Dynamic Contrast Enhanced MRI Assessment of Synovitis in Hemophilic Arthropathy

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Introduction: A preliminary study of 11 hemophilia subjects was performed to assess the degree of synovitis in the joint using dynamic contrast enhanced (DCE) MRI. Subjects with hemophilia suffer from recurrent hemarthroses as a consequence of their bleeding disorder which stimulates synovial proliferation(synovitis) and arthropathy causing hemophilic joint disease(HJD). After the development of synovitis (hypertrophied synovium characterized by villous formation, increased vascularity and chronic inflammatory cells) a vicious cycle of hemarthroses – synovitis – hemarthroses is established which is difficult to control. Increased perfusion associated with increased synovial vascularity was detected using DCE-MRI techniques and correlated with synovial thickness, synovitis and serum vascular endothelial growth factor (VEGF).

Methods: MRI studies were acquired on 11 hemophilia patients with bleeds into various joints including: knee (n=5), ankle (n=4), elbow (n=2). All studies were acquired on a 3.0T GE MRI scanner using a single channel linear extremity coil. Clinical imaging sequences assessed the degree of synovitis and synovial thickness and included: proton density weighted fast spin echo, gradient echo, fat suppressed inversion recovery and post-contrast T_1-weighted spin echo images. The degree of synovitis was assessed with conventional MRI sequences assigning the following grades: none (0), mild (1), moderate (2) and intense (3). Gadopentetate dimeglumine (Gd-DTPA) was administered at 0.1 mM/kg followed by a saline flush for the dynamic scans. DCE studies were acquired using a 3D fast gradient echo (FAME) sequence. The joint was covered contiguously with 3-4 mm thick sections yielding 12-24 slices at a temporal resolution between 4-8 seconds. Acquisition parameters included a 5-7 ms repetition time (TR), a 2-3 ms echo time (TE), 12° flip angle, 31.25 kHz receive bandwidth, 14-21 cm field of view (FOV) and a 256 x 128 matrix yielding a voxel resolution of 5-10 mm^3. Data were acquired for a total of 35-60 time points in scan times of less than 5 minutes yielding between 600-840 images. Figure 1 displays a representative FAME image (A) from the DCE study adjacent to a corresponding static post-contrast T_1-weighted image (B) and the resulting time intensity curve (TIC) (C) placed in a region of enhancing synovium with slope and model fits.

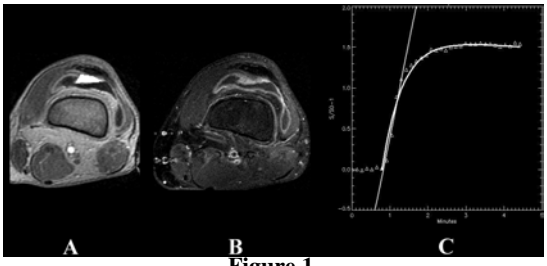


Figure 1

Analysis software was written in-house using IDL 6.2 (ITT Visual, Boulder,CO). A single region of interest (ROI) was placed on an area of synovitis and the time intensity curve was fitted with the initial uptake slope and perfusion parameters from the Brix two-compartment model. The model contains three parameters: A (signal amplitude), k_{ep} (exchange constant between plasma and extravascular compartments in min^{-1}), and k_{el} (elimination constant in min^{-1}). The product Ak_{ep} is related to the initial uptake slope while k_{el} represents the washout characteristics of the TIC. The 5 minute scan time prohibited complete evaluation of clearance in the synovium (k_{el}) as signal was still increasing in some cases. Non-parametric statistical tests were used to assess significance between data sets given the small sample size. A Spearman rank order correlation coefficient was used to determine statistical significance ($p<0.05$) between DCE-MRI parameters and clinical tests. A Mann-Whitney test was used to determine significance between serum VEGF levels of patients grouped by degree of synovitis.

Results: DCE perfusion parameters of initial uptake slope and Ak_{ep} model parameter were correlated with the degree of synovitis (Figure 2). Perfusion parameters were also correlated with synovial thickness and serum VEGF levels as shown in Table 1. Figure 3 compares serum VEGF level between patients categorized as having intense synovitis and all others. Patients having synovitis of grades 0,1,2 (n=6) yielded mean serum VEGF levels of 145.1 ± 96.4 pg/ml compared with those having grade 3 synovitis (n=4) 459.6 ± 272.7 pg/ml [Mann-Whitney Test, p=0.057]. One patient had three intracranial bleeds and was excluded from the serum VEGF data having a value of 1879.6 pg/ml which was 18 standard deviations above the mean level for all patients having degrees of synovitis ranging from grades 0 through 2.

Table 1	MRI Degree of Synovitis (0,1,2,3)	MRI Synovial Thickness (mm)	Serum VEGF Levels (n=10) (pg/ml)
MRI Slope (%/min)	$R^2 = 0.90$, $p<0.001$	$R^2 = 0.75$, $p=0.001$	$R^2 = 0.42$, $p=0.042$
MRI Ak_{ep} (1/min)	$R^2 = 0.88$, $p<0.001$	$R^2 = 0.62$, $p=<0.05$	$R^2 = 0.28$, $p=0.116$

Figure 2

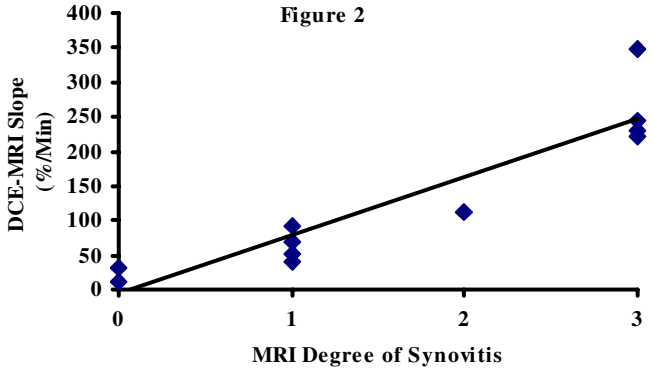
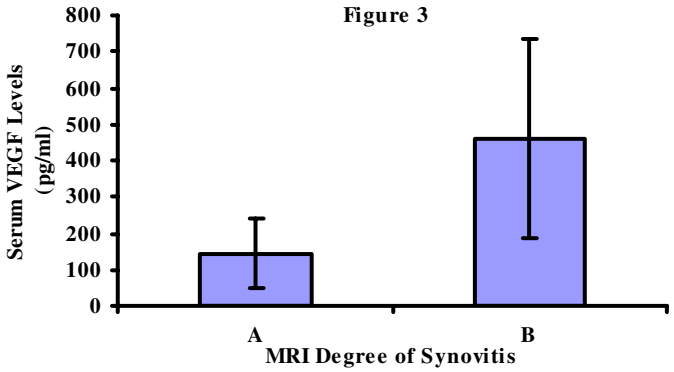


Figure 3



Discussion: DCE-MRI parameters correlated with the degree of synovitis, synovial thickness and the angiogenic growth factor VEGF in hemophilic arthropathy patients. Although having a different etiology, a study of rheumatoid arthritis (RA) patients reported serum VEGF levels in a control population of 169.7 ± 76.3 pg/ml (n=32) versus those of 632.6 ± 279.3 pg/ml (n=32) for all RA patients (1). Our study also showed elevated serum VEGF levels in hemophilic joint disease (HJD) patients having grade 3 synovitis compared with lower grades. Correlation of DCE-MRI parameters with clinical estimators of disease progression may provide a means of monitoring serial response to treatment in patients with hemophilic joint disease. **References:** 1) Clinical Rheum 2006;25:314-319.