Whole liver iron overload measurement by a non cryogenic magnetic susceptometer

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Abstract. Assessment of body-iron accumulation is essential for managing therapy in diseases such as thalassemia, hereditary hemochromatosis and other anemias. The invasive liver biopsy leads to large error due to the heterogeneous distribution of iron deposition in the liver. The susceptometer presented herein measures the difference (iron overload) between the total amount of iron within the patient liver and the quantity in the liver of a normal person with the same anthropometric data. All of its components operate at room temperature. Since February 05, about 150 patients and 90 healthy volunteer controls have been measured. The total iron content of a normal liver ranges from about 0.5 g to 1 g. Iron overloads up to 18±1 g have been measured. The reproducibility of the iron overload of the same patients, measured after a relatively short period of time, is better than 0.5 g. The data obtained shows that this susceptometer is a reliable instrument for the diagnosis of liver iron overload and for the follow-up further treatment. It is simple to operate, managed directly in the Clinical Center and more affordable than other competing techniques.

Keywords: Iron overload; susceptometer; thalassemia; liver iron concentration; LIC;

1. Introduction

Accurate assessment of body-iron accumulation is essential for managing therapy of iron-overload in diseases such as thalassemia, hereditary hemochromatosis, myelodysplasia and other anemias. The invasive liver needle biopsy leads to a large error, in assessing iron burden, due to the heterogeneous distribution of iron deposition in the liver [1]. The liquid helium cooled SQUID biosusceptometers [2-4] and MRI [5,6] are currently the only validated non-invasive methods for liver iron concentration (LIC) measurements.

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The signal measured by the susceptometer presented herein, named Magnetic Iron Detector (MID), has two sources: a possible contribution from liver iron excess (overload) and an overall magnetic signal (background) from the patient body, supposed with a normal iron content [7]. Statistical analysis method is employed to estimate this background signal for each patient, given his anthropometric data and the measurement of about 90 male and female healthy volunteers. These controls have been chosen to cover a large fraction of the anthropometric data of the adult human body. Liver-iron overload is then determined subtracting the estimated background from the total measured signal. The iron concentration in normal liver is a few hundred micrograms per gram of wet tissue (g_{ww}) and more than 10 mg/g_{ww} for overload states [1], [8]. The total iron content in normal liver ranges from about 0.5 g to 1 g; iron overload up to 18±1 g have been measured. The error (about 1 g) comes mainly from the background signal calculation, the contribution of the apparatus noise is at least three times smaller and by increasing the number of healthy volunteers measured would decrease the background error further. The reproducibility of the iron overload of the same patients, measured after a relatively short period of time, is better than 0.5 g. Since February 05, 150 patients have been measured in the "Centro per la Microcitemia" of the "E.O. Ospedali Galliera" in Genoa, Italy. The local Ethics Committee approved the study and all subjects gave informed consent.

2. Instrumentation

Susceptibilities arise from competition between the aligning effect of the applied field and thermal vibrations. For instance, the contribution to the body susceptibility of iron atoms with an effective magnetic moment of 4 Bohr magneton, a temperature of 310 K and a concentration of 0.5 mg/g_{ww} is 7 10^{-7} [9]. Normal body tissues have a magnetic susceptibility very close to that of water ($-9.0 \cdot 10^{-6}$).

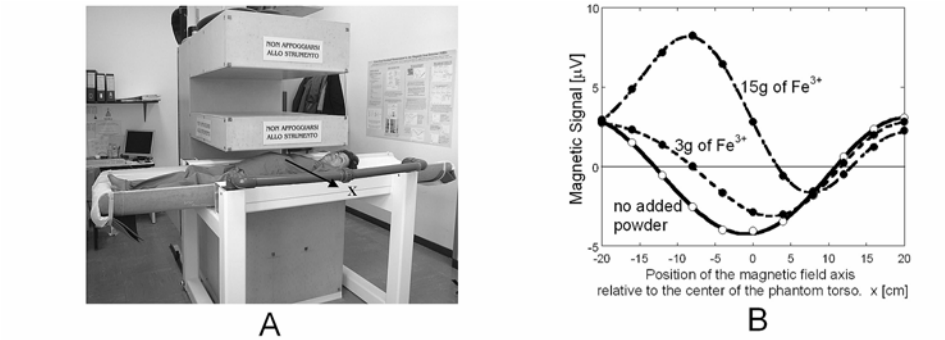

Fig. 1. A) A volunteer between the magnet and the lower pickup of the magnetic iron detector (MID). The higher pickup is symmetrically located in respect to the magnet. This body position is used to scan the liver region, a simple shift of the body allows to measure other body parts. The x values are the positions of the magnetic field axis relative to the center of the human body torso. B) Magnetic signal of an anthropomorphic plastic phantom, with paramagnetic powder, equivalent to 3 g of Fe^{3+} and 15 g of Fe^{3+}, evenly distributed within its liver region. The magnetic moment of Fe^{3+} is 5.9 Bohr magneton. The contribution of the iron atoms to the magnetic signal is proportional to the square of their magnetic moment.

The patient is positioned, between an AC magnet and a pickup, another identical pickup is symmetrically located in respect to the magnet (Fig. 1A). The non magnetic stretcher moves on rails. We average the signals, with the stretcher in and out of the sensitivity region, to account for the changes of the environmental magnetic properties. The symmetry and the accurate temperature control of the complete apparatus gives a sensitivity in the susceptibility better than 10^{-7}. This is necessary to detect the iron quantity of interest. All the susceptometer components operate at room temperature. The calibration (Fig. 1B) has been made using an anthropomorphic plastic phantom.

