T2* cardiovascular magnetic resonance in the management of thalassemia patients in Oman

Myocardial siderosis in thalassemia major remains the leading cause of death in developed countries despite the use of iron chelating agents over the past three decades. Once cardiac failure occurs, it is difficult to reverse, but early detection could result in a better prognosis through more effective treatment. Cardiovascular magnetic resonance (CMR) using myocardial T2* has been shown to be a highly sensitive, non-invasive and reproducible technique for detection of myocardial iron content.[1] Although serum ferritin is widely used as a measure of iron overload, there is no correlation between serum ferritin and cardiac T2*.[2] A recent study has shown detectable cardiac iron in patients aged 15-18 years and none in patients lower than 9.8years.[3] At Sultan Qaboos University Hospital, Oman, we investigated the prevalence of cardiac siderosis in a relatively young cohort of patients with thalassemia major (n=81, 10-35 years, mean ±SD: 19±5.8 years). Patients were being treated with either single agent (deferiprone, n=14; deferoxamine, n=1 or combined chelation therapy, n=66). Ejection fraction obtained by standard echocardiography was available for 61 patients. All subjects underwent cardiac and liver T2* studies at baseline and at 3-6 monthly intervals thereafter. Those with moderate or severe cardiac siderosis (cardiac T2* lower than 15 ms), had their therapy optimized with deferiprone doses increased from 75 mg/kg/day to 90-100 mg/kg/day (except one who had had deferiprone-induced agranulocytosis). Follow-up cardiac T2* results were analyzed for 79 patients 15-18 months after baseline studies.

We found that myocardial T2* had no correlation with either serum ferritin or age (Table 1A, Figure 1). As expected, there was a significant correlation between serum ferritin and liver T2* (p<0.001). We found no correlation between ejection fraction and cardiac T2*, which differs from the observations of Anderson.[1] However, ejection fraction in our patients was measured by routine echocardiography, which is a less accurate and reproducible technique than CMR.[4] The prevalence of myocardial siderosis (T2* <20 ms) in this cohort of Omani patients was high at 46%. This prevalence, however, is lower than the 65% reported in Italian patients who had been on monotherapy with deferoxamine.[5] This difference is possibly due to the fact that the majority of our patients had been on combined therapy with deferoxamine (×3-5/week) and deferiprone (75 mg/kg/day) for more than three years (3-7 years, mean 5.1 yrs) and confirms earlier observations that deferiprone appears to have a cardioprotective effect with improvement in myocardial overload and reduction in cardiac related deaths.[6-8] In 19 patients (23%), cardiac T2* values were 10 ms or less. All 3 patients who had clinical cardiac disease were in this group. What was of more concern was the fact that the other 16 patients were asymptomatic and had normal ejection fractions. These patients are at the highest risk of developing clinically significant myocardial complications such as cardiac failure and life-threatening ventricular arrhythmias. A tool like cardiac T2* is thus the only test that can help in identifying at-risk patients who can then be treated aggressively with optimization of their chelation protocols and then more closely followed for impending life-threatening complications.

Analysis of the 19 patients with very low cardiac T2* (lower or equal than 10 ms), showed that 4 had mean serum ferritin lower than 1,000 ng/mL and in 11 patients it was lower than 2,500 ng/mL. An earlier report by Olivieri suggested that patients whose serum ferritin remained below 2,500 ng/mL had excellent prognosis.[9] However, more recent studies have shown that serum ferritin levels are not always predictive of cardiac disease. Kolnagou demonstrated that 5 out of 56 patients with good chelation compliance and low serum ferritin presented with unexpected cardiomyopathy.[10] Amongst our patients, one family of 4 siblings had exceptional compliance with deferoxamine monotherapy as shown by their average serum ferritin levels over the previous 13 years (Table 1B). One of them, MM, had presented in 2004 with cardiac failure with an ejection fraction of 36%. Deferiprone (75 mg/kg/day) was added to her therapy and her ejection fraction has since improved to 66%. Three of these 4 siblings have substantial cardiac siderosis (lower than 13.5 ms) with very low liver iron content.

We have also observed that myocardial siderosis may present even in relatively young patients. Of 37 patients with myocardial T2* lower than 20 ms, 10 (27%) were aged 14 years or younger, comparable with the recent finding of Wood.[3] However, in Wood's study, no patient lower than 15 years had severe cardiac siderosis (lower than 10 ms), whereas in our cohort, 5 patients under 15

Table 1A. Cardiac T2* values (baseline) for 81 Omani patients with thalassemia major.

