TRISTAN TECHNOLOGIES

Biomagnetic Liver Susceptometer

Measurement of Liver Iron Stores by Magnetic Biopsy

The Biomagnetic Liver Susceptometer is a diagnostic instrument which measures iron stores rapidly and non-invasively. Its advanced design with a superconducting magnet and SQUID detection system gives an accurate measurement of iron concentration in the liver and spleen for adults and children.

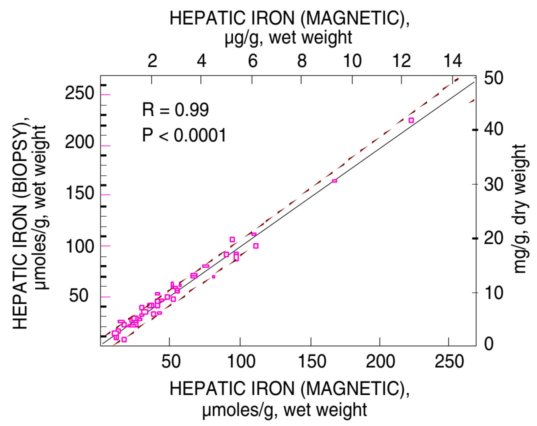
- **Non-invasive**
  Replaces Surgical Biopsy for Iron Measurements
  Eliminates Discomfort and Risk
- **Allows Pediatric Measurements**
- **Direct Measurement Method**
  Accurate and Reproducible
  Allows Frequent Serial Measurements
- **Rapid Results**
  Measurement Time Under 10 Minutes

Clinical Relevance

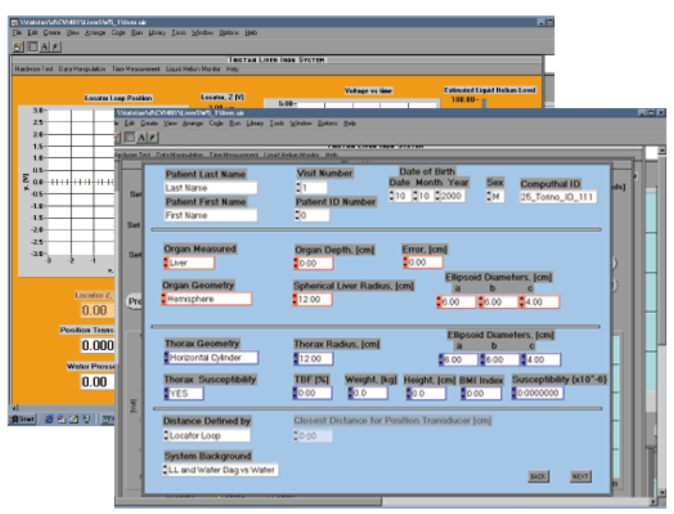
The standard quantitative measurement of iron stores has required a surgical or needle liver biopsy. This method requires a physiochemical analysis with its associated time delay in obtaining results. It also assumes that iron is evenly distributed throughout the liver. In addition, the needle biopsy is not without discomfort and, in some cases, significant risk.

The most common assessment of iron stores is the serum ferritin measurement. Clinical studies have shown serum ferritin measurements to be a poor predictor of actual iron stores with correlation coefficients (R) ranging as low as 0.24 for ß-Thalassemia intermedia patients[1]. Serum ferritin estimates can be incorrect by as much as a factor of ten.

Biomagnetic Liver Susceptometry (BLS) has long been recognized as providing accurate quantitative measurements of iron stores. The graph[2] shows a comparison of hepatic iron concentration as determined by BLS (x-axis) and by chemical analysis of liver tissue obtained by clinically indicated needle biopsy (y-axis).



With the ability to take into account the contribution of overlying tissues, BLS measurements can be extended to adults and children who have wide variations in organ depth and body fat. Another advantage of BLS is that it is a volumetric technique, giving an average iron concentration measured over many milliliters of organ tissue which more accurately portrays total iron stores. A typical needle biopsy which removes very small amounts of tissue can easily give erroneous total iron stores.



