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An alternating current superconductor susceptometric system to evaluate liver iron overload

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An ac susceptometric system to quantify liver iron overload composed of a second order axial gradiometer coil coupled to a rf superconducting quantum interference device detector and a large field coil array is presented. A homogeneous ac magnetizing field with low frequency (7.7 Hz) and low intensity (114 μ T) is used. Preliminary measurements over a group of 34 normal individuals and 20 patients with iron overload show the ability of the instrument to perform the measurement and to distinguish normal and pathological individuals. The diamagnetic signature of the surrounding tissues is minimized using a special water bag on the torso. In summary it was shown that with a relatively simple instrumentation it was possible to build a superconducting susceptometer dedicated to quantify *in vivo* iron concentrations, which is clinically important information in the assessment and management of patients with liver iron overload, mainly those who regularly receive blood transfusion. © 2003 American Institute of Physics.

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I. INTRODUCTION

Iron overload from genetic disorders and/or regular blood transfusion is a serious health problem in a large population around the world. The precise quantification and the continuous monitoring of the iron level in the body are of particular importance in the diagnosis and treatment of this problem. As approximately 70% of the iron stored in the body is deposited in the liver, heart, and spleen, these have been the target organs to evaluate the quantity of iron in the body, mainly the liver due to its large size and large store of iron. In the last 2 decades, many noninvasive techniques have been proposed to estimate the body iron stores but, until now, only the magnetic resonance imaging (MRI) and magnetic susceptibility (MS) have shown potential for such application.¹⁻⁶

With fast pulse techniques, shortening of the time of echo (TE), and the increase of the magnetic fields in new MRI systems, some studies have shown good correlation between the transverse relaxation rate (1/T₂) and liver iron concentration (LIC) for a low level of iron overload. Nevertheless, in patients with a severe degree of iron overload (LIC > 3 mg Fe/g_{wet tissue}) T₂ measurement presents poor ac-

curacy because of fast transversal relaxation of the spin of the proton when in the presence of a large quantity of paramagnetic iron ions. Another disadvantage of MRI is its dependence on tissue alterations such as: fibrosis and inflammation, common in patients with iron overload,^{7,8} although a recent publication shows improvement in the MRI method, making use of a single spin echo with a sort TE.⁹

MS measurement is the most precise noninvasive method to estimate iron overload in the body and as opposed to the MRI, the MS is a direct method able to quantify LIC at levels no matter how high they are.¹⁰ It uses a susceptometer based on the superconducting quantum interference device (SQUID).^{11,12} This susceptometric technique consists of the measurement of magnetic field variations produced in the region of the liver in response to an external magnetizing field. Normal tissue is diamagnetic and has susceptibility close to that of the water (-9.032×10^{-6} S.I.). But, when iron atoms are present, this value is modified and the variation in the intensity of the magnetization produced is proportional to the amount of iron present.

In susceptometric measurements (SMs) of the liver, besides the iron distributed in this organ, all the neighbor materials (air, skin, fat, blood, bone, etc.) also contribute to the measurement. Due to the asymmetry and volume variation of this organ and very small differences among the susceptibility values, it is impossible to determine precisely the suscep-

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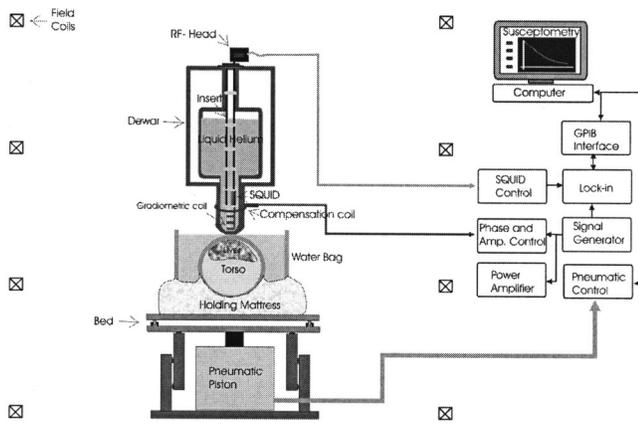


FIG. 1. Block diagram of the susceptometer system developed to measure the susceptibility of the human liver.

tometric contribution of each material individually. A way to minimize the diamagnetic contribution due to the presence of other tissues is to fill the space between the detector and the subject's torso with water. Thus, when the torso is moved away from the detector the water, which has practically the same susceptibility, substitutes the presence of the tissue.¹³ Improvements in the detector coil and in the magnetizing field system help also to reduce the diamagnetic contribution in the SM of the liver.^{3,14} To precisely evaluate the iron concentration from a SM, computer models taking into account the geometry of liver tissue, air, and fat, among others, should also be used. The MS method has been used only in a few centers in the world, in part, because expensive equipment is employed.

