Differences in perfusion parameters of the vertebral bone marrow in patients with chronic Philadelphia\textsuperscript{neg} myeloproliferative neoplasms (Ph\textsuperscript{neg}MPN's) using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI)

Poster No.: C-2388
Congress: ECR 2010
Type: Scientific Exhibit
Topic: Musculoskeletal
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Keywords: dynamic contrast enhanced magnetic resonance imaging, chronic Philadelphia-neg myeloproliferative neoplasms, bone marrow perfusion
DOI: 10.1594/ecr2010/C-2388

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**Purpose**

DCE-MRI is a noninvasive quantitative method for studying microvascular structure and function by tracking the pharmacokinetics of injected gadolinium-based agents as they pass through the tumor vasculature. This technique provides a direct quantification of blood vessel density, vascular flow and permeability.

The purpose of this study was to evaluate perfusion parameters of the vertebral bone marrow in patients with Ph\textsuperscript{neg}MPN's using DCE-MRI.

**Methods and Materials**

The study enrolled 24 patients with bone marrow biopsy proven Ph\textsuperscript{neg}MPN's, 12 with idiopathic (n=8) or secondary (n=4) myelofibrosis (group A) and 12 with polycythemia, including ET (n=6) and PV (n=6) (Group B). Seventeen normal individuals who were referred for back pain served as control group (Group C).

All patients and healthy control individuals underwent conventional and DCE-MRI of the lumbosacral spine on a 1T superconducting MR imager (General Electric, Milwaukee, USA). A standard quadrature RF body coil was used in all measurements for signal excitation and a spine array surface coil was used for signal detection. Conventional 2D Spin Echo (SE) and 2D Short Tau Inversion Recovery (STIR) sequences were utilized in sagittal anatomical planes. Conventional MR sequences included a 2D multislice T1-weighted SE (TR/TE : 440ms/12ms) and a 2D multislice T2-weighted STIR (TR/TE/TI : 3040ms/113ms/110ms).

Dynamic Contrast Enhanced -MRI (DCE-MRI) examination of the spine was performed utilizing a 2D multislice T1-weighted 2D fast gradient-echo sequence (TR/TE/FA : 7.6ms/2.3ms/350). A rectangular FOV of 300X196 mm\(^2\) and a reconstruction matrix of 256 X 168 pixels were used. Three consecutive slices of 8mm slice thickness and no interslice gap were obtained in sagittal plane. The sequence was repeated every 9s for a total of 7.08min, thus obtaining 50 dynamic acquisitions (images) with 9 s temporal resolution for each of the three slices. Immediately after the end of the third dynamic acquisition, a bolus of 0.1mmol/kg body weight of gadobutrol (Gadovist, Schering AG, Germany) was injected manually through a catheter inserted in the antecubital vein, with an injection time ranging from 7 up to 10 secs. The mid-sagittal anatomical slice with its relative dynamic image acquisitions were chosen for further DCE analysis.

Region of Interest (ROIs) were manually placed on every vertebra of the lumbar spine and time-intensity curves (TICs) were generated. Sites of degenerative end-plate changes, localized hemangiomas or Schmorl nodes were carefully excluded.
from the ROI surface. All basic dynamic images and ROI signals were transferred to a research PACS workstation for further analysis (EVORAD research RIS/PACS system, www.evorad.com, EVORAD, Athens, Greece). Fifty (50) time-signal values were obtained for each lumbar vertebra of each patient. The net dynamic contrast enhancement (DCE) values for each ROI were obtained by subtracting all ROI signal values from the initial unenhanced baseline signal prior to contrast administration. The final 50 discrete point DCE curve was subsequently constructed utilizing the net DCE values (arb.units) and the relative time (t) values (sec).

At a final step the 50 discrete point DCE curves obtained from each ROI were fitted by means of a non linear regression method based on the Marquardt algorithm, and to an Exponentially Modified Gaussian (EMG) equation (1,2,3) [Figure 1]. For all fits, r² was ≥ 0.8. This value was used as a threshold for the estimation of goodness of each fit. EMG function serves as an alternative analytical solution to the differential equation which thoroughly describes the two compartment model applied in T1 dynamic contrast enhancement studies according to Tofts and Brix formulation (4,5,6).

