



## ESTIMATION OF BONE MARROW CELLULARITY BY MEANS OF VERTEBRAL MAGNETIC RESONANCE

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### ABSTRACT

**Background and Objective.** A magnetic resonance (MR) signal shows an inverse correlation with bone marrow cellularity. In this study, we investigated the possibility of estimating the degree of bone marrow cellularity by means of this non-invasive technique.

**Methods.** In 25 patients with different hematological disorders and homogeneous bone marrow distribution, the percentage of bone marrow cellularity was compared to the MR signal of four mid-dorsal vertebrae in T<sub>1</sub> sequence. As internal control, the MR signal of the mid-dorsal spinal cord region was used. The results were expressed as the MR signal ratio (great mean MR signal of four vertebrae/MR signal of the spinal cord).

**Results.** The correlation coefficient (r) between both parameters was -0.93 (p < 0.0001). All

observed values fell within the 90% limits of predicted values. The mean difference between observed and predicted bone marrow cellularity was 5.6 (SD 4.0)%.

**Interpretation and Conclusions.** The measurement of the MR signal is not easy to standardize since it depends to a large degree on the control employed. The spinal cord proved to be a satisfactory internal control of the MR signal. Within defined conditions, MR can be useful for a rough estimate of bone marrow cellularity in several clinical situations, such as analysis of tumor burden for prognosis of some leukemias and the evaluation of response to therapy in both proliferative and hypoplastic disorders.

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*Key words:* magnetic resonance, hematopoiesis, bone marrow cellularity

Magnetic resonance (MR) imaging has become the non-invasive imaging modality of choice for contributing to the diagnosis of many bone marrow disorders,<sup>1-5</sup> such as aplastic anemia,<sup>6,7</sup> myelodysplastic syndromes,<sup>8-12</sup> acute and chronic leukemias,<sup>7,11</sup> hairy cell leukemia,<sup>13,14</sup> multiple myeloma,<sup>15-19</sup> malignant lymphomas,<sup>20-23</sup> myelofibrosis,<sup>24</sup> Gaucher's disease,<sup>25</sup> marrow necrosis,<sup>22</sup> marrow edema,<sup>26</sup> and metastatic cancer.<sup>27</sup> Additionally, MR can be useful for studying the normal age-related distribution of fatty and cellular bone marrow,<sup>28</sup> myeloid growth factor mediated expansion of bone marrow hemopoiesis,<sup>29</sup> as well as for prognosis<sup>19</sup> and evaluation of therapy in hematological malignancies,<sup>14,39</sup> and bone marrow assessment after transplantation.<sup>30,31</sup>

The MR signal depends chiefly on 3 factors: 1) proton density; 2) relaxation time (rapidity with which the energy of the magnetic field is liberated), and 3) presence or absence of flux (low signal of blood in movement, high signal of stagnant blood as in recent clots). As far as the relaxation time is concerned, MR signal intensity depends on the

sequence selected. Shortened T<sub>1</sub> relaxation time and prolonged T<sub>2</sub> relaxation time are associated with an increased MR signal, and viceversa. The MR image is the result of the computer-processed signal and its conversion into different degrees in the gray scale.

The MR signal of the bone marrow mainly depends on the proportion of fatty and cellular components. When studied in T<sub>1</sub>-sequence an increase in the cellular fraction is associated with a decrease in the MR signal, whereas an increase in the adipose tissue is associated with an increase in the MR signal. In the clinical setting, MR imaging is usually evaluated by qualitative means with reference to adipose and muscular tissue. Quantitative analysis has been carried out mostly by means of two different approaches: 1) *in vivo* measurement of T<sub>1</sub> relaxation time or rate<sup>10,32,33,39</sup> and 2) *in vivo* proton spectroscopy,<sup>26,29,30,34-36</sup> the latter being a relatively experimental method.

In the present study, we investigated the possibility of estimating the degree of bone marrow cellularity by using a MR signal.

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## Patients and Methods

### Patients

We studied 25 patients as part of the diagnostic evaluation. The criteria for inclusion were: 1) conditions with homogeneous distribution of bone marrow (estimated from MR signal) and maintenance of the reciprocity cell fraction/adipose fraction; 2) absence of iron overload; 3) absence of neurological disorders involving the spinal cord; 4) informed consent. The diagnoses of the patients were: aplastic/hypoplastic anemia (n = 4), myeloproliferative disorders (n = 8), myelodysplastic syndromes (n = 2) and lymphoproliferative disorders (n = 11).

