NOTE

Effects of contrast agents on relaxation properties of $^{31}$P metabolites

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Purpose: Phosphorous MR spectroscopy ($^{31}$P-MRS) forms a powerful, non-invasive research tool to quantify the energetics of the heart in diverse patient populations. $^{31}$P-MRS is frequently applied alongside other radiological examinations, many of which use various contrast agents that shorten relaxation times of water in conventional proton MR, for a better characterisation of cardiac function, or following prior computed tomography (CT). It is, however, unknown whether these agents confound $^{31}$P-MRS signals, for example, 2,3-diphosphoglycerate (2,3-DPG).

Methods: In this work, we quantitatively assess the impact of non-ionic, low osmolar iodinated CT contrast agent (iopamidol/Niopam), gadolinium chelates (linear gadopentetic acid dimeglumine/Magnevist and macrocyclic gadoterate meglumine/Dotarem) and superparamagnetic iron oxide nanoparticles (ferumoxytol/Feraheme) on the nuclear $T_1$ and $T_2$ of $^{31}$P metabolites (ie, 2,3-DPG), and $^{1}$H in water in live human blood and saline phantoms at 11.7 T.

Results: Addition of all contrast agents led to significant shortening of all relaxation times in both $^{1}$H and $^{31}$P saline phantoms. On the contrary, the $T_1$ relaxation time of 2,3-DPG in blood was significantly shortened only by Magnevist ($P = .03$). Similarly, the only contrast agent that influenced the $T_2$ relaxation times of 2,3-DPG in blood samples was ferumoxytol ($P = .02$).

Conclusion: Our results show that, unlike conventional proton MR, phosphorus MRS is unconfounded in patients who have had prior CT with contrast, not all gadolinium-based contrast agents influence $^{31}$P-MRS data in vivo, and that ferumoxytol is a promising contrast agent for the reduction in $^{31}$P-MRS blood-pool signal.

KEYWORDS
contrast agent, magnetic resonance spectroscopy, phosphorus-31
INTRODUCTION

Cardiac MR (CMR) imaging is the gold-standard non-invasive technique used to diagnose heart disease. It can quantify cardiac structure, function, viability as well as myocardial metabolism directly. The latter is commonly probed by in vivo phosphorus MR spectroscopy ($^{31}$P-MRS), which allows the assessment of high-energy metabolites, for example, adenosine triphosphate (ATP) and phosphocreatine (PCr). In particular, the PCr/ATP ratio remains a biomarker of high interest, as it changes in most cardiac pathologies, predicts mortality in patients with dilated cardiomyopathy, and decreases even in systemic diseases, such as obesity and type-II diabetes.

$^{31}$P-MRS is commonly combined with other imaging modalities, both MR and non-MR based, for a more comprehensive cardiac characterisation. Cine imaging, providing cardiac volumes and function, and late gadolinium enhancement (LGE) assessment of tissue viability are the most commonly used cardiac MR methods. In order to clearly resolve any necrotic or fibrotic tissue, $^{31}$P-MRS data sets are also acquired before LGE.

From non-MR imaging techniques, contrast-enhanced computed tomography (CT) is frequently used in cardiology, for example, for coronary artery imaging. CT contrast agents are radiopaque and not based on gadolinium, but rather iodine. From non-MR imaging techniques, contrast-enhanced computed tomography (CT) is frequently used in cardiology, for example, for coronary artery imaging. CT contrast agents are radiopaque and not based on gadolinium, but rather iodine. Still, they shorten the $T_1$ relaxation time, as well as the transverse ($T_2$) relaxation times of water signal in $^1$H MRI. These effects can influence the interpretation of native contrast in subsequent MR scans and can last for up to 24 h after the CT scan. Again, any potential confounding effects on $^{31}$P-MRS remain unknown.

