

**Disclosure:** All authors certify that they have no direct or indirect financial interest in the products, investigation or subject matter discussed in this abstract.

**CMR2009: 5.04**

**Post-mortem analysis of gadolinium distribution in NSF subjects**

P. Caravan,<sup>1</sup> J. Kay,<sup>2</sup> R. V. Mandal,<sup>3</sup> R. Uppal,<sup>1</sup> J. Welby,<sup>4</sup> A. Deb<sup>4</sup> and J. E. Penner-Hahn<sup>4</sup>

<sup>1</sup>A. A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA

<sup>2</sup>Rheumatology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

<sup>3</sup>Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

<sup>4</sup>Department of Chemistry, The University of Michigan, Ann Arbor, MI, USA

**Rationale and Objectives:** Nephrogenic systemic fibrosis (NSF) is a debilitating fibrosing disorder that develops in patients with underlying kidney disease, following exposure to gadolinium (Gd) MRI contrast agents. Gd has been quantified in the skin and internal organs of NSF subjects upon postmortem analysis (1,2). We sought to better understand the organ distribution of Gd in NSF subjects and hypothesized that *ex vivo* MR imaging and X-ray fluorescence (XRF) imaging may inform on the distribution and speciation of Gd in various organs. If the Gd is in a form accessible to tissue water, one expects shortened  $T_1$ ,  $T_2$  and  $T_2^*$ . If the Gd is highly concentrated and localized, e.g. precipitated, it should only have a strong  $T_2^*$  effect. XRF would indicate whether Gd deposits are strongly correlated with other element(s) like calcium or phosphorus.

**Methods:** Formalin-fixed tissue (skin, heart, kidney, liver, lung, muscle) from three confirmed NSF cases was obtained. Subjects had all received gadopentetate dimeglumine and Magnevist (Bayer Healthcare) in cumulative doses ranging from 35 (patient A, two doses over 14 month), 130 (B, seven doses over 16 months), to 198 ml (C, 9 doses over 64 months). Tissue from age-matched controls were used for comparisons. Gd was determined by ICP-MS. Tissue *ca* 5 mm<sup>3</sup> was suspended in an inert perfluorocarbon matrix and  $T_1$ ,  $T_2$ ,  $T_2^*$  maps were obtained at 9.4 T. XRF measurements for Gd, Fe, Cu, Zn, Ca, K, P and S were made on thin tissue slices.

**Results:** All tissues assayed by ICP-MS contained Gd (5–180 ppm in wet tissue). Organ distribution varied, but extremely high Gd values were observed in the kidney cortex and the heart (left ventricle), with lower levels in the liver and other tissues. MRI revealed uniform Gd distribution in the heart samples with a strong  $T_2^*$  effect, suggesting the Gd has little access to tissue water. Kidney showed regions with short  $T_1$ ,  $T_2$ ,  $T_2^*$  and these were heterogeneously distributed. XRF revealed Gd in all tissue types studied and qualitatively confirmed the MR findings of Gd

tissue distribution. There was no correlation of Gd with Ca or P, but in some samples, e.g. Figure 1, Gd showed clear correlation with Cu, Zn and/or Fe.

**Conclusion:** Very high Gd concentrations are found in kidney and cardiac tissue of NSF patients in contrast to Gd distributions observed in rodent models (3). *Ex vivo* MR and XRF may inform on Gd distribution and speciation within tissue.

**References**

1. Swaminathan S, High WA, Ranville J, Horn TD, Hiatt K, Thomas M, Brown HH, Shah SV. *Kidney Int* 2008; **73**: 1413.
2. Kay J, Bazari J, Avery LL, Koreishi AF. *New Engl J Med* 2008; **358**: 827.
3. Tweedle MF, Wedeking P, Kumar K. *Invest Radiol* 1995; **30**: 372.

All authors must certify that they have no direct or indirect financial interest in the products investigated or subject matter discussed in this abstract.

**Session 5 (Part 2): Gadolinium**

**CMR2009: 5.05**

**Stimulation of cultured human dermal fibroblast collagen production by gadolinium chelates**

S. Morcos,<sup>1</sup> S. Bains,<sup>2</sup> C. Johnson<sup>2</sup> and S. MacNeil<sup>2</sup>

<sup>1</sup>Department of Diagnostic Imaging, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

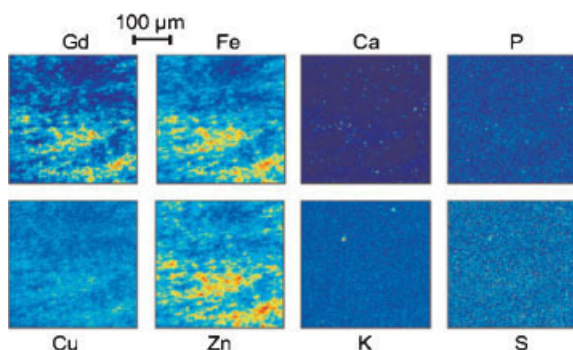
<sup>2</sup>Department of Engineering Materials, Kroto Research Institute, University of Sheffield, Sheffield, UK

**Purpose:** In patients with renal insufficiency who have been exposed to gadolinium-based contrast agents (Gd-CA) a syndrome of nephrogenic systemic fibrosis (NSF) with a spectrum of aberrant dermal remodeling has been identified. The exact pathogenesis is uncertain but low stability of Gd-CA leading to the release of free gadolinium has been proposed as an important factor in triggering this condition. The purpose of this study was to look at the direct effects of Gd-CA with different stability on cultured human dermal fibroblast proliferation and collagen production.

**Method and Materials:** Human fibroblasts were cultured from patients donating skin following elective operations. Cells were cultured in DMEM medium plus 10% fetal calf serum and exposed to a range of concentrations of Omniscan (low stability non-ionic linear chelate, GE Health Care, USA), Dotaram (high stability ionic macrocyclic agent, Guerbet, France) or GdEDTA (very low stability linear Gd-chelate, positive control) for 3 or 7 days. Cell proliferation was assessed using the MTT ESTA colorimetric assay and total collagen production by the use of Sirius Red.

**Results:** While indicative results could be seen at 3 days, clearly significant results were obtained after 7 days' exposure of cells to the gadolinium chelates. Gd-EDTA had a slight (15%) stimulatory effect on cell proliferation and concomitant collagen production at 0.1 mM. Higher concentrations significantly reduced proliferation and collagen production by 10% at 1 mM and by 80% at 10 mM in comparison to the control group (only culture medium). Dotaram, studied at concentrations from 0.01 to 1 mM had no significant effect on cell proliferation or collagen production. However, 10 mM Dotaram slightly reduced both proliferation and collagen production by approximately 20%. The most marked results were seen with Omniscan. Concentrations as low as 0.01 mM stimulated proliferation and collagen production and a maximum increase of 30–50% was observed with 1 mM concentration. Higher concentrations were less stimulatory.

**Conclusion:** These results clearly show that Gd-CA of low stability (Omniscan) have direct stimulatory effects on fibroblast proliferation and collagen production, readily demonstrated over 7 days. The highly stable macrocyclic agent Dotaram had no stimulatory effects on fibroblasts. The study offers some support for the importance of the stability of Gd-CA in the pathogenesis of NSF.



**Figure 1.** Representative XRF image of left ventricular tissue showing partial correlation of Fe, Zn and Cu distribution with that of Gd.