facilitate the blood sampling. In a study by Chen and Porte,\textsuperscript{29} the insulin and blood D-glucose responses to different D-glucose injection rates were investigated. Using three different injection durations (0.3, 3, and 12 min), they showed that a faster infusion gave a steeper rise in BGL without significantly affecting the peak level. A higher D-glucose infusion rate was associated with a faster disappearance of D-glucose from the circulation and a higher acute insulin response. In our study, it was difficult to compare the shape of the sampled venous blood glucose curves between participants because the sampling times sometimes varied between subjects. However, no significant difference in maximum BGL change (baseline value subtracted) was found (p = 0.96) between the 1.5- and 4.0-min infusion groups. Using these results together with the results from the study by Chen and Porte,\textsuperscript{29} we conclude that a longer infusion duration (e.g. 3–4 min) is preferable in glucoCEST experiments, because it could minimize the side
effects of the D-glucose infusion while not reducing the maximum BGL, and therefore preserving the DGE effect size. A longer infusion duration can thus reduce the risk of subject motion during and immediately after D-glucose infusion. In this study, all subjects were asked about their experiences during the D-glucose infusion. We observed that a longer infusion duration was experienced as being more pleasant for the participant, and this is in agreement with previous observations.13

5 CONCLUSIONS

DGE imaging at 3 T remains challenging and the need for thorough postprocessing and analysis is emphasized, including motion correction and dynamic B0 correction, which would be possible by using multiple saturation frequencies in the acquisition. Movements of the order of 2 mm and 1.5 degrees obscure the ∆DGE signal and can lead to large signal changes in CSF. In spite of the challenges, we conclude that it is possible to measure arterial ∆DGE signal at 3 T. A longer infusion duration (e.g. 3–4 min) should preferably be used in glucoCEST experiments, because it can minimize the side effects of the D-glucose infusion while still producing a sufficient change in BGL. Future studies on larger cohorts are needed to address postprocessing, motion correction, dynamic B0 correction, physiological changes related to D-glucose infusion, as well as, most relevantly, new pulse sequences to increase the effect size.

ACKNOWLEDGMENTS

We acknowledge Dr. Frederik Testud (Siemens Healthcare, Sweden), Dr. Markus Nilsson (Lund University, Sweden), and Drs. Xiang Xu and Akansha Sehgal (both Johns Hopkins University and Kennedy Krieger Institute) for additional support and discussions. This project was supported by Swedish Research Council grant numbers 2015–04170, 2017–00995, and 2019–01162; Swedish Cancer Society grant numbers CAN 2015/251, CAN 2018/468, and CAN 2018/550; Swedish Brain Foundation grant number FO2017–0236; Regional Research Funding, F2018/1490; and National Institutes of Health grant number RO1 EB019934.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION
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How to cite this article: Seidemo A, Lehmann PM, Rydhög A, et al. Towards robust glucose chemical exchange saturation transfer imaging in humans at 3 T: Arterial input function measurements and the effects of infusion time. NMR in Biomedicine. 2022;35(2):e4624. doi:10.1002/nbm.4624.