On Contrast-Enhanced MR Imaging in the Presence of Pathological Plasma-Protein Concentrations

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Purpose

To measure the response of r_1 and r_2 relaxivities of commercially available gadolinium-based contrast agents (GBCA) to the individual variations of the concentrations of two plasma-proteins as they commonly occur in various pathologies and in a substantial fraction of patients routinely undergoing clinical GBCA-enhanced MRI.

Materials and Methods

In this in-vitro study contrast medium (gadofosveset trisodium, gadoxetate disodium, gadobutrol, and gadoterate meglumine) dilution series (0 to 2.5 mmol Gd/L) were prepared with plasma-protein (albumin, HSA, and immunoglobulin G, IgG) concentrations at physiological (42 and 10 g/L HSA and IgG, respectively, "Normal") and at 3 pathological levels (HSA/IgG, [g/L]: 10/10 "Alb low", 42/50 "IgG mild", 42/70 "IgG severe"). Contrast-agent molar relaxivities and relaxivity-enhancing protein-contrast-agent interaction coefficients were determined based on inversion-recovery and spin-echo data acquired at 1.5T and 3.0T at 37°C. Pooled relaxation rates of a contrast-agent dilution series at given field strength, at all protein concentrations levels and from both dilution series, were fitted by least-square linear regression to the following expressions: $R_{1,2}(c,\ c^{HSA},\ c^{IgG}) = R^{pre}_{1,2\,0} + r^{HSA}_{1,2}\,c^{alb} + r^{IgG}_{1,2}\,c^{IgG} + \left(r^{H_2O}_{1,2} + re^{HSA}_{1,2}\,c^{HSA} + re^{IgG}_{1,2}\,c^{IgG}\right)c$, (c: contrast-agent concentration, c^{HSA} and c^{IgG}: albumin and IgG concentrations, indices 1 and 2: referring to longitudinal and transverse magnetization). Protein-induced MRI signal changes were calculated.

Results

The measured parameters characterizing relaxation of longitudinal magnetization are summarized in Table 1 and Figure 1.

***Table 1a**: **Effective longitudinal molar relaxivities of 4 contrast media at varying protein concentration and field strength**.*
(Absolute and relative (in %) changes from the "Normal" solution in parentheses. Low and high limits of 90 % confidence intervals in brackets.)

	B0 = 1.5 T				B0 = 3.0 T			
	gadofosveset	**gadoxetate**	**gadobutrol**	**gadoterate**	**gadofosveset**	**gadoxetate**	**gadobutrol**	**gadoterate**
NaCl only	**5.91** (-9.36/-61) [5.75–8.26]	**5.36** (-2.22/-29) [5.30–5.50]	**3.56** (-0.65/-16) [3.37–3.62]	**3.31** (-0.40/-11) [3.22–3.45]	**6.95** (-2.71/-28) [6.25–7.43]	**5.70** (-1.49/-21) [5.24–6.15]	**3.72** (-0.67/-15) [3.40–4.03]	**3.46** (-0.48/-12) [3.10–3.81]
Alb low	**8.58** (-6.69/-44) [7.57–9.64]	**6.27** (-1.31/-17) [5.80–6.36]	**3.84** (-0.38/-9) [3.76–3.96]	**3.53** (-0.19/-5) [3.46–3.64]	**7.71** (-1.95/-20) [7.16–8.07]	**6.23** (-0.96/-13) [5.85–6.57]	**3.91** (-0.48/-11) [3.64–4.15]	**3.65** (-0.29/-7) [3.37–3.92]
Normal	**15.27** (0.00/0) [9.67–15.77]	**7.60** (0.00/ 0) [6.92–8.30]	**4.22** (0.00/0) [3.60–4.84]	**3.72** (0.00/0) [3.37–4.10]	**9.66** (0.00/0) [5.59–9.89]	**7.17** (0.00/0) [7.09–8.24]	**4.38** (0.00/0) [4.17–4.56]	**3.93** (0.00/0) [3.75–4.11]
IgG mild	**17.61** (2.32/+15) [15.52–18.64]	**9.60** (+2.00/ +26) [9.40-9.84]	**4.84** (+0.60/+14) [4.55-5.08]	**4.34** (+0.60/+16) [4.26-4.49]	**10.28** (+0.60/+6) [9.26-11.06]	**8.09** (+0.92/+13) [7.63-8.28]	**4.53** (0.16/+4) [3.89-4.85]	**4.34** (+0.40/+10) [4.20-4.44]
IgG severe	**18.78** (+3.48/+23) [14.79-19.70]	**10.58** (+3.00/+40) [9.30-11.67]	**5.14** (+0.90/+21) [4.46-5.42]	**4.64** (+0.90/+24) [4.38-4.70]	**10.58** (+0.90/+9) [9.30-11.67]	**8.55** (+1.38/+19) [8.06-8.87]	**4.60** (0.24/+5) [3.31-5.00]	**4.54** (+0.60/+15) [4.35-4.72]

