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Noninvasive liver iron measurements with a room-temperature susceptometer

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Abstract

Magnetic susceptibility measurements on the liver can quantify iron overload accurately and noninvasively. However, established susceptometer designs, using Superconducting QUantum Interference Devices (SQUIDS) that work in liquid helium, have been too expensive for widespread use. This paper presents a less expensive liver susceptometer that works at room temperature. This system uses oscillating magnetic fields, which are produced and detected by copper coils. The coil design cancels the signal from the applied field, eliminating noise from fluctuations of the source-coil current and sensor gain. The coil unit moves toward and away from the patient at 1 Hz, cancelling drifts due to thermal expansion of the coils. Measurements on a water phantom indicated instrumental errors less than 30 μg of iron per gram of wet liver tissue, which is small compared with other errors due to the response of the patient's body. Liver iron measurements on eight thalassemia patients yielded a correlation coefficient $r=0.98$ between the room-temperature susceptometer and an existing SQUID. These results indicate that the fundamental accuracy limits of the room-temperature susceptometer are similar to those of the SQUID.

1 Introduction

Iron overload, the accumulation of excess iron in the body, occurs in many diseases and causes a variety of health problems. Its effects are especially clear in hereditary hemochromatosis and in transfusion-dependent patients with thalassemia major, where severely elevated iron can cause heart failure, diabetes, cirrhosis or liver cancer, and survival may depend on removing iron by phlebotomy or chelation (Brittenham and Badman 2003). However, iron overload is also a problem in sickle-cell disease (Ballas 2001, Harmatz *et al.* 2001), hematologic malignancies and myelodysplastic syndromes (Strasser and McDonald 2004, Greenberg 2006), liver disease (Fletcher *et al.* 2003, Corengia *et al.* 2005), and possibly metabolic syndrome (Bozzini *et al.* 2005, Jehn *et al.* 2004).

Management of iron overload and research into its health effects have been impeded by the lack of an accurate, affordable, noninvasive method to monitor iron stores (Brittenham and Badman 2003). Serum indicators such as ferritin can be unreliable in patients with inflammation, infection, liver damage, hemolysis and ascorbate deficiency, all of which are common in diseases where iron overload is a concern (Brittenham *et al.* 2001). The liver iron concentration (LIC) reflects body iron stores more reliably (Brittenham and Badman 2003, Angelucci *et al.* 2000a, 2000b). However, liver biopsy, the traditional method for determining liver iron, is painful and carries a risk of severe bleeding (Cohen *et al.* 1992, Piccinino *et al.* 1986).

To avoid these risks, LIC can be measured noninvasively by magnetic resonance imaging (MRI) and biomagnetic liver susceptometry. However, these methods also have their own limitations of cost, accessibility and accuracy.

One advantage of MRI is that thousands of MRI scanners already exist. However, MRI scans still cost hundreds of dollars, and may involve delays in scheduling the scan and waiting for results. In addition, MRI senses iron indirectly, through its effect on the magnetic resonance of nearby water molecules (Jensen 2004). This interaction is complicated, poorly understood and dependent on a variety of factors such as tissue hydration, proton mobility and the clustering of iron deposits (Jensen 2004, Ghugre *et al.* 2005). However, recent studies have found good correlations with liver biopsy (Wood *et al.* 2005, St. Pierre *et al.* 2005). Ongoing research may help to understand the underlying physics, optimize and standardize techniques, and verify their accuracy for varied scanners and patient populations (Ghugre *et al.* 2005).

