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Contribution of Cardiac Magnetic Resonance to Hematochromatosis

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ABSTRACT

Hemochromatosis is a disease characterized by the progressive accumulation of iron in the body. It can be primitive or secondary. It affects several organs including the heart, liver, pancreas and pituitary gland.

The preponderant cardiac involvement is myocardial, related to the iron myocyte overload, causing a decrease in left ventricular distensibility.

Echocardiography is the first-line examination, showing an abnormality of left ventricular filling and, later, cavitary dilatation with left ventricular systolic dysfunction.

Cardiac MRI is the gold standard for measuring excess iron in the myocardium in the context of hemochromatosis using the T2 * technique. It plays a major role for the diagnosis of cardiac involvement and for monitoring the chelation treatment.

In this study, we report three cases of patients with hemochromatosis whose cardiac localization was confirmed or eliminated using cardiac MRI.

Cardiovascular magnetic resonance has been used to assess myocardial iron deposition using the relaxation parameters T2*. Heart T2* falls with increasing iron loading.

One patient had a myocardial T2* below 20 ms indicating myocardial siderosis.

The others patients had a T2 *> 20 ms. The late enhancement was absent in all our patients.

This study aims at detecting the myocardial iron overload using cardiac MRI.

The treatment is based on bleeding in primary hemochromatosis while in secondary hemochromatosis, it is based on excretion of iron by chemical chelation.

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KEYWORDS: Cardiac Magnetic Resonance, Hematochromatosis

INTRODUCTION

Hemochromatosis is a disease first described by Armand Trousseau in 1865. It is a clinical syndrome caused by abnormal accumulation of iron in parenchymal organs, leading to organ toxicity and dysfunction.

Cardiac hemochromatosis is characterized by a dilated cardiomyopathy with dilated ventricles, reduced ejection fraction and reduced fractional shortening.

The diagnosis of cardiac involvement is based mainly on echocardiography which shows left ventricular diastolic dysfunction secondary to a restrictive physiology. This will progress to a dilated cardiomyopathy with a reduced LVEF.

Cardiac magnetic resonance imaging is superior to other diagnostic modalities as it can assess myocardial iron load quantitatively. It evaluates also the cardiac impact of hemochromatosis by measuring right and left ventricular volumes and masses, systolic and diastolic function and by searching myocardial fibrosis.

The age of the beginning of symptomes and the type of organ involvement in hematochromatosis depend on the type of the mutation.

Appropriate screening, early diagnosis and treatment of iron overload are important to prevent or reverse cardiac dysfunction.

Removal of excess iron from the tissues minimizes generation of free radicals, reducing organ damage.

Therapy to remove excess iron includes therapeutic phlebotomy and iron chelating agents.

PATIENTS AND METHODS

In this study, 3 iron overload hemochromatosis patients were chosen: 2 men and 1 woman whose cardiac involvement has been confirmed or eliminated with cardiac MRI.

The objective of our study was to determine the contribution of cardiac mri to the diagnosis and the monitoring of cardiac hematochromatosis.

In addition to the clinical assessments, epidemiological data, a biological evaluation, complete imaging modalities with echocardiography and MRI cardiac study were performed.

RESULTS

- **Case 1:**

A 52-year-old man with a history of allograft for aplastic aneamia in 2012 was admitted with the diagnosis of hematochromatosis. The patient was asymptomatic. Standard laboratory testing showed high concentration of serum ferritin. Echocardiographic findings were normal. The cardiac MRI showed a left ventricular end-diastolic volume estimated at 108ml with a conserved LV ejection fraction at 69%. No global or focal wall motion abnormalities were found . However, we report an alteration of the intrinsic contractility determined by myocardial tagging at the inferior septal wall.

Cardiovascular magnetic resonance has been used to assess myocardial iron deposition using the relaxation parameters T2* and T2. Heart T2* falls when iron loading is increasing. Our patient had a myocardial T2* below 20 ms (18ms) indicating myocardial siderosis.

The late gadolinium enhancement was absent.

- **Case 2:**

A 61-year-old man with a history of Kidney failure at the hemodialysis stage was admitted for episodic dyspnea. Laboratory studies revealed serum ferritin at 5653 ng/ml. Echocardiography showed biauricular dilatation, parietal hypertrophy and pericardial effusion of moderate abundance.