Although it is possible to postpone contrast enhanced examinations until after the $^{31}$P scan, this delay might be scientifically/logistically undesirable and negatively affect patient comfort. Therefore, our aim was to determine the effects of gadolinium- and iodine-based contrast agents on the relaxation times of $^{31}$P metabolites in order to evaluate potential influence of prior contrast enhanced scans on the quantification of the cardiac PCr/ATP ratio. In addition, we have investigated an iron oxide nanoparticle agent, ferumoxytol, which is an iron replacement product that is licensed and used to treat iron deficiency anaemia. However, it has recently been shown that ferumoxytol has a $T_2$ shortening effect on $^1$H signals and may act, therefore, as a negative-contrast agent in MR examinations, in an off label use. This could help suppress the signals originating in the blood pool, for example, 2,3-diphosphoglycerate (2,3-DPG) that contaminate cardiac $^{31}$P-MRS spectra and, especially at lower fields, obscure the inorganic phosphate (Pi) resonance in the cardiac spectra.

METHODS

All measurements were performed using a vertical bore 11.7T MRI system (Magnex Scientific/Varian DDR2) equipped with a dual-tuned $^1$H/$^{31}$P radiofrequency, transmit/receive birdcage coil (20 mm diameter, Rapid Biomedical) under temperature-controlled conditions at $21 \pm 1°C$ (Bruker BVT3000). This temperature was chosen as a compromise between physiological state, isothermal homogeneity, and blood viability (which is maximized at lower temperatures). Fresh human blood was obtained from four healthy volunteers via antecubital fossa venepuncture and stored in 4 ml aliquots in an ethylenediamine tetraacetic acid (EDTA) buffer containing 1.8 mg EDTA per milliliter of blood (Vacutainer, BD Healthcare). All experiments performed on human tissue adhered to the Declaration of Helsinki and Caldicott principles, and all volunteers gave informed consent following local institutional procedures and ethical review. All samples were manually shimmed on a third-order shim set to obtain an adequate linewidth of water signal, typically $\sim 30$ Hz, desirably $\leq 50$ Hz and always $\leq 100$ Hz (~0.1-0.2 ppm). A flip angle power calibration was performed before each set of acquisitions on a given phosphate buffered saline (PBS) or saline sample, and this calibration was also performed on each separately drawn tube of blood.

$T_1$ relaxation times were measured on both channels ($^1$H and $^{31}$P) in one vial sequentially after sampling using a pulse-acquire progressive saturation sequence with eight repetition times (TRs) ranging from 0.11 s to 12 s for $^{31}$P and 13 TRs ranging from 0.007 s to 6 s for $^1$H. Other measurement parameters were as follows: 50 $\mu$s 90° rectangular pulse, 16 averages, 10 kHz bandwidth. 512 dummy scans were used before each set of averages, effectively acting as a spoiler between TRs. $T_2$ relaxation times were computed via the Carr-Purcell-Meiboom-Gill (CPMG)$^{17}$ pulse sequence (with $\tau = 2.9, 5.8, 11.5, 23, 46, 92$ ms; 64 averages on $^{31}$P in blood, 1 on $^1$H with 16 dummy scans, with a TR chosen to be far longer than $T_1$, that is, $7$ s TR for $^1$H, 50 s TR for $^{31}$P in phantoms; $15$ s in blood.). Short rectangular radiofrequency (RF) pulses were again used in the canonical CPMG phase cycling scheme, that is, 50 $\mu$s 90°, followed by a chain of 100 $\mu$s 180° pulses. Phase cycling was performed between averages as described previously to ameliorate imperfect refocusing.

Owing to signal-to-noise ratio (SNR) limitations of short TR and long TE data primarily, only the dominant signals in their
TABLE 1  Relaxation times (T₁ and T₂) of 2,3-DPG and water measured in human blood and saline