Susceptometry measures LIC more directly, by placing the patient's abdomen in a magnetic field and measuring the change in field produced by the magnetization of iron stored as ferritin or hemosiderin (Fischer 1998). This magnetization does not depend on interactions with surrounding tissue, and should be unaffected by many of the tissue properties that affect MRI. Susceptometry, like MRI, does depend on the magnetic moment per iron atom, and this parameter may not be the same for all diseases and iron concentrations (Fischer 1998, Hackett *et al.* 2007). However, susceptometry's accuracy is supported by two comparisons with liver biopsy. Brittenham *et al.* (1982) found a correlation coefficient r of 0.98 over the full range of LICs studied. Fischer *et al.* (1992) found unexplained discrepancies at the highest LICs, but $r = 0.98$ for LICs from 0 to 5000 micrograms per gram of wet tissue ($\mu\text{g/gwet}$).

One limitation of liver susceptometry has been the cost of the instrumentation. Existing susceptometers use an exotic sensor technology, Superconducting QUantum Interference Devices (SQUIDS) cooled by liquid helium. One recent SQUID susceptometer cost \$0.7M (Italian Catholic Federation 2004), and only four such systems are in regular clinical use (Brittenham and Badman 2003).

This paper describes our tests of a less expensive susceptometer that works at room temperature. These tests were designed to establish two key points:

1. For the room-temperature (RT) susceptometer, as for the SQUID, the noise of the susceptometer itself is small compared with other error sources such as the diamagnetic response of the patient's body.
2. When applied to iron-overloaded patients, the RT susceptometer produces a signal that is well correlated with liver iron values from an existing SQUID susceptometer.

Our results indicate that this new system can potentially make LIC measurements substantially equivalent to those of current SQUID systems. We discuss below our methods, our results and the relationship of this work to other recent work on liver susceptometry.

2 Methods

2.1 Background and motivation

Recent developments in liver susceptometry have been driven largely by two main issues: (1) the cost of the susceptometer itself and (2) the errors produced by the susceptibility responses of the lung and the tissue overlying the liver. Both of these issues are affected by

the design of the devices that produce the applied magnetic field and detect the magnetic susceptibility response.

Today's clinical susceptometers use SQUID magnetic sensors and superconducting field coils enclosed in a liquid-helium dewar (Farrell *et al.* 1980, Paulson *et al.* 1991). This classic design has been validated by liver biopsy (Fischer *et al.* 1992, Brittenham *et al.* 1982), used clinically on hundreds of patients, and subjected to an intensive analysis of measurement errors (Fischer *et al.* 1999, 2002). This design's main drawback, aside from its cost, is the need to apply a large correction for the response of the overlying tissue, especially in obese patients (Fischer *et al.* 2002). This problem arises from the relatively small diameters of the source and sensing coils. The response of these coils dies away rapidly with distance, reducing the lung error, but making the liver response smaller in relation to that of the overlying tissue.

Other susceptometers have used less expensive technologies to produce or detect magnetic fields. One system uses a pre-existing general-purpose SQUID magnetometer, with an applied magnetic field produced by Helmholtz coils at room temperature (Bastuscheck and Williamson 1985, Carneiro *et al.* 2003).

A room-temperature susceptometer by Marinelli *et al.* (2006) uses copper source and sensing coils with diameters comparable to that of the torso. The large coils reduce the overlayer error, but increase the signal from the lung. The lung signal is subtracted out by scanning the patient past the susceptometer, and using a statistical analysis trained on subjects with normal and elevated LIC.

Each of these designs differs from the others in the geometry of the magnetic field source and field sensor, as well as the technology that produces and detects magnetic fields. This situation complicates comparisons of different systems, because any disagreements that we might observe could be attributed either to differences in the susceptometer technology, or to differences in the lung and overlayer errors.

In this paper, our aim is to make a direct comparison between our room-temperature susceptometer and an established SQUID susceptometer. Our design uses room-temperature source and sensing coils instead of superconducting ones, but keeps the coil geometry and measurement procedures as close as possible to those in current SQUID susceptometers. With this approach, the lung and overlayer effects should be essentially the same for our system and the SQUID. If we can make the noise of the instrument itself small compared with these other errors, the room-temperature susceptometer should then make liver iron measurements equivalent to those of the SQUID.