In an attempt to further characterize the nature of the cardiac involovment, a series of magnetic resonance studies were conducted.

The cardiac MRI showed a dilated left ventricular end-diastolic volume estimated at 186ml with a conserved LV ejection fraction at 56%.No global or focal wall motion abnormalities were found . However, we report an alteration of the intrinsic contractility determined by myocardial tagging at the anterolateral wall.

Our patient had a myocardial T2* at 33ms.

- **Case 3:**

A 62-year-old woman was admitted on May 28 with episodic dyspnea and palpitations . She denied any recent chest pain, dizziness, syncope, fever or recent hospitalization .

During examination,jugular venous distention was noticed and heart examination showed irregular heartbeats. Laboratory studies revealed serum ferritin at 3003 ng/ml .

Electrocardiogram showed atrial fibrillation with transthoracic echocardiogram showing restrictive cardiomyopathy.

A right heart catheterization was performed and had eliminated chronic constrictive pericarditisis.

The cardiac MRI showed a dilated right ventricule with a moderate right ventricular systolic dysfunction. Myocardial T2* measured in the septum was at 32 ms.

- MRI examinations were performed using a 1.5 Tesla Siemens. The findings of cardiac MRI are presented in Table 1.

		Case 1	**Case 2**	**Case3**
Left chamber	End diastolic diameter LV	48 mm	55mm	32 mm
	End Systolic diameter LV	26 mm	34 mm	18 mm
	Myocardial thickness	Average : 7 mm	Septal: 12 mm Anterior : 13mm Lateral : 18mm Inferior : 8mm	Septal: 8 mm Anterior : 6mm Lateral : 6mm Inferior : 6mm
	End diastolic volume	108 ml =67 ml/m²	186 ml =126 ml/m²	47 ml =32 ml/m
	End systolic volume	33 ml =20 ml/m²	85 ml =58 ml/m²	20 ml =14 ml/m²
	Ejection fraction	69%	56%	58%
	Left ventricular mass	107 g = 65 g/m²	149 g = 101 g/m²	82 g = 56 g/m²
	Left atrium	Diameter : 40 mm	Diameter : 50 mm Area : 30 cm²	Diameter : 42 mm Area : 26 cm²
	Segmental kinetic	normal	normal	normal
	Myocardial Tagging	Alteration of intrinsic contractility at the inferior septal wall	Alteration of intrinsic contractility at the anterolateral wall	No alteration of intrinsic contractility
	Haste sequence	No hyperintensity No perfusion defect	No hyperintensity No perfusion defect	No hyperintensity No perfusion defect
	Late enhancement after gadolinium injection of 10 min	No late enhancement	No late enhancement	No late enhancement

Right chamber	End diastolic diameter RV	24 mm	34 mm = 23 mm/ m²	127mm = 87 mm/m²
	Sidewall thickness of the RV	-	4 mm	-
	Right atrium	Diameter: 33 mm	Diameter : 43 mm Surface : 19 cm²	Diameter : 44 mm Surface : 24 cm²
	Segmental kinetic	normal	normal	normal
	Haste sequence	No hyperintensity No perfusion defect	No hyperintensity No perfusion defect	No hyperintensity No perfusion defect
	Late enhancement after gadolinium injection of 10 min	No late enhancement	No late enhancement	No late enhancement
Measure T2*		18 ms	33 ms	32 ms