| Metabolite       | Contrast agent | No Contrast | Iopamidol | Dotarem | Magnevist | Femuroxytol |
|------------------|----------------|-------------|-----------|---------|-----------|-------------|
| 2,3-DPG T₁/s     |                | 1.65 ± 0.24 | 1.58 ± 0.77 | 1.59 ± 0.43 | 1.24 ± 0.29* | 1.64 ± 0.44   |
| T₂/ms            |                | 8.03 ± 1.06 | 9.00 ± 2.02 | 7.64 ± 3.41 | 8.34 ± 1.40 | 6.26 ± 0.47*  |
| Waterblood T₁/s  |                | 0.89 ± 0.16 | 0.83 ± 0.14 | 0.20 ± 0.32* | 0.16 ± 0.23* | 0.27 ± 0.09*  |
| T₂/ms            |                | 8.12 ± 5.64 | 11.08 ± 7.11 | 9.44 ± 7.48 | 8.54 ± 7.43 | 2.14 ± 0.43*  |
| Water saline T₁/s|                | 1.87 ± 0.14 | 1.61 ± 0.06* | 0.12 ± 0.04* | 0.14 ± 0.01* | 0.36 ± 0.01*  |
| T₂/ms            |                | 2248.3 ± 68.4 | 738.0 ± 6.4* | 113.2 ± 6.2* | 107.4 ± 3.5* | 15.2 ± 0.3*   |
| PBS₃¹P T₁/s      |                | 7.50 ± 0.35 | 6.58 ± 0.32* | 0.89 ± 0.06* | 0.22 ± 0.02* | 1.49 ± 0.06*  |
| T₂/ms            |                | 1770.3 ± 15.5 | 1609.7 ± 58.9* | 249.8 ± 15.2* | 31.7 ± 1.9* | 33.5 ± 2.4*   |
| PBS₃¹P T₁/s      |                | 1.59 ± 0.05 | 1.46 ± 0.01* | 0.06 ± 0.001* | 0.14 ± 0.01* | 0.36 ± 0.01*  |
| T₂/ms            |                | 1575.0 ± 15.6 | 455.1 ± 2.7* | 57.9 ± 1.0* | 98.6 ± 2.4* | 18.7 ± 0.4*   |

All results are given as mean ± standard deviation.

A significant difference to the “No Contrast” experiment (via unequal-variance t-test; P < .05) is marked with an asterisk. Please note that the variability in Waterblood T₂ is caused by the physiological differences between subjects as confirmed by a repeated measurement of Waterblood T₂ in “No Contrast” blood in three volunteers with a mean coefficient of variation of 3 ± 2%.

RESULTS

All calculated relaxation times are given in Table 1, and depicted in Figure 1. Figure 2 depicts representative fits of T₁ and T₂ relaxation curves of blood signals. Significantly shorter T₁ relaxation times (by 71-83%) of blood water signal were observed after adding any of the investigated contrast agents except iopamidol (P = .490). The T₁ relaxation time of 2,3-DPG was significantly shortened (by 25%) only when Magnevist was added to the blood sample (P = .033). The only contrast agent that influenced T₂ relaxation times in the blood samples was ferumoxytrol (P = .017 and P = .048 for 2,3-DPG and water, respectively).

In normal saline, the native ¹H T₁ was significantly shortened after mixing with any of the investigated contrast agents. Both gadolinium-based contrast agents shortened T₁ by over...
FIGURE 1  Measured $T_1$ (left) and $T_2$ (right) relaxation times of 2,3-DPG (top), water in blood and in saline (middle) and PBS water and $^{31}$P signals (bottom) are depicted for each contrast agent. Bars represent mean values; whiskers depict SD, and asterisks denote statistical difference to contrast free sample ($P < .05$)
90%, while iopamidol and ferumoxytol by 14% and 81%, respectively. As expected, analogous results were observed in $^1$H spectra of PBS, with $T_1$ shortening by over 95% with gadolinium-based contrast agents, by 88% with ferumoxytol and by 22% using iopamidol. Similar shortening effects were observed on the $^1$H $T_2$ relaxation times of saline and PBS, where each of the contrast agents caused a decrease in $T_2$ by a minimum of 67%. However, unlike in the blood data, the $^{31}$P
relaxation times in PBS were significantly shortened by addition of any contrast agent, including Iopamidol ($P = .029$ for $T_1$ and $P = .035$ for $T_2$). More details can be found in Table 1.