### MR imaging

All patients underwent MR imaging with a 1.5-T superconducting MR unit (Magnetom 63 SP 1.5 Siemens, Erlangen, Germany). Sagittal images of the dorsal spine were obtained for qualitative analysis. For acquisitions used in quantitative analysis, the center of the magnetic field was placed at a point located 3 cm above the xyphoid process. The slices were 4 mm thick. The field of view (FOV) was 280 mm, and the matrix was 256×190 pixels (each pixel corresponding to 1.2 sq.mm). The spin-echo (SE) technique was employed and the T<sub>1</sub>-weighted images were obtained with a repetition time (TR) and echo-time of 550/15. The intensity of the MR signal was calculated from the following formula:

$$S_1 = (1 - \exp[-TR_{\text{eff}}/T_1])$$

where TR<sub>eff</sub> = TR - TE.

The acquisitions corresponded to a central sagittal slice with good definition of the dorsal spinal cord. Only cases with a homogeneous MR signal (both within and between vertebrae) were included in this study. The four central vertebral bodies were used for the quantitative estimation since they were placed near the center of the surface coil and therefore not subjected to a decrease in the signal at the edge of the image.<sup>7</sup>

User-defined cursors for regions of interest were placed on each of four central dorsal vertebrae, encompassing more than 50% of the central field of each vertebral body (area of interest 10×10 mm, corresponding to 62 pixels). The great mean of T<sub>1</sub> vertebral values was computed. As internal control, the MR signal of the mid-dorsal spinal cord (area of interest 4×14 mm, corresponding to 46 pixels) was used. The results were expressed as the MR ratio (great mean of MR dorsal vertebral bodies/MR signal of spinal cord) (Figure 1).

### Bone marrow biopsy

An iliac bone marrow biopsy was performed during the same period as the MR imaging (with less than 2 weeks difference and without any treatment). A Jamshidi needle was used for the bone marrow biopsy. Bone marrow was fixed in Bouin's fixative, decalcified with 10% nitric acid, and paraffin-embedded sections 4 μm thick were stained with hematoxylin and eosin. For a histomorphometric analysis of cellularity, a computer-assisted image analysis system (Microm España, Barcelona, Spain) was employed with "MIP" software. In each case, 10 fields at 50× magnification were randomly selected. Each image was segmented in order to obtain a separation between marrow cellularity and the remaining tissue. The percentage of the cell fraction was computed in each field. The mean percentage of cellularity was calculated.

### Statistical methods

Regression analysis was used to compare the MR ratio and percentage of bone marrow cellularity. In addition to calculating the correlation coefficient and its statistical significance, 90% limits of the predicted values were computed and graphically represented with *Statgraphics* software.

## Results

Table 1 presents a detailed analysis of the results in the four diagnostic groups: 1) aplastic/hypoplastic anemia (cases #1-4); 2) myeloproliferative disorders

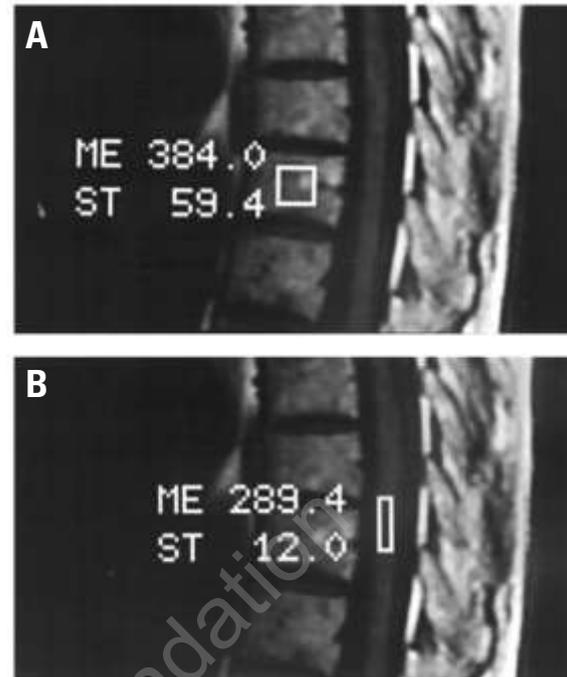


Figure 1. Method of computing the MR signal ratio. The MR signal corresponding to the vertebral bodies (only one of the four values is represented here) (A) is divided by the MR signal corresponding to the spinal cord (B), giving in this example a MR signal ratio of 1.33.

(cases #5-12); 3) myelodysplastic syndromes (cases #13 and 14), and 4) lymphoproliferative disorders (cases #15-25).

A comparison between the MR signal ratio and bone marrow cellularity is illustrated in Figure 2. A highly significant inverse correlation ( $r = -0.93$ ;  $p < 0.0001$ ) was found. Moreover, all observed values fell within the 90% predicted values.