Once we have validated our room-temperature susceptometry technique, we can apply it to new coil geometries, scanning measurements and other improved methods for reducing the lung and overlayer errors. This approach lets us change only one key element at a time: First the sensing technology, then the methods for minimizing lung and overlayer effects.

Our design also tries to keep the instrumentation simple, compact and inexpensive. As described below, our apparatus consists essentially of copper coils, a motor and crank, amplifiers and a computer. The key element, the coil unit, is roughly the size of a soft-drink can. The rest of the structure, with the patient bed folded up, could be reduced to the size of a grandfather clock. Such a device could be kept in a haematology or hepatology clinic. Unlike MRI, it would provide LIC values in minutes, without sending the patient to an imaging center, scheduling a scan, and waiting for a radiology report.

In presenting our susceptometry technique, we first explain how we make sensitive liver iron measurements with room-temperature technology. We then describe how we have designed our instrument and measurement procedures to make a direct comparison with the existing SQUID susceptometer at Columbia Presbyterian Hospital in New York, U.S.A.

2.2 Room-temperature susceptometer

Viewed as a problem in magnetic measurement, liver susceptometry is difficult because the magnetic field from liver iron may be 10^7 or 10^8 times smaller than the field we apply to the patient. This small response must be measured in the presence of the applied field, since the magnetization disappears when the field is removed. As a result, the liver-iron signal can easily be obscured by small variations in the applied field, the gain of the sensor electronics, or the geometric relationship between the sensor and the source of the applied field.

SQUID susceptometers address these problems by exploiting the low noise of SQUID magnetic sensors, the stable magnetic fields produced by persistent currents in superconducting coils, and the stable geometry of source and sensing coils immersed in liquid helium (Paulson *et al.* 1991).

The RT susceptometer has to deal with the higher noise of room-temperature magnetic sensors, the fluctuating magnetic fields from room-temperature sources, and the thermal expansion and contraction of the apparatus. We address these problems by (1) use of oscillating magnetic fields, (2) cancellation of the applied-field signal and (3) periodical motion of the coil unit (Kumar *et al.* 2002):

2.2.1 Oscillating fields—To reduce the noise of the magnetic-field measurement, we use rapidly oscillating magnetic fields. We apply a field at 570 Hz, using a source coil of copper wire. We detect the patient's response at the same frequency, by measuring the voltage induced in a second coil of copper wire. As estimated in section 2.2.4, the noise of this sensing coil is roughly 10^9 times smaller than our applied field.

2.2.2 Cancellation of applied-field signal—When the applied magnetic field is much greater than the desired resolution of the magnetic-susceptibility measurement, significant errors may arise from fluctuations of the current in the source coil, or the gain and phase of the electronics that amplify and acquire the signal from the sensing coil. To minimize these errors, we arrange the source and sensing coils to cancel out the signal voltage induced by the applied field.

The RT susceptometer uses a coil geometry similar to that in existing SQUID susceptometers (Paulson *et al.* 1991). The source coil is arranged as a first-order axial gradiometer: two oppositely wound, co-axial loops connected in series. The sensing coil is a second-order axial gradiometer: three coaxial loops in series, with two loops at either end having equal polarities and numbers of turns, balanced by a central loop having the opposite polarity and twice as many turns. Both gradiometers are arranged symmetrically about a common mid-plane, so that the source coil's opposed loops induce voltages of opposite sign and approximately equal magnitude in the sensing coil.

We adjust this field cancellation by using a resistor network to divert a small portion of the source-coil current through a trimming coil next to one loop of the sensing coil. An additional compensating coil is connected in a closed circuit with a variable resistance. The alternating field from the source coil induces a current in this compensating coil, out of phase with the current in the source coil. By varying the resistances in both compensating circuits, we adjust the currents in the compensating coils so as to cancel the sense-coil signal in phase and out-of-phase with the applied field. We periodically readjust the balance to

keep the net sense-coil voltage less than 10^{-5} of the voltage corresponding to the applied field at the surface of the patient's body. Turning on the source-coil current then increases the noise in the sensing coil by less than 10%.