This work presents details of a susceptometer based on a rf SQUID detector and on an ac homogenous magnetizing field dedicated to measure liver volume susceptibility. The instrumentation employed follows the principles proposed by Bastuscheck and Williamson,¹¹ leading to a relatively low cost and high sensitivity instrument for noninvasive LIC determination.

II. THE ac SUPERCONDUCTING BIOSUSCEPTOMTER

An overview of the whole instrumentation is shown in Fig. 1. The apparatus consists of three specific modules: magnetizing coils and detector, subject bed, and a system to reduce the diamagnetic contribution from the surrounding tissues.

A. Magnetization and detection coils

The magnetizing coils were designed to apply a spatially uniform field on the liver region to guarantee a good balance on the gradiometer detector. These coils consist of an array of four, geometrically identical, rectangular coils (2.98 m × 2.18 m), equally spaced (0.91 m). The end coils (up and down) have 144 turns and middle coils have 105 turns, wound with AWG 19 copper wire. For this configuration, the homogeneity of the field in a cubic volume of 0.3 m in the middle of the coil array was approximately 450 ppm in the horizontal direction and 10 ppm in the transversal direction

of the magnetizing field (z direction). The intensity of the field in the center of the coils used in the measurements was 114 μT at 7.7 Hz.

The magnetization induced in the sample was detected by a second-order axial gradiometer (20 mm in diameter and 40 mm of baseline) coupled to a rf SQUID model 330X BTi. This gradiometer was built on a Macor substrate with 12 loops of superconductor wire (NbTi): three at the bottom coil (pick up coil), three at the top coil, and six at the middle coil. The distance between two loops was 1 mm. The data acquisition was made using a digital lock-in amplifier model SR 530 interfaced with a computer.

When a homogeneous magnetizing field is used, the typical signal from an iron overload in the liver is in the order of 100 ppb of the applied field.¹¹ So, to use a lock-in to acquire the data, the net magnetizing flux threading the gradiometer needs also to be rejected by a factor of approximately 100 ppb. When the gradiometer was positioned in the center of the magnetizing coils its common mode rejection was approximately 10⁻⁴. Total cancellation of flux threading the gradiometer when no sample was present was guaranteed using an active compensation field. This compensation was made by applying a magnetic field with the same frequency using a small coil (130 mm in diameter and five loops) coupled externally to the neck of the Dewar and approximately 5 cm above the top coil of the gradiometer. It was energized with a fraction of the same power used to drive the magnetizing coils, having the phase and amplitude controlled independently through a dedicated electronic circuit, thus working as an offset of the output susceptometer's signal.

B. Performance and calibration of the susceptometer

The response (*V*) of a superconducting magnetic susceptometer, due to the presence of a sample is proportional to the magnetic flux (Φ) threading the gradiometer ($\Delta V \propto \Phi$). From the reciprocity theorem for susceptometry, the output signal from a SQUID, during a SM, follows the equation¹⁵

$$V = V_0 + \frac{C}{\mu_0} \int_{Vol} \chi(\mathbf{r}) \mathbf{B}_m(\mathbf{r}) \cdot \frac{\mathbf{B}_d}{I_d}(\mathbf{r}) d^3r, \quad (1)$$

where *V*₀ is the output signal without sample, *C* the calibration constant, μ₀ the permeability of free space, **B**_{*m*} the magnetizing field density, and **B**_{*d*} the magnetic field density that the detector coils would generate in the element of volume (*d*³*r*) if energized with a current *I*_{*d*}, also known as "lead field."