Saturated, high-SNR $^{31}$P spectra did not show any visible differences in any metabolite signals after the addition of contrast agents, as can be seen in the representative example in Figure 3A. Similarly, there were no significant differences between the fitted signals of the $^{31}$P blood metabolites pre- and post-addition of any of the contrast agents investigated (Figure 4). In contrast, high-SNR $^1$H spectra of human blood show the significant influence of the investigated contrast agents (Figure 3B), with a significant increase in water signal intensity observed for Magnevist and Ferumoxytol. The pH of free blood in the vials was 7.4 ± 0.2 throughout the acquisition. No contrast agent effected the blood pH significantly with mean values of 7.5 ± 0.1 for iopamidol, 7.4 ± 0.1 for Dotarem, 7.4 ± 0.1 for Magnevist and 7.4 ± 0.2 for ferumoxytol. Similar results were found in PBS (free PBS pH 6.2; PBS + iopamidol pH 6.2; PBS + Dotarem 6.2; PBS + Magnevist pH 6.2; PBS + ferumoxytol pH 6.3) and saline.
Similarly, there were no significant differences in the chemical shift between any of the groups of metabolites throughout the experiments.

4 | DISCUSSION

As contrast agents form an invaluable part of many clinical imaging protocols, it is desirable to understand their effects on subsequent scans to avoid misinterpretation. However, the mechanisms of contrast agents are diverse, physically complex and often difficult to predict. In this study, we have experimentally investigated the influence of several different contrast agents on \(^{31}\)P and \(^1\)H MRS resonances in human blood and saline. We found differences in their effect on the relaxation times of saline, PBS, and blood signals, and more importantly that effects observed in \(^1\)H signals are not directly transferrable to \(^{31}\)P data.

Both investigated gadolinium-based contrast agents caused a significant shortening of the \(^1\)H \(T_1\) of water signal in blood and in saline and PBS phantoms, which is in accordance with the literature.\(^8\)\(^-\)\(^10\) This chelate-dependent relaxivity has previously been demonstrated also for several non-proton nuclei,\(^23\) including inorganic phosphate in solution.\(^24\) This is in good agreement with our results in PBS where the \(T_1\) relaxation times of the \(^{31}\)P signal were shortened after adding gadolinium-based contrast agents. However, this relaxation mechanism is only expected to occur in freely diffusible small molecules in solution, which permit a proton exchange mediated relaxation mechanism between molecule and agent. In the case of \(^{31}\)P-MRS in freshly sampled blood, which simulates the \textit{in vivo} situation, metabolite signals are localized within the cell, and these contrast agents are extracellular. Thus, the relaxation agent cannot interact with the metabolite; hence, a direct first-sphere exchange mechanism would not predict a decrease in \(T_1\) after addition of a gadolinium-based contrast agent. While our Dotarem results support this hypothesis, as the \(T_1\) remained unchanged, we observed the shortening of the \(^{31}\)P \(T_1\) of the 2,3-DPG blood signal using Magnevist. This might be explained by the different structure of these two gadolinium-based substances: Dotarem is a macrocyclic chelate and Magnevist a linear one. Similar effects have been recently observed in the \(^{13}\)C signal of hyperpolarised pyruvate, where linear, open-chain contrast agents reduced the \(T_1\) of \([1-{^{13}\text{C}}]\) pyruvate by up to 62%, while macrocyclic agents only by up to 25%.\(^25\) In our case, this could be potentially related to the reported ability of 2,3-DPG to directly change the biophysical membrane properties in erythrocytes, pointing toward a biophysical interaction between 2,3-DPG and cell membranes.\(^26\)\(^,\)\(^27\) Thus, by an interaction of the agent to the extracellular membrane alone, allowing Magnevist to effect 2,3-DPG via an exchange mechanism that is possible because of the different solvation spheres of the two gadolinium agents considered, forming a second-order relaxation effect. Albeit significant, this \(T_1\) shortening effect of Magnevist on \(^{31}\)P signal in blood observed in our current work was only minor (25%) compared to the effect on \(^1\)H water signal (83%). Furthermore, neither of the gadolinium contrast agents affected the \(T_2\) of water, nor 2,3-DPG, in human blood. Importantly, while future metabolic studies should take into account that linear chain contrast agents could potentially influence the \(T_1\) of \(^{31}\)P metabolites, the effect of macrocyclic contrast agents on \(T_1\) of \textit{in vivo} \(^{31}\)P-MRS data might be potentially ignored.