2.2.3 Reciprocating motion of coil unit—In a room-temperature susceptometer, temperature fluctuations due to the environment or the patient's body heat can modulate the geometric relationship between the source and sensing coils. As a result, the sensing coils pick up a varying signal from the applied field. In our susceptometer, this effect produces a 570-Hz signal whose fluctuations over minutes to hours may be ten times the diamagnetic response of water. Similar effects were a major problem in the first attempts at liver susceptometry with a room-temperature apparatus (Bauman and Harris 1967).

To keep thermal fluctuations from affecting the LIC measurements, we wind the source and sensing coils on a rigid coil form. We move this coil unit up and down, toward and away from the patient, at 1 Hz. In synchrony with this sensor motion, the 570-Hz signal due to liver iron varies in amplitude. We determine the LIC from this periodic modulation. Thermal drifts contribute very little to this periodic signal because they are slow and not synchronous with the sensor motion.

With oscillating magnetic fields, cancellation of the applied-field signal and periodic motion of the coil unit, the RT susceptometer minimizes sensor noise, applied-field fluctuations, and effects of thermal expansion. Our data in section 3 show that the susceptometer resolves magnetic signals below 10^{-8} of the field applied to the patient.

2.2.4 System parameters—For the experiments presented here, the source and sensing coils had the dimensions shown in table 1. The coil unit's reciprocating motion had an amplitude of 2.5 cm. At the bottom of the motion, the center of the sensing coil's bottom-most loop came within 1.2 cm of the outer surface of the susceptometer's outer enclosure.

The maximum 570-Hz magnetic field at the enclosure's outer surface was approximately 3×10^{-4} T (root-mean-square, or rms), as calculated from the source-coil current (0.22 A rms) and coil dimensions. By Faraday's law, a 570-Hz field of this magnitude, applied to the lower loop of the sensing coil, would induce a voltage of approximately 2 V (rms). In comparison, the noise of the sensing coil was approximately $2 \text{ nV/Hz}^{1/2}$, as estimated from the noise specification of the preamplifier (Burr-Brown INA 103) and the Johnson noise of the sense-coil resistance (160 Ω).

2.2.5 Susceptometer layout—Figure 1 is a picture of the RT susceptometer. The patient lies on a bed below the susceptometer coils. The coils are enclosed in a rigid fiberglass cylinder, which is lowered until it just touches the patient's abdomen. A water bag (not shown) fills any gaps between this enclosure and the abdomen. During magnetic susceptibility measurements, the coil unit moves up and down within the outer cylinder, driven through a crank and connecting rod by a synchronous electric motor at the top of the figure. The susceptometer also includes a waveform generator to produce a 570-Hz sine wave (Hewlett Packard 33102a), an amplifier to drive the source coils (AE Techtron 5050), signal pre-amplifiers of our own design, data acquisition cards, and a personal computer to demodulate the 570-Hz signal and calculate the LIC.

2.3 Other aspects of liver susceptometry

The main differences between our susceptometer and previous SQUID systems are in the methods used to generate the applied field and measure the weak magnetic susceptibility response. In other areas, we have tried to make our system as similar as possible to the SQUID, as described below.

2.3.1 Water-bag method—In liver susceptometry, the response of liver iron is superimposed on a background signal due to the diamagnetism of the patient's body. This diamagnetic background is as large as the signal from liver iron at a concentration of several thousand $\mu\text{g/g}_{\text{wet}}$, and is different for each patient because it depends on the shape of the body.