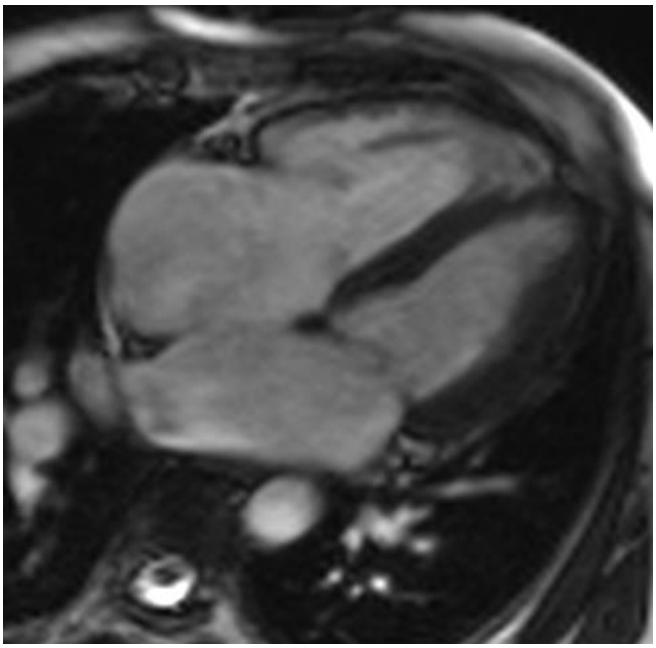


Figure 1 : Slice 4 chamber cine sequence showing atrial dilatation related to atrial fibrillation and non hypertrophied ventricle walls in a patient referred for hematochromatosis.

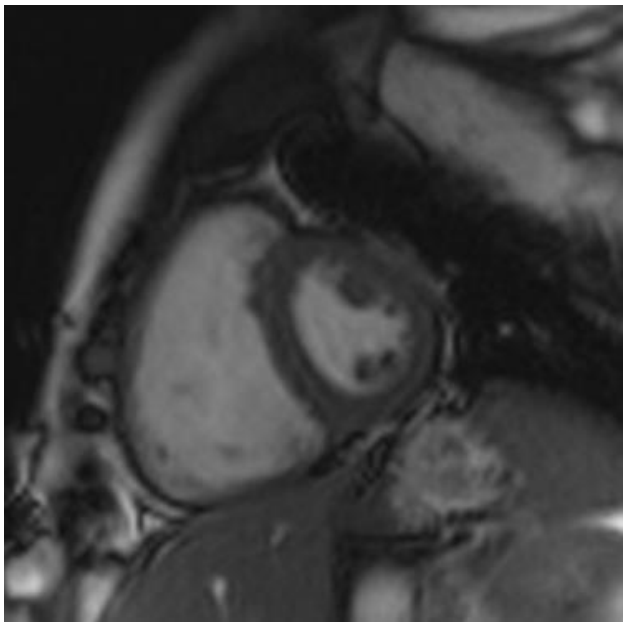
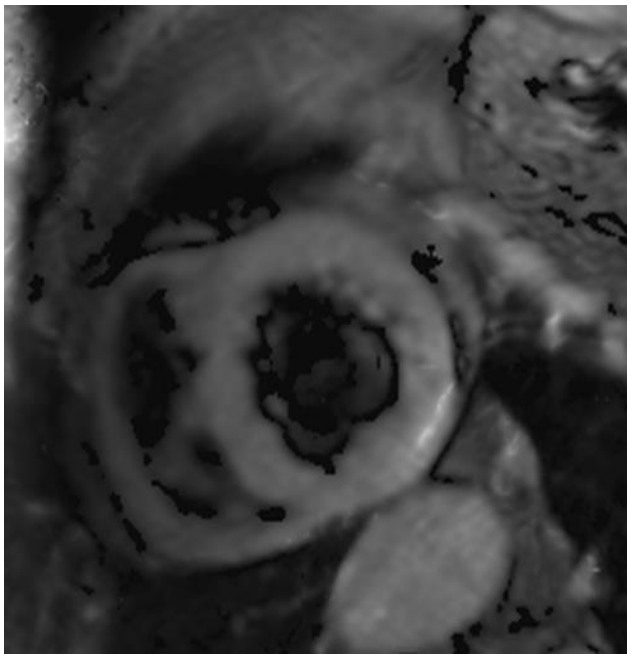


Figure 2: Short axis slice showing non hypertrophied ventricle walls.