[1]R. Galanello *et al* (against atomic absorption after percutaneous biopsy) and B. R. Saxon *et al* (surgical biopsy and magnetic biopsy)
[2]Courtesy, G. M. Brittenham. Magnetic and biochemical measurements were made within 1 month; patients with cirrhosis or with biopsy specimens less than 5 mg, wet weight, were excluded.

Applications

The most relevant applications of Biomagnetic Liver Susceptometry (BLS) are related to iron overload diseases such as hereditary hemochromatosis and siderosis caused by blood transfusions. To date, the following applications have been demonstrated:

- Monitoring iron overload in patients with transfusional siderosis (genetic ß-thalassemia major and sickle cell disease, or other transfusion dependent anemias) for the onset or intensification of chelation therapy and during this therapy
- Assessment of iron overload in patients scheduled for Interferon alfa therapy in viral liver infections such as Hepatitis B or C.
- Assessing iron overload in patients with ß-thalassemia scheduled for bone marrow transplantation (BMT) or monitoring iron overload after BMT during iron depletion therapy
- Assessment of the long-term efficacy of different iron chelators under study
- Diagnosis of hereditary hemochromatosis and assessment of the degree of iron overload in known hereditary hemochromatosis
- Monitoring liver iron concentration in the initial assesement and long term phlebotomy therapy of hereditary hemochromatosis

Measurement Protocol

On the first visit, patient information including name, age, height, weight and total body fat is taken.

The depth and shape of the liver (or spleen) is measured by ultrasound and entered into the patient data base.

The patient is positioned on a movable bed such that the central mass of the liver (or spleen) is directly beneath the detector.

The bed is elevated until the patient just touches the detector and the water bellows is filled.

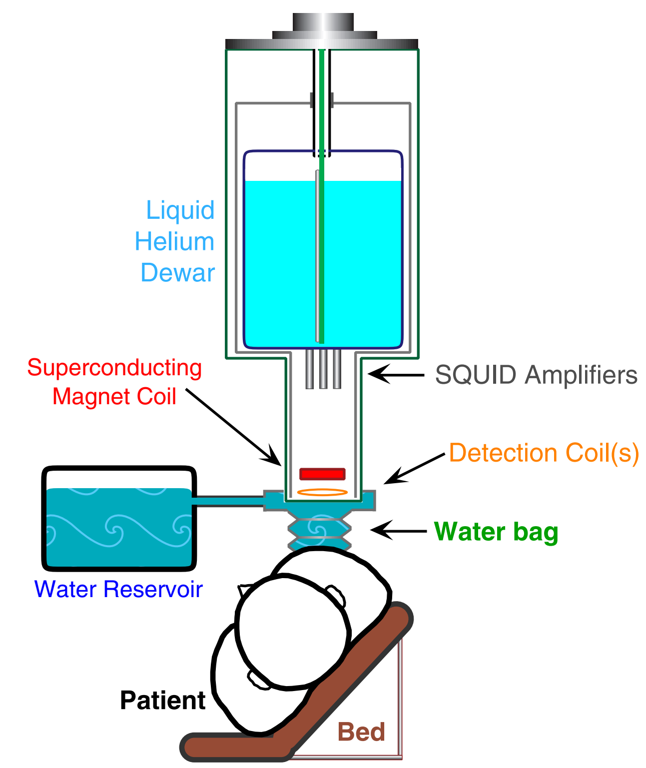
The patient is then automatically lowered about 10 cm over 10 seconds. As the bed lowers, water flows into the bellows keeping the space between the patient and detector filled.

The change in magnetic field measured by the magnetometer is recorded as a function of the distance of the liver from the detector coils.

The computer immediately analyzes the data and gives a preliminary result as soon as the bed motion stops.

The measurement sequence is generally repeated one or more times to improve accuracy.

