Thalassemia, one of the most common genetic diseases worldwide, causes defects in hemoglobin production, resulting in anemia. It occurs most frequently in people of Mediterranean (especially Italian and Greek), Middle Eastern, Southern Asian, and African ancestry. Children who inherit two β-globin genes that carry a severe thalassemia mutation suffer from thalassemia major, also known as Cooley’s anemia. They require frequent blood transfusions and extensive medical care. Despite initially overcoming the lack of hemoglobin, however, the transfusions inevitably cause buildup of iron levels – iron overload – in the body, particularly in the liver and the heart, where it leads to cardiac dysfunction and death. Despite the introduction of a drug to remove the iron from the heart (iron chelator therapy), the death rate from heart disease among thalassemia patients has
remained high. Data for the United Kingdom shows that in the year 2000, 50 percent of thalassemia patients were dying by age 35. But new magnetic resonance imaging (MRI) techniques, developed by Professor Dudley J. Pennell, MD, FRCP, Director of the Cardiovascular Magnetic Resonance (CMR) Unit at the Royal Brompton Hospital, London, UK, and the MR physics team of David Firmin, PhD, in partnership with Siemens Medical Solutions, are increasing life expectancy and quality of life for thalassemia patients worldwide. For Pennell, who trained as a cardiologist, the high rate of these patients dying prematurely of heart failure was the main reason why thalassemia was of enormous interest. “When affected children are born, they appear healthy, but within the first two years of life, they become anemic and generally fail to thrive,” says Pennell. Without frequent blood
transfusions to maintain their hemoglobin levels, these children would normally die between the ages of two and five. However, each unit of blood transfused contains about 250 mg of iron, so patients receiving two units of blood per month will absorb six grams of iron per year, “a vast amount,” Pennell stresses. Iron uptake is also increased by a secondary mechanism, via the gut, and humans are not able to excrete this iron. This buildup leads to the appearance of heart disease in children around the age of ten or in their early teens. Although the first drug that gets the iron out of the heart, an iron chelator, deferoxamine, became available in the late 1960s and had a huge effect on the survival of thalassemia patients, many continued to die of the effects of iron overload. This was partly due to difficulties in complying with the treatment regimen, which consists of five eight-hour painful subcutaneous infusions per week. “It is a very unpleasant treatment and a nightmare for the children and their parents,” Pennell explains. Deferoxamine is also associated with side effects such as deafness and stunting of growth.

Until Pennell and his team started using cardiac MRI for these patients, iron was measured as serum ferritin from blood samples or in the liver by biopsy, an invasive technique that is often not very reliable, particularly when the liver is affected by fibrosis, which happens frequently in thalassemia patients. Pennell began investigating MRI of iron overload in the heart in 1998 with J. Malcolm Walker, MD, FRCP, of University College Hospital, London.

**Measuring Iron in the Heart with MRI**

“When we started,” says Pennell, “we found it very difficult, because the literature suggested that you needed to use spin-echo T2 imaging techniques to measure iron in the body, and other people were using signal intensity ratios, but we could not get either of those techniques to work satisfactorily. So we thought we might try a different sequence technique based on gradient-echo T2*, which is much more sensitive to iron than T2, and not only did T2* work the first time, it was very easy to do in the heart.” Although measurement of iron in the heart has eventually become possible using more advanced T2 imaging techniques, Pennell and his team have continued to use T2*. “Myocardial T2* is measured from MRI images, which are fast and easy to acquire,” he says. “The T2* technique is robust to cardiac motion and more sensitive to iron levels than T2. In addition, adjustment of the imaging parameters, to detect moderate or severe iron overload with very short T2* values, is significantly easier using the T2* sequence. As soon as we started using T2* we realized that it was going to be a winner.”

To date, Pennell’s team has done about 3,000 T2* scans in thalassemia patients using a 1.5 Tesla MAGNETOM Sonata™ mobile MRI system and a MAGNETOM Avanto. There is a known cohort of 845 people with thalassemia major in the UK, and Pennell’s unit has scanned about 75 percent of them. The CMR Unit at the Royal Brompton Hospital is the only unit in the UK doing T2* measurements of cardiac iron overload. Work is under way to calibrate the T2* technique for absolute iron quantification sup-

**Dudley J. Pennell, MD**

Professor Dudley J. Pennell, MD, FRCP, is director of the Cardiovascular Magnetic Resonance (CMR) Unit at the Royal Brompton Hospital, London, which is one of the largest units of its kind in the world, operating two MAGNETOM Avanto and one mobile MAGNETOM Sonata MRI systems. He is a graduate of Cambridge University and St Thomas’ Hospital, London, and is trained in cardiology. He has specialized in cardiac MRI since 1987.
ported by a grant from the National Institutes of Health (NIH) in the United States. Iron overload is measured by scanning post-mortem hearts from thalassemia patients and comparing the results of iron measurements in myocardial samples.

Managing Chelation Based on T2*

One of the key findings with T2* has been the demonstration that there is no relation between liver and heart iron, highlighting the unreliability of assessing cardiac risk and making clinical management decisions based on liver biopsy. From scans in 28 patients with heart failure, Pennell’s group established that 89 percent had a heart muscle T2* of below 10 ms, indicating a high risk of mortality. Values between 10 ms and 20 ms represented lower-risk. The lower limit of normal for a person with thalassemia is defined as 20 ms. “Once we had validated the technique, and had shown that it works well in clinical practice, we used it for determining new treatment options,” says Pennell.