From the regression equation, bone marrow cellularity was calculated as follows:

$$\text{bone marrow cellularity (\%)} = 131.2 - (79.6 \times \text{MR signal ratio})$$

The mean difference between observed and predicted bone marrow cellularity was 5.6 (SD 4.0)%. In order to further analyze the linear regression model, 15 cases were randomly selected for computation of the formula and the remaining 10 cases were used as a test population. The results were similar in this experiment. The mean difference between observed and predicted bone marrow cellularity was 6.6% (SD 3.6). Thus estimation of bone marrow cellularity can be considered to be roughly accurate.

Table 1. Detailed analysis of the results.

N°	Age	Sex	Diagnosis	BM cellularity (%)	MR signal ratio
1	15	F	AA	1.9	1.47
2	72	F	AA	19.5	1.32
3	22	F	AA	27.0	1.32
4	48	F	HA	37.2	1.12
5	72	M	CML	84.6	0.73
6	58	M	CML	81.5	0.75
7	50	F	CML	66.0	0.69
8	52	M	CML	61.2	0.90
9	83	M	ET	50.9	1.11
10	57	M	ET	47.3	1.13
11	44	M	ET	42.2	1.02
12	58	M	PV	55.9	0.93
13	56	M	MDS (RAEB-t)	71.5	0.71
14	25	M	MDS (RA)	42.0	1.07
15	59	M	CLL	44.2	1.23
16	57	M	CLL	60.5	0.71
17	36	F	HD*	40.9	1.16
18	14	F	HD*	56.0	1.00
19	59	M	HD*	31.7	1.28
20	70	F	HD*	22.0	1.36
21	41	M	HD*	40.0	1.20
22	69	F	NHL-low grade	51.8	1.03
23	73	F	NHL-low grade	68.8	0.78
24	53	M	NHL-high grade*	48.6	0.98
25	63	M	NHL-high grade*	55.1	1.03

Abbreviations: BM, bone marrow. MR, magnetic resonance. AA, aplastic anemia. HA, hypoplastic anemia. CML, chronic myelogenous leukemia. ET, essential thrombocythemia. PV, polycythemia vera. CLL, chronic lymphocytic leukemia. HD, Hodgkin's disease. NHL, non-Hodgkin lymphoma. MDS, myelodysplastic syndrome. RAEB-t, refractory anemia with excess of blasts in transformation. RA, refractory anemia. \*BM not involved.

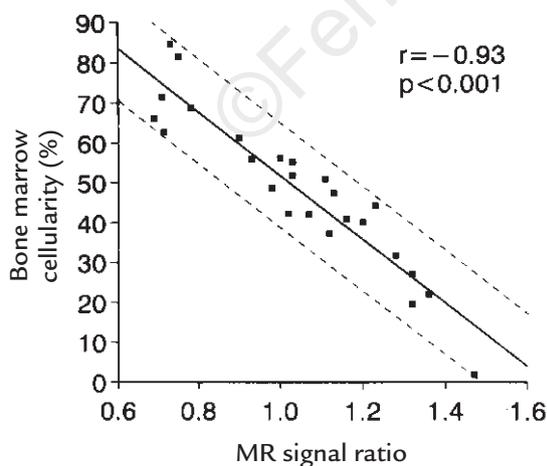


Figure 2. Comparison of the MR ratio and bone marrow cellularity. The straight line represents the least-square regression fit to the data. The outer lines correspond to the 90% prediction limits.

## Discussion

MR imaging provides a non-invasive means of roughly examining a large fraction of bone marrow in a relatively easy way. MR is complementary to bone marrow biopsy. Although it shows only the gross anatomy of the marrow, it can sample a large fraction of the active marrow in a single, non-invasive clinical investigation.

The inverse relationship between the prevalence of hemopoietic cellular components and adipose tissue is an established fact. The reciprocal variations in hemopoietic and adipose tissue are age related in healthy subjects and can also be observed in numerous pathological conditions. Since a bone marrow MR signal chiefly depends on the proportion of cellular and fatty components, the measurement of MR images yields useful information for diagnosis and follow-up. In the clinical setting, the intensity of the MR signal is usually evaluated by qualitative means with reference to adipose tissue, muscular tissue or cerebrospinal fluid (CSF), as shown in several studies.<sup>1-6,8,9,13-20,22-24,28</sup> In some instances, a description of particular MR patterns with prognostic significance have been recognized in multiple myeloma (focal, diffuse and variegated type).<sup>15-19</sup> Simple examination of the MR image can be useful for the detection of clonal disease in patients with hypoplastic marrow disorders.<sup>8</sup> MR imaging can be usefully exploited for the diagnosis of BM involvement in malignant lymphomas, particularly in Hodgkin's disease<sup>20-23</sup> and metastatic cancer.<sup>27</sup> In all these circumstances the MR imaging patterns are heterogeneous.