Excluding the ultrasound portion, it typically takes less than 10 minutes to make a BLS measurement and determine hepatic iron concentration.



Schematic of Major Subsystems

BLS Methodology

Non-invasive Biomagnetic Liver Susceptometry (BLS) exploits the effects of magnetism and superconductivity. Biological materials such as ferritin and hemosiderin are weakly attracted to an applied magnetic field (paramagnetic behavior) while water and body tissue are very weakly repelled (diamagnetic). Ferromagnetic materials e.g., nickel and steel, are strongly attracted to applied fields. No naturally occurring human tissue is ferromagnetic.

In the BLS method, a weak magnetic field of 0 - 20 millitesla is generated within the body tissue by an external superconducting field magnet, similar to that used in a MRI scanner, but a hundred times weaker. The applied fields are measured by a superconducting magnetometer known as a SQUID (Superconducting QUantum Interference Device). The SQUID sensing system has the ability to measure distortions in the magnetic field at the part per billion level.

When an organ, such as the liver, is placed in a magnetic field, it will slightly distort the applied field. If the liver is normal or anemic, the local field will be reduced slightly. If the liver is iron overloaded, the local field will be enhanced. Hence the change in the detected magnetic field is directly related to the iron concentration in the liver.

To minimize the body's contribution to the distortion in magnetic field, a small bag of water is placed between the detector and skin surface. Since the susceptibility of body tissue is close to that of water, the resultant measurement is essentially that of a magnetized liver (or spleen) moving in a magnetic field within a uniform (diamagnetic) environment; the only change seen by the detection coils is due to the liver (or spleen) itself.

For higher accuracy, our software removes the actual contribution of overlying tissues (skin, bone, muscle, fat, etc.). This gives the iron concentration of the liver (or spleen) alone, allowing accurate measurements for obese patients and normal patients with atypical liver/spleen depths.

To date, the BLS method has been applied to organs such as livers and enlarged spleens (> 300 ml) with a total error of [Fe] = 0.05 - 0.4 mg/g tissue (wet weight). Repeatability (serial measurements over three weeks) on single subjects of better than 95 % has been demonstrated.

Specifications

Magnetic Field: 20 mT at coil face, stability better than 0.1 ppm/hour. 5 Gauss line 14 cm from dewar tail.
Detection Coil Sensitivity: 100 fT/$\sqrt{\text{Hz}}$.
Liquid Helium Capacity: 35 liters/10 day hold time.
Patient Bed Capacity: 135 kg.
Ultrasound: 3.5 MHz linear array, ±0.5 mm resolution
Data Base: Open file structure with ability to customize to user preferences.
Total System Noise: 0.02 mg/g [Fe] concentration (wet weght), as measured by a liver phantom at a distance of 15 mm.
Measurement Range: 0.05-30 mg/g (wet weight), equivalent to 0.2 to 100 mg/g (dry weight).

Options

For researchers interested in extending measurement capabilities, Tristan offers the following options:

- Additional Detection Channel
  This includes a third detection coil with different spatial sensitivity.
- Active Noise Cancellation
  Needed for sites with high environmental noise.
- AC Field Capability
  AC-field modulation of the magnetic field. This can allow research on alternate methods of BLS.

The Tristan Biomagnetic Liver Susceptometer is classified as an investigational device and is offered for research use only. Tristan is in the process of seeking both CE (European) medical device directive and FDA (U.S.) certification for clinical use. Specifications subject to change without notice.

Site Requirements

The model BLS requires a minimum 3.7 m x 4.6 m x 6 m (12' x 15' x 20') space. Total system weight is 1,500 kg. Power requirement is 7 kVA. A vibration free platform for the gantry is required and the system should be sited in a magnetically quiet environment. Contact Tristan to discuss site surveys for magnetic and vibration measurements. All Tristan products are covered by a 1-year warranty. Service contracts may be purchased to provide post warranty coverage.

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