Wash-in (WIN) and wash-out (WOUT) rates were calculated for the vertebrae of each patient from the maximum and minimum slopes recorded on the Y-axis of the first derivative function d(DCE)/dt = f(t), respectively [Figure 1]. Time to peak (TTPK) and time to maximum slope (TMSP) values were obtained from the X-axis of the first derivative function d(DCE)/dt =f(t) (1,2,3) [Figure 1]. The maximum Contrast Enhancement (CE max) value was obtained from the function peak recorded on the Y-axis of the standard DCE = f(t) curve [Figure 1]. The ratio WTSP (WIN/TMSP) was also calculated. WIN and WOUT are expressed in (sec⁻¹) units and reflect the rate of contrast medium inflow and outflow, respectively. TMSP is measured in (sec) units and reflects the specific time point where WIN is maximum. TTPK is expressed in (sec) units and reflects the specific time point where contrast enhancement is maximum (1,2,3). WTSP ratio is expressed in (sec⁻²) units and reflects the rate of change of WIN values. CEmax is expressed in arbitrary units and reflects the maximum amount of contrast material that accumulates into the bone marrow vertebra under study.

All the curve fitting procedures for the calculation of perfusion data were performed utilizing the Table Curve 2D (Systat, Software Inc., Chicago IL, USA) software. Further statistical analysis on perfusion data was performed utilizing the MedCalc (MedCalc Software, 9030 Mariakerke, Belgium) software. All measurement data were expressed as mean ± Standard Error of the Mean (SEM). Student-Newman-Keuls test for all pair wise comparisons and Statistical results (p values) using ANOVA analysis for differences between mean WIN, WOUT, CEmax, TTPK and TMSP values, and WTSP ratios were performed amongst sample groups. ROC analysis was performed to estimate the sensitivity and specificity of each calculated perfusion parameter. A Kolmogorov-Smirnov test was used for test the normality of the data samples.
Fig. 1: Figure 1: Perfusion parameters according to Marquadt algorithm fitted to an Exponentially Modified Gaussian (EMG) equation.
Results

DCE MRI of the lumbar spine demonstrated significant differences in perfusion parameters between the Group A and Groups B or C. On the contrary, there were not significant differences amongst Group B and C. Our data indicate an increased perfusion in patients with MF.

The mean and median values of the calculated parameters WIN, WOUT, CEmax, TTPK, TMSP and WTSP related to the three study groups (A, B and C) are presented in [Figure 2].

WIN, DCE\textsubscript{max}, and WTSP parameters were higher in Group A than in Group C (ANOVA post hoc, Student-Newman-Keuls test, P<0.05). ROC analysis gave area under the curve (AUC) for WIN (= 0.798), for DCE\textsubscript{max}, (=0.887) and for WTSP (=0.805) and these parameters were significant (P<0.0001) in discriminating patients with myelofibrosis from normal individuals with sensitivities 74.14%, 86.21%, 74.14% and specificities 81.48%, 79.01%, 81.48%, respectively.

WIN, WOUT, DCE\textsubscript{max} and WTSP were higher in Group A than in B (P<0.05). In ROC analysis, WIN, WOUT, CEmax parameters and WTSP ratio were significant (P<0.0001) with sensitivities 69.64%, 75%, 87.5%, 67.86% and specificities 82.76%, 75.86%, 82.76%, 81.03% respectively.

Group B exhibited no differences as compared with Group C with the exception of WOUT (AUC=0.809, P<0.0001) showing sensitivity 75.0% and specificity 60.49% in discriminating Group B from C patients.

Images for this section:
**Fig. 1:** Figure 2: Group A corresponds to patients with myelofibrosis. Group B corresponds to patients with polycythemia vera and essential thrombocytemia. Group C corresponds to norma individuals - control group.
Conclusion

Patients with myelofibrosis exhibited increased perfusion parameters in vertebral bone marrow indicating increased vascularity, probably related to neoangiogenesis. Lumbar vertebral involvement in polycythemia was not associated by increased perfusion. Perfusion parameters may be of value in diagnosing and discriminating patients with Ph$^{neg}$MPN's.

References


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