To compensate for the body's diamagnetic response, we use a water-bag technique similar to that used with existing SQUID susceptometers (Fischer 1998, Paulson *et al.* 1991). The water bag fills the space between the patient's body and the rigid shell that encloses the susceptometer coils (figure 2a). Since body tissues have diamagnetic susceptibilities close to that of water, the water bag erases most of the change in susceptibility at the surface of the body. The main change in susceptibility then occurs at the boundary between the air space surrounding the susceptometer coils, and the water and water-like body tissues outside the susceptometer's outer shell. This air-water boundary is the same for every patient, because it is defined by the rigid outer shell of the susceptometer.

For our comparison with the SQUID at Columbia Presbyterian Hospital, both our susceptometer and the SQUID used water bags with the same design, dimensions, materials and construction. We used the water bag somewhat differently, however. The SQUID system measures the change in susceptibility response while lowering the patient away from the sensing coils. Water is continually added to the bag, to fill the expanding space between the patient and the susceptometer. The resulting change in the SQUID signal represents the difference in magnetic susceptibility between the patient's body and water.

In our system, the patient, the water bag and the susceptometer's outer shell remain fixed, while the coil unit moves up and down within the outer shell. As the coil unit moves, we see a modulation in the amplitude of the 570-Hz voltage from the sensing coil. This modulation includes not only the response of liver iron, but also a background contribution from the susceptibility responses of the outer enclosure and the air-water transition. This background signal may also include other effects that are synchronous with the 1-Hz motion, such as distortion of the coil unit as it accelerates up and down.

We evaluate the background signal by making a separate magnetic susceptibility measurement with a water-filled plastic container in place of the patient's body (figure 2b). The difference in susceptibility between the patient's body and water is represented by the difference in the modulation of the 570-Hz signal amplitude, between the measurements on the patient and on the water phantom.

2.3.2 Effect of overlayer susceptibility—Both our procedure and the SQUID procedure measure the difference between the patient's magnetic susceptibility response and that of water, as a function of the distance between the patient and the susceptometer coils. To the extent that the other materials in the patient's body have susceptibilities close to that of water, this difference signal is mainly due to the magnetization of iron in the liver. However, there is also a contribution from the few-percent difference in susceptibility between water and the fatty tissue overlying the liver. This overlayer correction varies between subjects, and can be hundreds of $\mu\text{g/g}_{\text{wet}}$ for obese patients (Fischer *et al.* 2002).

Fischer *et al.* (2002) have described methods to estimate the overlayer correction for each patient. We plan to use these methods in future LIC measurements. However, in the work reported here, our goal was to make as direct a comparison as possible with the SQUID at Columbia Presbyterian Hospital. The Columbia system assumes that each patient's overlayer susceptibility differs from that of water by the same amount. To match the

Columbia results, we used the same approach in analyzing our data from the RT susceptometer.

As discussed in section 2.1, the overlayer effect depends on the dimensions of the susceptometer's source and sensing coils. For this comparison study, we chose coil diameters to match one of two coil sets in the Columbia SQUID susceptometer. In section 3.2, we compare our results to the SQUID data obtained with that coil set. We get similar results using the data from the other set of SQUID coils. By using the same coil dimensions and overlayer correction that the Columbia system uses, we hope to ensure that, if there are any errors due to the overlayer, they are the same for our system and the SQUID.

2.3.3 Converting susceptometer output to liver iron—As described in section 2.2.3, our liver iron measurement is based on the modulation of the 570-Hz signal amplitude as the coil unit moves toward and away from the patient. To convert this signal modulation into a quantity proportional to the LIC, we use a model based on the one used in the Columbia SQUID system.