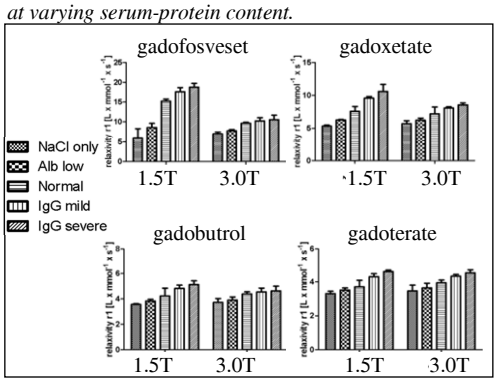
Table 1b**: **Longitudinal relaxivity parameters of 4 contrast media, albumin and IgG at 1.5 and 3 Tesla

r_1^{H2O} b)	**5.91** [5.75–8.26]	**5.36** [5.30–5.50]	**3.56** [3.37–3.62]	**3.31** [3.22–3.45]	**6.95** [6.25-7.43]	**5.70** [5.24-6.15]	**3.72** [3.40-4.03]	**3.46** [3.10-3.81]
re_1^{HSA} c)	209 [152-516]	41 [21-62]	12 [(-7)-32]	6 [(-5)-19]	61 [11-80]	30 [17-47]	15 [4-27]	9 [(-2)-20]
re_1^{IgG} c)	58 [(-16)-76]	50 [35-63]	15 [(-1)-31]	15 [7-22]	15 [(-8)-55]	23 [5-30]	4 [(-13)-12]	10 [4-16]
r_1^{HSA} d)	-3 [(-18)-2]	1 [(-1)-2]	1 [(-2)-4]	1 [0-4]	1 [0-2]	0 [0-1]	0 [(-2)-2]	0 [(-1)-2]
r_1^{IgG} d)	1 [0-3]	2 [1-3]	2 [1-3]	2 [1-5]	2 [0-2]	2 [1-3]	3 [2-5]	3 [2-5]
re_1^{HSA} / re_1^{IgG}	3.6	0.8	0.8	0.4	4.1	1.3	3.8	0.9
r^2 e)	0.987	0.999	0.990	0.997	0.990	0.997	0.995	0.995
$rmse$ f)	4.19	2.87	3.56	4.37	2.36	1.92	3.94	4.42

b) contrast-agent relaxivity in aqueous sodium chloride solution, in units of L s^{-1} $mmol^{-1}$, c) protein-specific relaxivity-enhancement due to contrast-agent- protein interaction, in units of $L^2 s^{-1}$ $mmol^{-1}$ kg^{-1}, d) protein-specific relaxivity, also affecting pre-contrast relaxation rates, in units of L s^{-1} kg^{-1}, e) squared linear regression coefficient, f) root of mean squared error, in units of s^{-1}.

Effective r_1 and r_2 consistently increased with albumin and IgG concentrations; r_1 by 10.2 (1.5T) / 2.9 L s^{-1} $mmol^{-1}$ (3.0T) from "Alb low" to "IgG severe" (gadofosveset), 4.3 / 2.3 (gadoxetate), 1.3 / 0.7 (gadobutrol), and 1.1 / 0.9 (gadoterate). Excess IgG most strongly increased r_1 of gadoxetate (+40 and +19 % at 1.5T and 3.0 T, respectively, from "Normal" to "IgG severe"). Albumin deficiency most strongly decreased r_1 of gadofosveset (-44 % and -20 % at 1.5T and 3.0T, respectively, from "Normal" to "Alb low"). The modelling confirmed strong gadofosveset r_1 enhancement by albumin and suggested stronger IgG than albumin effects on the relaxivity of the other agents per protein mass concentration at 1.5 T.

***Fig. 1:** Relaxivities r_1 at 1.5 T and 3.0 T, at 37 °C, and at varying serum-protein content.*



Conclusions

Our results show that GBCA molar relaxivities strongly depend not only on human serum-protein concentration but also on protein composition. Pathological deviations of protein concentrations like those found in liver failure, chronic inflammation, and multiple myeloma affect the r_1 and r_2 relaxivities in a way that is specific for the pathological condition. The signal characteristics of commonly applied MR imaging sequences may strongly be affected by alteration of albumin and immunoglobulin G. By extrapolation, similar variations may be expected for concentration variations of other proteins and for the variation of protein content and composition in the extracellular space, and, possibly, in different kind of lesions.