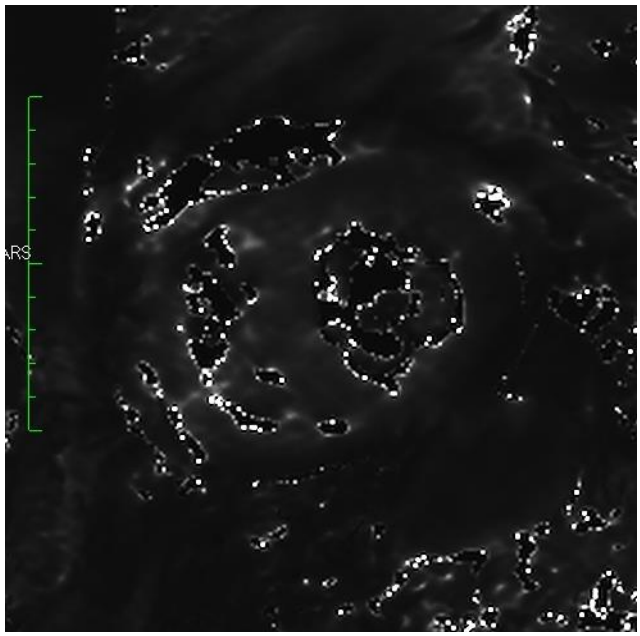


Figure 3: T2* sequence short axis slice in a patient referred for cardiac hematochromatosis.

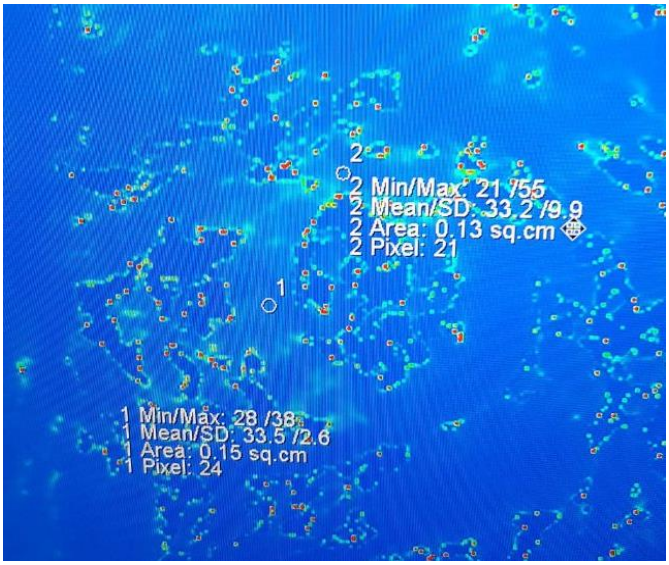


Figure 4: T2* sequence short axis slice in a patient referred for cardiac hematochromatosis.Myocardial T2* measured in the septum was at 28 ms.

DISCUSSION

Cardiac magnetic resonance (CMR) imaging is superior to other diagnostic modalities as it can assess myocardial iron load quantitatively. [1]

In noniron-loaded hearts, the microwave signals induced by exciting protons in the body in a high magnetic field are homogenous. The relaxation time lasts for a longer duration. In patients with hemochromatosis, the iron overloaded heart shows changes in signal intensity and susceptibility with shortening of the relaxation time and quicker darkening of the image due to the paramagnetic effect of iron . [2]

The greater the iron content in the myocardium, the shorter are the T2 and T2*. [3, 4,5]

The relaxation time may be measured using the spin echo technique, the signals are refocused using a special radiofrequency pulse, or by using the small magnetic fields called gradients (gradient echo) at specific time intervals called echo time. The time constant of decay for the relaxation time is inversely proportional to the myocardial iron content. [6]

However, in a study by Barrera and al, no association was observed between the myocardial T2* values and ferritin in the blood . One of our patients had a T2* at 18 ms with a low iron overload. [7]

Despite the success of the breath-hold T2* technique, myocardial T2* measurements are subject to artifacts generated from myocardial motion, and those from blood such as ghosting artifacts and partial volume effects. **[8]**

For the measurement of myocardial T2* *in vivo*, a mid-ventricular short axis slice is acquired and a homogeneous region of interest (ROI) is defined encompassing both epicardial and endocardial regions as iron is preferentially laid down in the epicardium compared with the endocardium.

In addition, T2* in the septum has proven to be a good indicator of the global iron in the heart. [9]

To date, no significant clinical advantage has been demonstrated using the multi-slice technique. The single slice T2* technique remains the preferred protocol in the practice. [10]

The signal intensity of the ROI is measured for each of the T2* images, and the data is plotted against the echo time to form an exponential decay curve. Initially, the decay rate T2* was derived by fitting a mono-exponential trend line to the exponential decay curve.