Based on measurements by Farrell *et al.* (1980), this model assumes that the response of the susceptometer falls off exponentially with distance. It represents the susceptometer response as

$$S(t)_{patient} - S(t)_{water} \cong a\{C_{Fe} \exp[-b(z_{ss}(t) + z_{ls})] + C_0 \exp[-bz_{ss}(t)]\} \quad (1a)$$

$$= c_{fit} \exp(-bz_{ss}(t)), \quad (1b)$$

where

$$c_{fit} = a[C_{Fe} \exp(-bz_{ls}) + C_0]. \quad (1c)$$

Here, t is time. $S(t)_{patient}$ and $S(t)_{water}$ are the varying amplitudes of the 570-Hz signals from the patient and the water phantom. C_{Fe} is the LIC and C_0 is a constant representing the slight magnetic susceptibility difference between water and the patient's body. z_{ls} is the fixed distance from the liver to the patient's skin, which is measured by an ultrasound scan. $z_{ss}(t)$ is the varying distance from the patient's skin to the susceptometer coils, as determined from the voltage induced by the susceptometer's applied field in a small wire loop taped to the patient's skin. b describes the exponential decay rate of the susceptometer response. To match the Columbia group's analysis, we use $b = 0.076 \text{ m}^{-1}$.

In equation (1b), we determine the coefficient c_{fit} by a least-squares fit of the time-dependent susceptometer output to the quantity $\exp(-bz_{ss}(t))$. We then calculate the LIC as

$$C_{Fe} = a^{-1} \exp(bz_{ls})(c_{fit} - aC_0) \quad (2)$$

To determine the LIC in absolute terms, we would need to know the scale factor a^{-1} and the tissue-susceptibility parameter C_0 . Following Brittenham *et al.* (1982), we could determine C_0 by measuring volunteers with normal liver iron, and a^{-1} by comparing our susceptometer to a SQUID or to liver biopsy, in patients with iron overload. Following Fischer (1998), we

might also determine a^{-1} by measuring the response from a phantom of known magnetic susceptibility. In future work, we hope to do both kinds of calibration.

For the tests reported here, we did not do those kinds of calibration. Our first goal in these tests was to check the correlation of our system with a SQUID. This correlation is completely independent of the overall calibration factor a^{-1} .

The correlation is also nearly independent of the tissue susceptibility constant C_0 . C_0 changes the LIC value by a nearly constant amount, which varies slightly from patient to patient because of the factor $\exp(bz_{ls})$ in equation 2. Following Brittenham *et al.* (1982), our results in section 3.2 are calculated using $C_0 = 85 \mu\text{g/g}_{\text{wet}}$. However, tripling C_0 or setting it to zero changes the SQUID- RT correlation coefficient by only 0.005.

Our second goal in this study was to estimate the contribution of susceptometer noise to the error in the LIC measurement. For this purpose, we needed to estimate a^{-1} , so that we could convert the susceptometer noise to units of liver iron. We estimated a^{-1} from our comparison of the RT and SQUID susceptometers (section 3.2). Using equation (1c) above, we did a linear least-squares regression of $C_{Fe} \exp(-bz_{ls})$ versus c_{fit} , taking C_{Fe} from the SQUID data and c_{fit} from our results. We took a^{-1} to be the slope of the least-squares regression line.

The analysis above is presented in terms of the time-dependent amplitude of the 570-Hz signal. In practice, we take data in eight-second segments, Fourier transform the data from each segment, take the amplitudes of the peaks in the Fourier transform at 1, 2, 3 and 4 Hz, and do all of the computations in terms of these four peak amplitudes.

2.3.4 Patient positioning—Our liver iron measurements followed procedures used by the Columbia SQUID group. An ultrasound scan determined the liver-skin distance and the margins of the liver and lung. The patient was positioned under each susceptometer as shown in Paulson *et al.* (1991), using a flat patient bed with no angled back support. The liver was centered under the susceptometer coils by maximizing the magnetic signal from a loop of wire (diameter 2.5 cm) taped to the patient's skin. In our system, the locator loop sensed the 1000-Hz magnetic field from a source loop (diameter 1 cm) mounted on the center axis of the susceptometer coils. Patients breathed normally during the measurements. With the RT susceptometer, each measurement took one minute, the water bag was emptied and refilled before every measurement and the patient was re-centered for every second measurement. The same person positioned the patient for measurements with both susceptometers.