3. Results

The signal of a patient, with 12 g of liver-iron overload, is compared with that of a healthy volunteer, having close anthropometric data (Fig. 2A).

Please note, the measure of a patient with iron overload in the spleen gave the curve (a) in Fig. 2B and the calculation of the background signal gave the curve (c). The measure of the same patient, after the splenectomy, gave the curve (b). According to the chemical analysis of the cut off spleen, the amount of iron was about 2.7 g. The liver biopsy showed no iron overload in his liver.

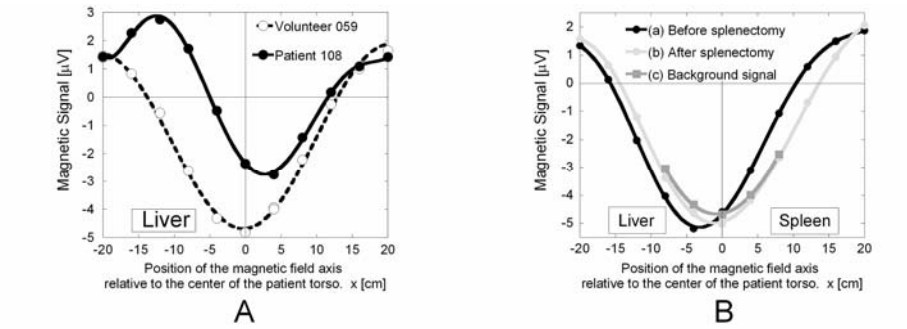

Fig. 2. Examples of MID measurement. A) Signal of a patient with 12 g of liver-iron overload and the one of a healthy volunteer, having close anthropometric data. B) Signal of the same patient **before** (a) and **after** (b) the splenectomy. Curve (c) is the signal calculated for his body, assuming no iron overload, as expected **before** the splenectomy.

Fig. 3 shows the follow-up, for more than one year, of a thalassemia major patient (Fig. 3A) and a hemochromatosis patient (Fig. 3B). The differences between the measured (a) and the calculated background (b) signals give the iron overloads reported in Fig.3 C and D. From the removed blood, according to the phlebotomy therapy, we estimated the iron reduction of two hemochromatosis patients (P03 and P68) and we compared it (Fig. 3E) with the measured iron reduction (R=0.94).

In 26% of the measured patients the liver iron overload was greater than 3 g, in 34% was between 1 g and 3 g and in 40% was lower than 1 g. The LIC obtained from the MID measurements of 7 patients was correlated with the one obtained from their liver biopsy (R=0.89). The comparison of the LIC, measured by MID, with the LIC measured by SQUID (Dr. A. Piga, Turin, Italy) on the same 43 patients gave R=0.86.

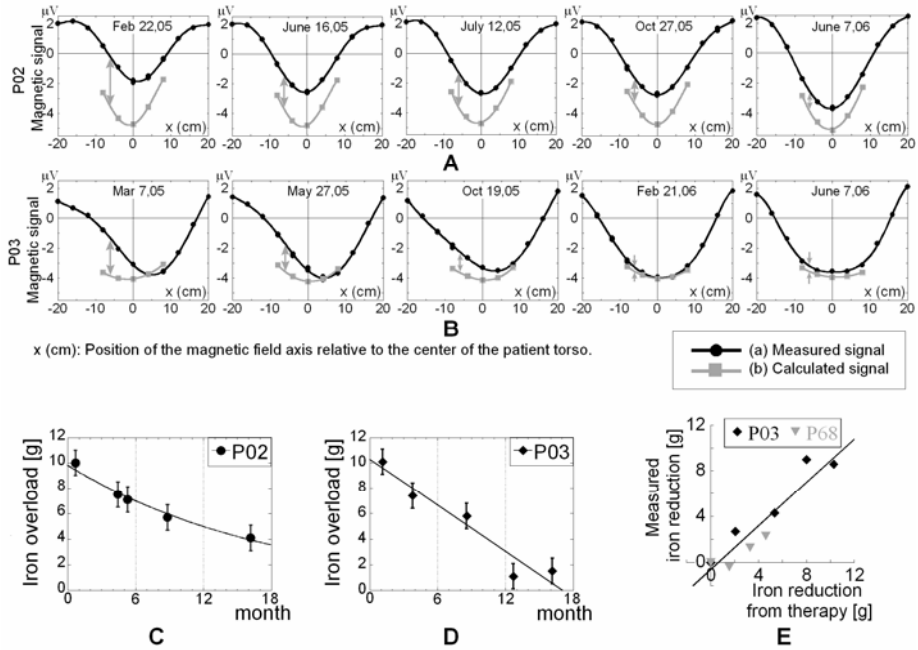

Fig. 3. Examples of patient monitoring. A and B show the follow-up, for more than one year, of the thalassemia major P02 and the hemochromatosis P03 patients. The background signal has been calculated every time according to the present anthropometric data of the patient. The iron overloads of the thalassemia (C) and hemochromatosis (D) patients are obtained from the differences between the measured (a) and the calculated background (b) signals. The thalassemia patient has been treated, 5 days per week, with 45 mg/Kg of DFO and, 7 days a week, with 75 mg/Kg of Deferipron. The measured iron reductions of two hemochromatosis patients (P03 and P68) are compared (E) with the ones estimated by the blood removed from the phlebotomy therapy.

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