As indicated by Eq. (1), the spatial sensitivity of the susceptometer is proportional to the scalar product of the magnetizing field density and the detector coil lead field, i.e.,

$$\left(\mathbf{B}_m(r) \cdot \frac{\mathbf{B}_d(r)}{I_d} \right).$$

To better understand the profile of the response of the susceptometer, the equal-sensitivity contour map associated with spatial sensitivity function is presented in Fig. 2. These contours were mapped in a plane (30 × 60 cm) that coincides with the axial symmetry axis of the gradiometer and is 1 cm

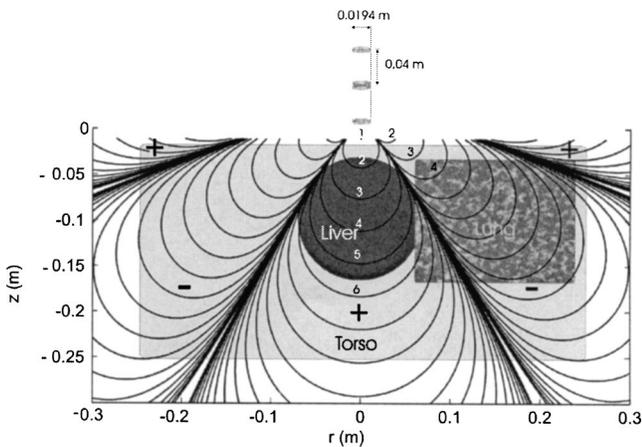


FIG. 2. Calculated equal-sensitivity contours for a second order axial gradiometer associated with uniform axial field. The intensity of the contours is equal to, $\mathbf{B}_m(r) \cdot \mathbf{B}_d(r)/n^5$, where n is the number of the contour.

below the pickup coil. The values of fields B_m and B_d in the center of the voxels were calculated numerically using elliptical integrals.¹⁶

The sensitivity of the susceptometer was evaluated by making measurements in a hexahydrated iron III chloride solution ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$) inside a 560 cm^3 spherical reservoir of polyethylene. A range of iron concentrations equivalent to the range of ferritin from normal to overloaded human liver was evaluated. The $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ is a paramagnetic substance with mass susceptibility value equal to $0.709 \times 10^{-6} \text{ m}^3/\text{kg}$, approximately half of the mass susceptibility of hepatic iron ($\sim 1.6 \times 10^{-6} \text{ m}^3/\text{kg}$). The measurement was made by placing the phantom on the bed and below the magnetic detector. In the beginning the sample was 12 mm far from the pickup coil (vacuum gap inside the Dewar) and, during the acquisition, the sample was moved down 8 cm with a velocity of approximately 2 mm/s. Figure 3 shows the correlation ($R=0.999$) of the maximum variation in the responses of the susceptometer versus the iron concentrations in the sphere volume. In this figure, it is clearly shown the

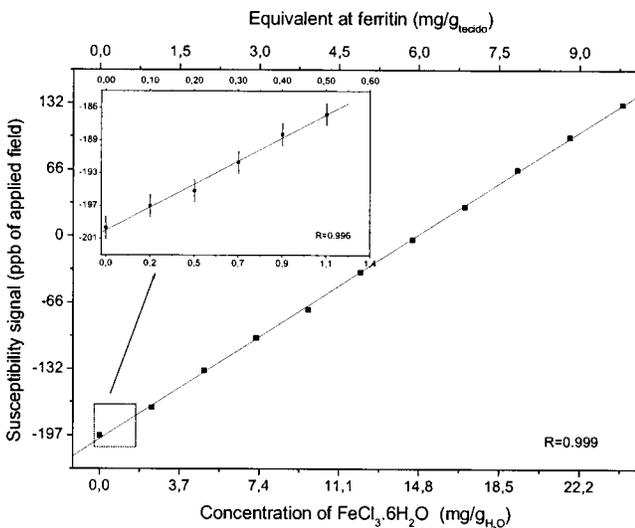


FIG. 3. Maximum variation of the output signal of the SQUID vs iron concentration in the phantom of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ solution. The inset shows the correlation for low iron concentration.

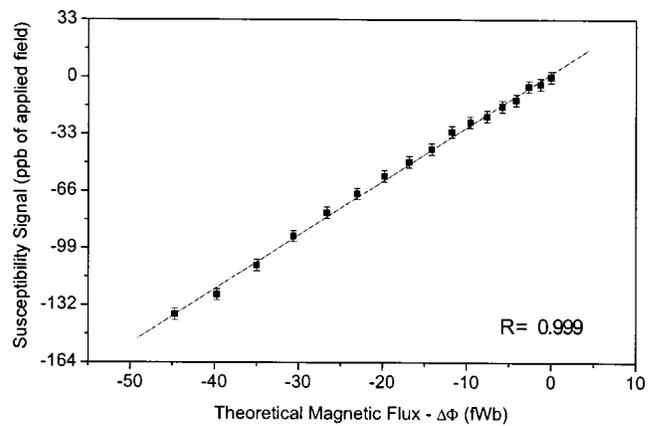


FIG. 4. Susceptometer output variation vs the theoretical magnetic flux threading the detector coils for a SM in a cylindrical phantom with water.