2.4 Human subjects

Measurements on human subjects were done with written informed consent, under the supervision of the institutional review board at Columbia Presbyterian Hospital. A group of twenty patients had come to the hospital for medically prescribed LIC measurements. All subjects had been diagnosed with thalassemia by the referring physicians. One patient had also been diagnosed with hepatitis C, and one patient with sickle-cell disease. The patients ranged from 13 to 46 years in age, 140 to 183 cm in height, 36 to 114 kg in weight and 11 to 19 mm in liver-skin distance.

We took the following steps to minimize bias in selecting the patients and interpreting the results: Our Columbia collaborators measured each patient with the SQUID, discussed the results with the patient, then asked if the patient wanted to participate in our comparison study. Our own group members remained outside the room during the SQUID measurements and discussion. Eight patients agreed to participate in the comparison study.

All eight were measured with our susceptometer and are included in the results presented below. We analyzed our data and sent the results to the Columbia group before they told us the results they had obtained with the SQUID.

3 Results

Our goals in testing the RT susceptometer were, first, to show that its noise was below other errors in the LIC measurement and, second, to show that it could make LIC measurements that tracked those made by an existing SQUID.

3.1 Susceptometer noise

As described in section 2.3.1, we determine liver iron by subtracting the response of a water phantom from that of the patient. The accuracy of the result depends on the stability of the water background measurement over the time required to measure both the patient and the phantom.

To characterize the stability of this background measurement, we immersed the outer enclosure of the susceptometer in water, producing a background signal approximately equal to that of the water bag and water phantom in figure 2b. We measured the signal produced by the one-hertz motion of the coil unit, and used equations (1) and (2) to translate that signal into units of liver iron. We assumed a liver-skin distance of 16 mm and estimated the overall calibration constant a^{-1} as described in section 2.3.3. We took data at ten-second intervals for 57 – 67 minutes, smoothed the data by a one-minute running average, then calculated the standard deviation of all the data points collected during those 57 – 67 minutes. This standard deviation includes fluctuations on all time scales from the one-minute averaging time to the length of the data-collection period.

We did this experiment three times in a row. In each case, we obtained a standard deviation less than 30 $\mu\text{g/g}_{\text{wet}}$.

The corresponding fluctuations of the sensing-coil signal were approximately 0.25 nV, based on the standard deviation of the 1-Hz modulation amplitude of the 570-Hz signal voltage. This rms voltage fluctuation is within 50% of the value that we calculate from the bandwidth of the measurement, the Johnson noise of the sensing coil and the input noise voltage of the preamplifier. This result suggests that, in this experiment, a significant part of the baseline fluctuation came from the noise of the magnetic sensor itself.

In addition to the relatively rapid fluctuations that we might expect from sensor noise, the data appear to include an irregular fluctuation over periods of many minutes, as shown in figure 3. We suspect that these slower drifts reflect inconsistencies in the 1-Hz coil motion, since they are absent when we do the same measurement without the motion. Irregularities in the motion could change the forces experienced by the coil unit or the distance between the coils and the diamagnetic materials of the water bag, patient and outer enclosure. Either effect would change the 1-Hz modulations of the susceptometer signal, from which we derive the LIC measurement.

We got the results in figure 3 by running the motion continuously, starting two hours before taking data. In other experiments, mainly during the first half-hour after starting the motion, we have seen baseline drifts of hundreds of $\mu\text{g/g}_{\text{wet}}$ over 5 to 30 minutes. Similar baseline drifts may have occurred during our comparison with the Columbia SQUID, since the motion was stopped and restarted frequently during those experiments.

We have not systematically investigated the effects of environmental noise. However, during our comparison with the Columbia SQUID system, we did successfully operate the susceptometer in a hospital room in Manhattan, with no magnetic shielding or active noise cancellation.