In the presence of severe myocardial iron overload, a rapid decay in myocardial signal intensity can lead to a plateau in the later echo time images. [11]

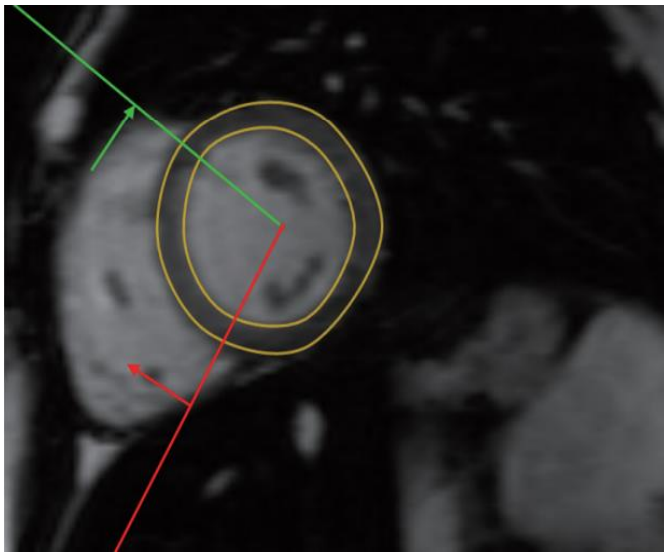


Figure 5: A typical image shows the full-thickness ROI in the interventricular septum for T2* measurement. ROI, region of interest. [12]

In addition to quantifying the myocardial iron load in patients with cardiac hemochromatosis, CMR imaging can assess stress induced myocardial ischemia, myocardial viability, resting LVEF, left ventricular end-systolic and end-diastolic volumes, and left ventricular mass.

Another consideration in Hematochromatosis is the development of heart failure. Dilated cardiomyopathy is well recorded in Hematochromatosis, and reports recommend that serum ferritin should be measured in newly presenting cases of dilated cardiomyopathy.

One of our patients had a left ventricular end-diastolic volume increased at 126ml/m2.

The T2* method, being more sensitive and highly specific, is useful for quantitation and longitudinal tracking of iron deposition. There is a good inverse correlation between patient's myocardial T2* and LV ejection fraction. [11] The ejection fraction was conserved in all our cases.

The clinical severity of myocardial iron overload in cardiac hemochromatosis is assessed by T2* values. One of our patients had a myocardial T2* below 20 ms indicating myocardial siderosis.

Patients with a T2* relaxation time greater than 20 ms are at low risk for developing congestive heart failure. Patients with a T2* relaxation time between 10 and 20 ms probably have deposition of iron in their myocardium and are at intermediate risk for developing congestive heart failure. Patients with a T2* relaxation time of less than 10 ms are at high risk for developing congestive heart failure and need chelation therapy [13].

Therapy of cardiac hemochromatosis should be guided by abnormal CMR results. The CMR is an excellent tool for early diagnosis of heart involvement, risk stratification, treatment evaluation, and long term follow-up of patients with cardiac hemochromatosis [14].

There is a significant correlation between the patient's myocardial T2* and the need for therapy of the cardiac hemochromatosis.[11]

After a decade of efforts, T2* is recognized as the method of choice for the assessment of tissue iron.There have been attempts to develop T2 and T1 techniques. The interest of comparing these relaxation parameters is to know if additional useful information can be found. With the recent development of the modified Look-Locker Inversion recovery (MOLLI) sequence[15], T1 changed in response to myocardial iron deposition . The study demonstrated that there is a linear correlation between T1 and T2 in the human heart and that T1 can also be used to assess myocardial iron [16].

From a clinical perspective, it would be useful if CMR relaxometry could be used to distinguish between different forms of storage iron. A novel method has been developed to separate the two principal forms of tissue storage iron: ferritin and hemosiderin **[17] ,** further studies are needed to demonstrate its clinical benefit.

Tissue iron overload is a global disease, and it is important to expand patient access to cardiac iron assessment. Therefore any such measurement needs to be simple, robust and preferably automated to ensure accurate and reproducible measurements. A fully automated T2* analysis software integrated with a standardized acquisition protocol is therefore crucial to improve global healthcare. **[12]**

CONCLUSION

Tissue iron overload is a global disease, and it is important to expand patient access to cardiac iron assessment. CMR T2* is currently recognized as the method of choice for the assessment of tissue iron. With the introduction of T2*, advancement of new chelation drugs and personalized patient management, the mortality rate attributed to tissue iron overload has been decreasing worldwide. Further development is required to improve patient access to reliable T2* measurement.

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