transition from diamagnetic to paramagnetic in the solution with the increasing of the iron concentration. The susceptometric signal due to pure water is canceled when a concentration of approximately $13.3 \text{ mg/g}_{\text{H}_2\text{O}}$ of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ is homogeneously dissolved in it. The equivalent hepatic iron to obtain the same results would be 5.6 mg/g . This quantity of iron in the liver volume is considered an overload. Making five repeated measurements in the spherical reservoir with pure water, the relative standard deviation in the susceptometric signal was found to be 1%.

The system was calibrated making measurements in a cylindrical phantom filled with pure water. The calibration factor C of the system was obtained fitting the output signal of the SQUID using Eq. (1). The integral was performed by a summation of small voxels ($0.5 \times 0.5 \times 0.5 \text{ mm}^3$). When the phantom is moved away from the detector, the space between the phantom and the Dewar tip is occupied with air so the total susceptibility used was $\chi = \chi_{\text{water}} - \chi_{\text{air}}$. Figure 4 shows the agreement between the experimental and theoretical data for different sensor-sample distances.

In a real measurement of the human hepatic region using a susceptometer as described here, the main contribution to the signal is due to the presence of the tissues (skin, fat, and bone), the iron in the liver, and the air in the lungs. However, to estimate how much each one of these substances contributes to the susceptometric signal, a theoretical evaluation of the magnetic flux change ($\Delta\Phi$) threading the detector coil due to the presence of each volume was independently made. The sample model used to represent the torso consisted of three compartments representing liver iron, lung volumes, and all other surrounding tissues. The susceptometric contributions ascribed to each volume was based on the following considerations: (1) the liver iron was considered homogeneously distributed in a spherical volume with volumetric susceptibility equal to $c_{\text{fe}}\chi_{m,\text{fe}}$ where c_{fe} is the liver iron concentration and $\chi_{m,\text{fe}}$ is the mass susceptibility of the iron ($\chi_{m,\text{fe}} = 1.6 \times 10^{-6} \text{ m}^3/\text{kg}$); (2) the air in the lungs was considered distributed in a single cylindrical volume with length and diameter equal to liver spherical diameter and the susceptometric contribution deriving from this volume was attributed to the presence of air and the absence of the tissue, i.e., $\chi_{\text{lung}} = \chi_{\text{air}} - \chi_{\text{tissue}}$ [$\chi_{\text{air}} = 0.36 \times 10^{-6}$ and

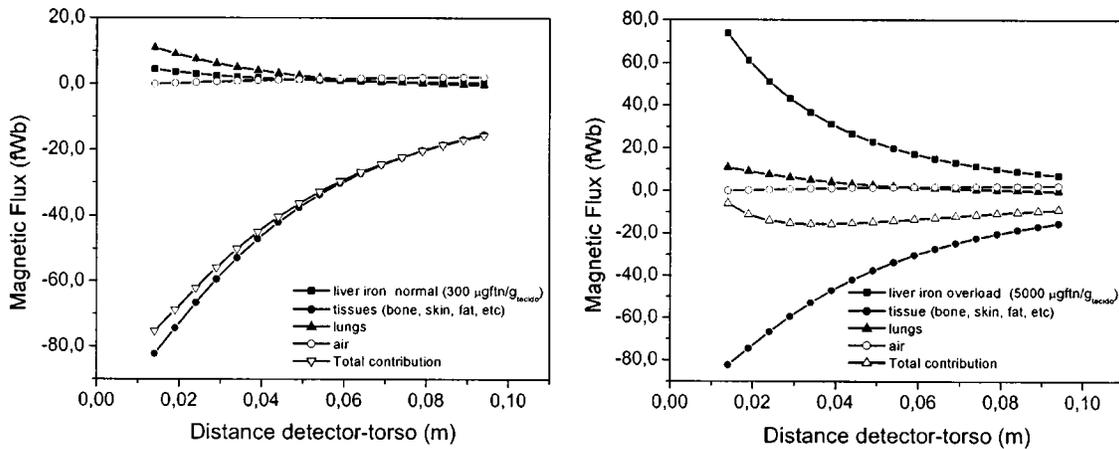


FIG. 5. Calculated magnetic flux threading the detector coil as a function of distance between the pickup coil and the torso for two liver iron concentration: Normal (left) and overloaded (right). Each curve represents the individual contribution of each volume present in the torso model.