3.2 Liver iron measurements on human subjects

Figure 4 shows the results of LIC measurements on eight patients, with the RT susceptometer and the SQUID susceptometer at Columbia Presbyterian Hospital. The horizontal axis in the figure shows the LIC measured by the SQUID, in $\mu\text{g/g}_{\text{wet}}$. The vertical axis shows the liver iron response from the RT susceptometer, in arbitrary units, as calculated in section 2.3.3. The data points and errors bars in the figure give the averages and standard deviations of four to six measurements on each patient with each susceptometer. The Pearson product moment correlation coefficient for the SQUID and RT results was $r = 0.98$.

4 Discussion

The noise of SQUID susceptometers is less than $20 \mu\text{g/g}_{\text{wet}}$ (Paulson *et al.* 1991). Yet, Fischer *et al.* (1999, 2002) estimate that the overall rms error of SQUID LIC measurements is 50 to $400 \mu\text{g/g}_{\text{wet}}$, depending on how obese and how iron-overloaded the patient is. This error comes mainly from the response of the lung, the liver-skin distance measurement and the variable magnetic susceptibility of the tissue overlying the liver. These errors depend on the positioning of the patient, the geometry of the susceptometer's source and sensing coils, and the distributions and susceptibilities of the patient's body tissues. These factors being equal, the accuracy of susceptometric liver iron measurements should not depend on the technology used to produce and detect magnetic fields, as long as the noise of the susceptometer itself is small compared with these other errors.

Our results on eight patients indicate that the RT susceptometer can make LIC measurements that track those of an existing SQUID system. Our results on a water phantom indicate that the noise of our susceptometer can be small compared with the other errors in the LIC measurement. If we can combine this low instrumental noise with the best available methods for reducing these other errors, the RT susceptometer can make measure LIC with accuracies comparable to those of current SQUID systems.

To achieve this goal, we plan to address three main issues. First, we hope to improve the susceptometer's baseline stability, by running the sensor motion continuously and reducing friction and play in the motion mechanism. Second, we need to match the best measurement practices used with SQUID susceptometers, including (1) locator loops that center the patient more precisely (Paulson *et al.* 1991), (2) a pressure sensor to fill the water bag consistently and (3) overlayer susceptibility correction using the methods of Fischer *et al.* (2002). Finally, we need to validate the new susceptometer more rigorously, with data on larger numbers of patients and comparison to liver biopsy as well as SQUID susceptometers.

5 Conclusions

Our room-temperature susceptometer uses oscillatory magnetic fields and cancels the signal from the applied field. It cancels thermal drifts by moving the coil unit periodically toward and away from the patient. Water-phantom measurements indicate instrumental noise less than $30 \mu\text{g/g}_{\text{wet}}$, which is small compared with other errors due to the response of the patient's body. LIC measurements on eight iron-overloaded patients show a correlation of 0.98 between the room-temperature susceptometer and an existing SQUID. These results, taken together, indicate that the fundamental error limits for the new system are similar to

those of existing SQUID susceptometers. Our hope is that this simplified susceptometer technology will make accurate, noninvasive body iron measurements more available.

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Figure 1.
Room-temperature susceptometer.

Figure 2.

LIC measurement with water bag: (a) Water fills space between susceptometer and patient's body. Susceptometer coils move up and down within fixed enclosure. (b) Water phantom in place of patient to measure diamagnetic background response.

Figure 3.
Susceptometer stability: Response of water phantom versus time.

Figure 4.
LIC values for room-temperature susceptometer versus SQUID.

Table 1

Loop dimensions in source and sensing coils.

Coil	N	z	r	Δz	Δr
Source	-100	6.50	3.24	1.03	0.64
"	+100	-6.50	3.24	1.03	0.64
Sense	+550	7.50	3.24	0.66	0.64
"	-1100	0.00	3.24	1.32	0.64
"	+550	-7.50	3.24	0.66	0.64

Dimensions in cm. N = number of turns; +/- indicates polarity; z = axial position of coil center; r = mean coil radius; Δz and Δr = axial and radial extent of windings.