Cardiac T2* range	No.	Cardiac T2* [ms] mean	Liver T2* [ms] mean (SD)	Serum ferritin[1] [ng/mL] mean (SD)	Age [years] mean (SD)
0-10	19	7	1-9.6 (3.0)	639-9838 (2808)	12-32 (20)
10-20	18	16	1.3-12.9 (5.0)	570-6595 (2577)	11-22 (17)
>20	44	33	0.9-19.5 (5.5)	402-8709 (2496)	10-33 (19)
	Total 81	23	0.9-19.5 (4.9)	402-9838 (2552)	10-33 (19)

[1]*Serum ferritin- average over 12 months prior to T2* CMR, minimum 6 values.*

Table 1B. Family HKM. See text for details.

Patient	Age	Sex	Average serum ferritin over past 13 years	Cardiac T2* (ms)	Liver T2* (ms)	Cardiac symptoms
HM	21	M	1603	10.5	7.6	No
MM	18	F	1082	8.5	9.6	Yes
AM	16	F	1085	13.3	11.5	No
SM	14	M	951	41	2.5	No

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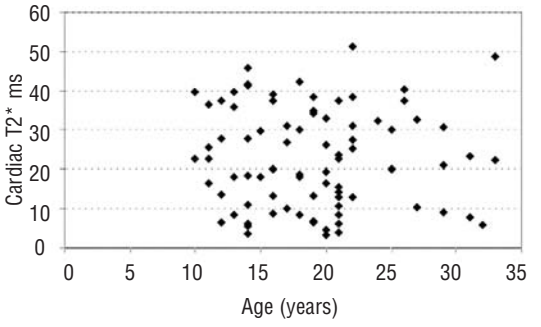

Figure 1. Correlation between cardiac T2* and age.

years had cardiac T2* lower than 10 ms. This could be due to sub-optimal chelation therapy but this is unlikely in view of their reasonable serum ferritin levels. The possibility of a genetic component for the susceptibility of cardiac iron loading in some populations should also be considered. A polymorphism of the glutathione S-transferase gene (*GSTM1* null genotype) has been associated with decreased signal intensity ratios on CMR in 41 Taiwanese patients.[11] However, our analysis of 81 Omani patients in this study found no correlation between null genotypes of either *GSTM1* or *GSTT1*.

Finally, adjusting chelation in heavily iron loaded patients, in particular increasing deferiprone dose, has resulted in a marked improvement in cardiac siderosis. The most severely affected patients (cardiac T2* lower or equal than 10 ms) showed a significant improvement from a mean of 7.3 ms±2.2 at baseline (range 3.4-10.2 ms) to 9.4 ms±3.6 (range 4.8-18.9 ms) at 18 months follow-up ($p<0.005$).

The availability of T2* MR at our institution has had a significant impact on patient management. All patients with substantial cardiac siderosis (T2* lower than 15 ms) (except one who had had deferiprone-induced agranulocytosis) have had combination therapy,[12] with optimization of deferiprone dose from 75 mg/kg/day to 90-100 mg/kg/day, in addition to deferoxamine ×3-5 weeks if serum ferritin was greater than 500 ng/mL. T2* CMR is a powerful tool in assessing cardiac siderosis and our results have allowed us to focus on those patients who are at most risk.

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Characterization of 35 new cases with four different *MPL*W515 mutations and essential thrombocytosis or primary myelofibrosis

Recently, mutations of *MPL*, the gene coding for the thrombopoetin receptor, were demonstrated in ~5% of cases of primary myelofibrosis (PMF) and in ~1% of all cases of essential thrombocytosis (ET).[1,2] They represent gain-of-function mutations that confer constitutive activation of the JAK-STAT pathway like *JAK2V*617F.[1,2] Two different amino acid exchanges of codon W515 resulting in a tryptophane to leucine (W515L) or lysine (W515K) were described. So far, W515 mutations have been found in ET and PMF, but were never detected in polycythemia vera (PV). Most cases had wild type *JAK2*V617.[1,3] To evaluate the *MPL*W515 mutations as markers for routine diagnostics of *JAK2*V617 unmutated myeloproliferative neoplasms (MPN), we performed analyses for *MPL*W515 mutations in a total of 869 selected MPN patients (399 males; 470 females; 12.2–90.3 years; median 60.5 years) from January 2006

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