$\chi_{\text{tissue}} = -9.032 \times 10^{-6}$ (S.I.); (3) in the absence of liver iron and air in the lungs, the flux changes threading the detector coil should be practically due to the presence of the tissues. The adult torso was represented by a cylinder 50 cm in length and 12 cm in diameter and the tissue volume was considered as the total torso volume less the lung volume. In a differential SM, this tissue contribution is practically canceled by using a water bag between the magnetic detector and the subject's torso.

The liver spherical volume was estimated using Eq. (2), although it had been deduced to estimate liver volume in patients without liver disease.¹⁷ For example, in a normal adult 170 cm in height and 70 kg in weight, the liver volume is about 1520 cm³ corresponding to a sphere with radius of approximately 7.13 cm. In cases where the liver disease increases the volume a correction was estimated using ultrasound images

$$[\text{liver volume (ml)}] = [13 \times \text{height (cm)}] + [12 \times \text{weight (kg)}] - 1530. \tag{2}$$

According to Eq. (1) and the torso model described above, the magnetic flux (Φ) threading the detector coil for contributions deriving from tissues, liver iron and lung volumes can be represented by

$$\begin{aligned} \Phi_{\text{tissue}} &= \frac{\chi_{\text{tissue}}}{\mu_o} [\text{Int}_{\text{torso}} - \text{Int}_{\text{lung}}], \\ \Phi_{\text{iron}} &= \frac{c_{\text{fe}} \chi_{m,\text{fe}}}{\mu_o} \text{Int}_{\text{liver}}, \\ \Phi_{\text{lung}} &= \frac{\chi_{\text{air}}}{\mu_o} \text{Int}_{\text{lung}}, \\ \Phi_{\text{air}} &= \frac{\chi_{\text{air}}}{\mu_o} \text{Int}_{\text{torso}}, \end{aligned} \tag{3}$$

where Int_{vol} is the value of each integral

$$\int_{\text{vol}} B_m(r) \cdot \frac{B_d(r)}{I_d} dr^3$$

integrated in each of the three volumes appearing in Eq. (3), χ_{issue} and χ_{air} are the volumetric susceptibility of the tissue and the air, c_{fe} is the iron concentration homogeneously distributed in the liver volume, and $\chi_{m,\text{fe}}$ is the mass susceptibility of the iron.

Figure 5 shows the profile of the magnetic flux threading the detector coil, described by Eq. (3), for two levels of iron in the liver: (left) normal level (300 µg Fe/g_{tissue}) and (right) overload level (5000 µg Fe/g_{tissue}).

According to Fig. 5 the diamagnetic contribution from the tissue is equivalent to the paramagnetic contribution of an overload of 5000 µg/g_{tissue} of iron homogeneously distributed in the liver volume. It is approximately 20 times stronger than the LIC in a normal subject. This diamagnetic contribution, deriving from the water, was practically canceled using a large water bag between the torso and the magnetic detector. An outline of this coupling device is shown in Fig. 1. The goal of this water bag was to increase the diamagnetic volume close to the magnetic detector in order to, according to the equal-sensitivity map (Fig. 2), make the negative contribution deriving from this volume equivalent to the positive one.

C. Water bag coupling and measurement procedures

The water bag consists of a rubber sheet attached to the lower opening of a cylindrical tube of 40 cm in diameter, forming a saddle geometry. With this bag, the volume and the geometry of diamagnetic substance (tissue+water) around the detector will be practically the same in all torsos.