When dealing with a homogeneous appearance in a MR image, quantitative analysis may provide information on the proportion of cellular and non-cellular BM content. Such studies have been performed mainly through two different approaches: 1) *in vivo* measurement of T<sub>1</sub> relaxation time or rate,<sup>10,32,33</sup> and 2) *in vivo* proton spectroscopy.<sup>26,29,30,34-36</sup> The MR signal of hemopoietic bone marrow depends on proton density and the relaxation times. Most tissues have one dominating proton signal which causes more than 95% of the total signal intensity. For brain, muscle tissue, liver and kidney most of the signals stem from water protons. Peripheral yellow bone marrow and subcutaneous fat show that lipids represents nearly 100% of the source of the MR signal. Hemopoietic bone marrow differs from all other tissues in one important property: in normal individuals there are nearly equal fractions of water (hemopoietic cells) and lipids (fat cells). Standard MR images are the result of two opposing signals coming from cellular and adipose components. Standard imaging is sensitive only when T<sub>1</sub> weighted methods are applied. The signal is higher as the adipose tissue increases. A low signal is recorded in cases of a decreased num-

ber of fat cells. In such circumstance, high cellularity is mostly responsible for the signals but trabecular density and myelofibrosis may also influence them since bone and connective tissue exhibit a very low signal intensity. Standard  $T_1$  weighted images do not distinguish the BM of healthy individuals with high cellularity from those with acute leukemia, although this separation may be achieved by employing volume selective MR spectroscopy.<sup>34-36</sup>

In this study, we investigated the possibility of estimating the degree of bone marrow cellularity by means of MR. Considering that in a previously published study,<sup>32</sup> a highly significant but relatively poor correlation coefficient (-0.74) was found between  $T_1$  relaxation time and BM cellularity, we tried to improve the experimental conditions. Thus, only patients with a homogeneous distribution of bone marrow (as estimated from homogeneous MR signals both within and between vertebrae) who maintained a reciprocal relationship cellularity/adipose tissue were studied. Furthermore, cases with a history of heavy transfusion were not included since the typical appearance of fatty marrow (bright signal in  $T_1$  weighted images) can be altered by the presence of hemosiderosis.<sup>8</sup> Similarly to other authors,<sup>7</sup> we used only the centrally placed dorsal vertebrae for quantitative analysis, since these are not subject to a decrease in the signal at the edge of the image. All these conditions, except for the maintenance of a reciprocal relationship cellularity/adipose tissue, can be defined without bone marrow biopsy. In the great majority of cases of homogeneous bone marrow distribution, the reciprocal relationship cellularity/adipose tissue is kept. There are, however, a few exceptions which must be taken into account, namely myelofibrosis, marrow necrosis and gelatinous transformation of bone marrow as observed in anorexia nervosa. In these cases, in which adipose tissue is not replaced by cells but by other substances, the present method would not yield valid results.

Measurement of the MR signal is not easy to standardize since it depends to a large degree on the control employed. In some studies external phantoms have been employed as standard reference, while subcutaneous fat, muscle and CSF have been used as internal control. However, in a prolonged search for a reliable reference point, we have not succeeded in obtaining satisfactory results by employing subcutaneous fat, muscle or CSF, probably because these are either placed on the extremes of the gray scale (fat, CSF) or are too separated from the vertebral bodies (muscle). Other unsuccessful attempts to standardize the MR signal with subcutaneous fat have been reported.<sup>32</sup> From an empirical analysis of many MR images, we envisaged the possibility of employing the spinal cord as a reference point since it is located in the vicinity of the vertebral bodies. Furthermore, we became

aware from qualitative examinations that in general patients with decreased bone marrow cellularity displayed a brighter image than the spinal cord, whereas the reverse was true for patients with increased cellularity. In other words, the spinal cord seemed to represent roughly a middle point on the gray scale. For this reason, we selected the spinal cord for internal control of the MR signal. Obviously, this cannot be used if a spinal cord disorder is present. Moreover, an important technical detail was the selection of an area of the spinal cord instead of a single point in order to avoid the error caused by the inhomogeneity of nervous tissue.

With the improvement of the experimental conditions, namely the selection of a reliable internal standard, we observed a fairly good correlation coefficient (-0.93) between the MR ratio and bone marrow cellularity. Moreover, all observed values fell within the 90% predicted limits. In other words, within the defined experimental conditions, MR may be suitable for a rough estimation of bone marrow cellularity and might be usefully exploited in certain clinical situations, such as an analysis of tumor burden for prognosis of some leukemias, evaluation of response to therapy in both proliferative<sup>39</sup> and hypoplastic disorders, and others.

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