While iopamidol is a widely used CT contrast agent not typically used in MRI, it has slow clearance kinetics, and hence, can still be present in the body 24 hours after a contrast enhanced CT scan. We have observed significant
shortening of both $T_1$ and $T_2$ relaxation times in saline and PBS solutions, which is in good agreement with literature.\textsuperscript{12,14,28} However, these effects are highly concentration dependent, with negligible impact in tissues when the contrast agent is diluted.\textsuperscript{13,29} Our results support this hypothesis, as after adding the prescribed clinical dose of Iopamidol (\textsim 2\% concentration of contrast agent), it was not possible to observe any effect on the blood $^1H$ relaxation times. Similarly, no effect was observed on the $^{31}P$ signals in fresh human blood. We, therefore, conclude that differences in perfusion kinetics dominate, and that any potential confounding caused by prior CT would be pathology dependent.

Ferumoxytol is known to be an MR negative-contrast agent and, thus, was expected to have a significant $^1H$ $T_2$ shortening effect. This was observed for both $^1H$ as well as $^{31}P$ blood signals, with blood water $T_2$ decreasing from 8.12 $\pm$ 5.64 ms to 2.14 $\pm$ 0.43 ms ($P=0.048$) and $^{31}P$ 2,3-DPG $T_2$ reducing from 8.03 $\pm$ 1.06 ms to 6.26 $\pm$ 0.47 ms ($P=0.017$), respectively. Furthermore, a shortening of the $T_1$ relaxation time after the addition of Ferumoxytol was observed in blood $^1H$ signal as well as in saline phantoms, but not in the $^{31}P$ blood pool signal. This discrepancy is most probably again caused by the intracellular location of $^{31}P$ metabolites: while the comparatively far-field alterations to magnetic field homogeneity caused by Ferumoxytol can affect the $^{31}P$ metabolites bound within cells shortening their $T_2$, there is no direct interaction between the contrast agent and $^{31}P$ metabolites to affect their $T_1$. However, the $T_2$ shortening effect, together with the long blood pool phase of ferumoxytol suggest that it might be of great use in suppressing blood pool signals in $^{31}P$-MRS.\textsuperscript{30}

All our experiments were performed at ultra-high field, which could be considered a limitation of our study, as relaxation times vary with the external magnetic field. We note also that the experiments were not performed at 37°C, which will further quantitatively alter the measured relaxation times and contrast agent relaxivities, approximately linearly with temperature,\textsuperscript{31,32} but argue that this compromise was necessary to the success of the experiment, as evidenced by the stability of the pH of the blood. We note that a simple phantom experiment would not represent the \textit{in vivo} situation well and, as our data show, would result in incorrect conclusions. Therefore, in order to secure sufficiently high SNR and scan times short enough to ensure the \textit{ex vivo} viability of small blood samples, the use of ultra-high field, constant slightly reduced temperature, and RF coils matched to the size of the sample vials was essential. We also note that, in particular, the $T_2$ and, for larger $^{31}P$ metabolites also the $T_1$, shortens with increasing field strength.\textsuperscript{33} Therefore, although quantitatively likely to be different in magnitude, these effects of the tested contrast agents will exist at clinical field strengths, and may well be more pronounced at lower fields.\textsuperscript{34}

\section{CONCLUSIONS}

$^{31}P$-MRS is affected distinctly by different contrast agents to conventional proton MRS/MRI, and in particular is not subject to the potentially confounding effects from Dotarem (Gd-DOTA) or iopamidol that may have been administered separately. This fact both aids protocol planning within an MR session, and additionally enables greater flexibility in multi-parametric investigations. Moreover, we have provided the novel demonstration that ferumoxytol does significantly reduce the $^{31}P$ $T_2$ of 2,3-DPG in blood, which may be exploited by future studies to suppress unwanted blood signal in cardiac $^{31}P$ MRS.

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