To perform the measurement, first the subject should be laid down in a bed in supine position below the magnetic detector, with the body rotated around 35°–40° to leave the liver region as close as possible to the detector coil. The depth, size, and position of the liver and the distance between the liver and the lung should be estimated using an ultrasound, while other parameters like the cylindrical radius of the upper curvature of the torso, height, weight, age, etc., should also be recorded. After that, the empty bag should be placed on the torso, coinciding its center with a point previously marked on the torso. This point corresponds to the center of the liver, estimated by ultrasound. The upper sur-

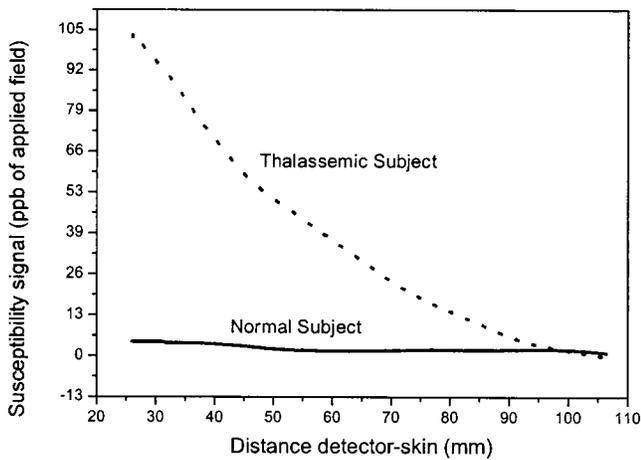


FIG. 6. Profile of the signal in the susceptometer output for the measurement realized in a normal subject (solid line) and beta-thalassemic major patient with moderated iron overload (dotted line).

face of the bag remains open and the water is poured in it. When placed surrounding the subject's torso the weight of the bag is supported by a special mattress (VAC FIX®), an air tight bag containing small Styrofoam balls that mold the subject's torso when vacuum is made. During the measurement, the level of water in the bag is fixed forming a flat surface 40 cm in diameter and about 1 cm above the torso. At the beginning of the measurement the torso is placed 1.5 cm below the tip of the Dewar to avoid contact with water, precluding interference in the measurement. The relative horizontal position of the pickup coil with the point of measurement is controlled using a template clipped onto the bag. The vertical position of the bed is recorded with a precision of 0.1 mm. A nonmagnetic and nonconducting bed is used to accommodate the subject and its vertical displacement is made using a special pneumatic system, built with nonmagnetic and nonconducting materials.

III. *IN VIVO* MEASUREMENTS

Figure 6 shows the profile of the response of the susceptometer versus the detector–skin distance for a measurement performed in a normal subject (solid line) and in a thalassemic patient with a iron overload of approximately $4000 \mu\text{g Fe/g}_{\text{wet tissue}}$ ($\sim 61 \mu\text{mol Fe/g}_{\text{wet tissue}}$) (dotted line). The LIC was evaluated fitting the SQUID output using the following equation:

$$V = V_0 + C \times \Delta\Phi + \delta, \quad (4)$$

where V_0 is the system contribution without a subject, C is the calibration factor of the SQUID, $\Delta\Phi$ is the total flux presented by Eq. (3) and δ is a factor of correction.

Due to the presence of the water bag, the diamagnetic volume (tissue+water) was considered as a cylindrical tube in a vertical position with a diameter of 40 cm and height equal to the maximum diameter of the torso.

Figure 7 shows liver iron level measurements performed in 54 subjects: 34 normal volunteers (13–28 yr) and 20 β -thalassemic major patients (6–40 yr), regularly transfused and undergoing chelation treatment. Six measurements were made in the same one normal subject during 6 consecutive

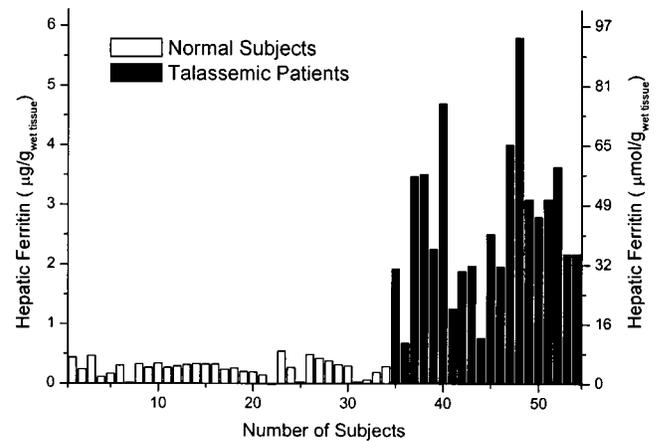


FIG. 7. LIC level obtained in normal subjects and patients regularly transfused.

days, obtaining a standard deviation in the evaluated liver iron of $97 \mu\text{g Fe/g}_{\text{wet tissue}}$ ($\sim 1.5 \mu\text{mol Fe/g}_{\text{wet tissue}}$).