**Thalassemia Trials in Sardinia**

Using T2* measurements, researchers from Royal Brompton’s CMR Unit have conducted two international randomized controlled trials of iron chelation therapy, the first of which demonstrated that monotherapy with deferiprone, a new orally administered iron chelator, was more effective at getting iron out of the heart than deferoxamine, which requires injections. The second trial showed that combined administration of deferiprone and deferoxamine chelates more iron out of the heart than deferoxamine alone. This study was conducted in cooperation with Italian investigators using Royal Brompton’s mobile 1.5 Tesla MAGNETOM Sonata scanner, which was installed on a trailer and hauled from London to Cagliari on the Mediterranean island of Sardinia and returned to London three times during the study.
Driving the scanner to Cagliari took the team three days, crossing the English Channel and the French and Italian Alps, and boarding a ferry across the Tyrrhenian Sea. “We had the machine and they had the patients,” Pennell says, explaining the reason behind this unusual trip. There are approximately 1,200 people with thalassemia major in Sardinia. Working with Professor Renzo Galanello, MD, of the University of Cagliari, the team scanned 167 patients and selected 65 to be randomized to one-year of treatment with either deferoxamine plus deferiprone or deferoxamine plus placebo.

T2* imaging of the heart and liver was done at the start of the trial and when the scanner returned to Cagliari at six and twelve months. At the end of one year, patients who received deferoxamine plus deferiprone showed a 40 percent increase in T2* values, indicating a significant decrease in myocardial iron, compared with patients who received deferoxamine plus placebo. “This trial gave us answers that we could not get any other way,” says Pennell. There are no plans to take the scanner abroad again in the near future, although he and his colleagues will cooperate in another international comparative study of a new oral iron chelator, deferasirox (ICL670) versus deferoxamine.

**New Treatment Options**

Based on their experience of treating patients with a heart T2* of below 10 ms, Pennell and his team today strongly recommend that the patient goes on additional therapy with deferiprone. If T2* is between 10 and 20 ms, they recommend either monotherapy with deferiprone or combination therapy with deferiprone and deferoxamine. “If T2* is
above 20 ms and the patient is doing well on chelation therapy, then there is little imperative to change their treatment,” says Pennell. Patients with a T2* of 10 to 20 ms but who are not happy on deferoxamine may be switched to the more convenient deferiprone. Patients who have a T2* of less than 10 ms are scanned again at three, six and twelve months. Patients with a T2* of more than 20 ms are not usually scanned again for two years.

Validation of MRI Worldwide

The MRI T2* sequence for the heart is being transferred to other Siemens scanners and thus has the potential to be used worldwide. To date, Pennell and his team have set up the sequence on recipient scanners at sites in 20 countries, including the United States (Philadelphia, PA), Italy, Greece, Cyprus, Sweden, Turkey, Thailand, Singapore and Hong Kong. After each setup, five to ten patients were flown to London to cross-validate the results. When one center has been validated nationally, its facilities can be used to validate other centers in the same country instead of the patients having to fly to London. The next center to be validated will be in Mumbai (Bombay) in India, at the imaging center of B. Jankharia, MD.

Pennell emphasizes that it is essential to set up with a well-validated technique. “Correct results with T2* scanning of the heart will only be obtained using proper protocols, properly validated T2* sequences, and analysis software,” he says. He has been working with Siemens to produce a product sequence of T2* so that customers will be able to run the T2* sequence on their own scanner without needing extra validation. “This will have a huge effect on the mortality of thalassemia patients,” he says. “We have been able to reduce the mortality in the UK by 80 percent, and mortality has also been decreasing dramatically in other countries, especially Italy and Cyprus, since this technology, and oral chelation therapy, were introduced.”

**T2* Information**

The broad variety of different contrasts in MR images is mainly based on the tissue specific relaxation parameters T1, T2 and T2*, leading to the well known and excellent soft tissue differentiation of MRI. These parameters characterize the MRI signal behavior over time.

Once the equilibrium state of the magnetization has been destroyed by a radio frequency (RF) pulse, the magnetization returns to its equilibrium state with characteristic time constants, T1 and T2, with T1 describing the recovery of the longitudinal magnetization, and T2 the decay of the transverse component.

Other than T1 and T2, the T2* value is in addition influenced by purely static differences in the magnetic field that remain constant over time within a specific location. These are mainly local field variations caused by the patient’s body, as well as by small inhomogeneities of the main magnetic field. The stronger the static field variations, the faster the transverse magnetization decays, and the lower the corresponding T2* value, describing this exponential decay.

In thalassemia patients with iron overload, the main reason for static field changes is the iron in the tissue, especially in the heart and the liver, where it strongly accumulates. There is a direct correlation between the amount of iron in the heart and the shortening of the T2* value: The more iron is present in the heart muscle, the lower the measured T2* in the tissue. While normal values in thalassemia patients are above 20 ms, most patients with heart failure show T2* values below 10 ms.

**Author:** Linda Brookes is a freelance medical writer and editor who commutes between London and New York working for a variety of clients in the healthcare and pharmaceutical fields.