IV. EXPERIMENTAL UNCERTAINTIES

The experimental uncertainties in the determination of LIC from the SM are primarily due to the uncertainty in the position and size of the liver and lungs volume. Table I shows the calculated quantity of LIC corresponding to the estimated uncertainty on the main experimental parameters.¹⁸ Based on this table, the total uncertainty in the liver iron concentration determination through the SM with the susceptometer was estimated as being $\pm(150 + 0.08 \cdot \text{LIC}) \mu\text{g Fe/g}_{\text{wet tissue}}$.

V. DISCUSSION

We have shown that the ac susceptometer composed of a homogeneous magnetizing field and a second order axial gradiometric detector coupled to a rf-SQUID has enough sensitivity to evaluate liver iron concentration at levels as low as in normal subjects. *In vitro* measurements (Fig. 3) show that this system is able to quantify iron concentrations smaller than $100 \mu\text{g}$ at samples with size equivalent to adult human liver.

TABLE I. Uncertainty of the LIC determination corresponding to estimated uncertainty on the main parameters involved in the SM of the hepatic volume.

Parameters	Estimated uncertainties	Uncertainty in the LIC ($\mu\text{gFe/g}_{\text{wet tissue}}$)
Liver		
liver depth	0.002 m	$0.075 \cdot \text{LIC}$
horizontal position of the liver	0.01 m	$0.0632 \cdot \text{LIC}$
volume of the liver	20%	$0.024 \cdot \text{LIC}$
Lung		
lung depth	0.003 m	100
horizontal position of the lung	0.01 m	50
cylindrical radius of the lung	0.01 m	90
instrumental uncertainty	0.001 V	20

With the use of a very homogenous magnetizing field and of an electronic flux compensation system, the resulting flux threading the SQUID coil can be reduced to almost zero.

SM performed in normal subjects and in thalassemic patients known to have iron overload in their bodies, show the feasibility to discriminate levels of iron deposited in the hepatic volume. According to Table I, the uncertainty in the determination of the LIC increases with the liver iron level. The uncertainty related to the presence of the lungs is equivalent to that related to the presence of liver iron overload with approximately $2000 \mu\text{g Fe/g}_{\text{wet tissue}}$. Due to its large volume and its proximity to the detector coil, it is expected that lung volumes give a larger contribution to a susceptometric signal. However, according to the equal-sensitivity map shown in Fig. 2, with the geometries and dimensions used in the detector coils, part of the lung closer to the liver gives a positive contribution and another part gives a negative one so that its total contribution is minimal. For the same reason, it was possible to find the geometry and size of the water bag able to homogenize the upper surface of the torso, minimizing the diamagnetic contribution on the susceptometric signal.

The standard deviation in measurements performed in a normal subject ($91 \mu\text{g Fe/g}_{\text{wet tissue}}$) on 6 consecutive days was lower than the one between 22 measurements realized in different normal subjects ($197 \mu\text{g Fe/g}_{\text{wet tissue}}$). The low intensity of the susceptometric signal deriving from the diamagnetic substance and low variation of the iron concentration evaluated in the normal group shows the feasibility of using the water bag uncoupled from the magnetic sensor using an ac susceptometer. Besides, the way the bag was coupled on the torso renders the patient comfortable and help to keep him/her still during the measurement.

According to Table I, the uncertainties in the hepatic iron quantification in a normal subject is practically due to uncertainties in the size, geometry, and position of the liver and lung ($\sim 150 \mu\text{g Fe/g}_{\text{wet tissue}}$), but in a patient with liver iron overload this uncertainty is increased by $0.08 \cdot \text{LIC} \mu\text{g Fe/g}_{\text{wet tissue}}$. Considering that a range of liver iron from 100 to $500 \mu\text{g Fe/g}_{\text{wet tissue}}$ is considered normal, we concluded that the total uncertainty in the LIC measurement using the present technique and instrumentation is

equivalent to the quantity of LIC in normal subjects. The apparatus presented shows the possibility of further improvement of biomagnetic susceptometry through the development of magnetic susceptibility tomography. The use of a large water bag uncoupled from the detector allows the patient to be scanned and the use of a homogenous magnetizing field allows use of an array of gradiometer detectors with active compensation.

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