Abstract

Regular monitoring of left ventricular ejection fraction (LVEF) for thalassemia major (TM) is widely practiced, but its value in informing iron chelation treatment is unclear. 81 TM patients without previous cardiac history received quantitative yearly LVEF monitoring by radionuclide ventriculography for a median of 6.0 years (inter-quartile range: 2-12 years). Intra-and inter-observer reproducibility for LVEF determination were both <3%. LVEF values pre- and post-transfusion did not differ and exercise stressing did not reliably expose underlying cardiomyopathy. An absolute LVEF of <45% or fall of >10 percentage units was significantly associated with subsequent development of symptomatic cardiac disease (p<0.001) and death (p=0.001), with a median interval between the first abnormal LVEF and development of symptomatic heart disease of 3.5 years, allowing time for intervention. In 34 patients where the LVEF was <45% or fell by >10 percentage units, intensification of chelation was recommended (21 with subcutaneous and 13 with intravenous deferoxamine). All 27 patients who complied with intensification survive, while the 7 who failed to comply died (p<0.0001). The Kaplan-Meier estimate of survival beyond 40 years for all 81 patients is 83%. Sequential quantitative monitoring of LVEF is valuable for assessing cardiac risk and for identifying TM patients requiring chelation intensification.
Introduction

Cardiac disease due to transfusional iron overload remains the principal cause of death in β-thalassemia major, despite improvements in iron chelation therapy over the last 25 years. For this reason, regular evaluation of cardiac function is recommended for all patients with thalassemia major and is now an integral part of their management. However, the value of monitoring cardiac function to the long-term management of thalassemia is unclear. This is partly because the prognostic significance of diastolic abnormalities, which appear early in the disease process, is unknown. Additionally, congestive heart failure (CHF) is often already present by the time systolic abnormalities have become manifest using echocardiography. These observations have led some workers to question the value of non-invasive monitoring of cardiac function in the management of thalassemia.

Although recovery is possible in a proportion of patients with established CHF, overall long-term prognosis remains poor. Cardiac monitoring should therefore ideally identify patients at highest risk of cardiac decompensation before CHF develops. Sequential and reproducible quantification of ventricular function can in principle identify early changes in the left ventricular ejection fraction (LVEF) from baseline for each patient and could be used as a rationale for identifying high-risk cases. Radionuclide ventriculography using multi-gated acquisition (MUGA) gives a highly reproducible quantification of LVEF in normal and abnormal hearts. MUGA has been used prospectively as a part of annual assessment at our center since 1981, and it is the value of these prospective data which is addressed in this paper. Over a 20-year period, we have used LVEF changes (absolute value <45% or a fall >10 percentage units below baseline for each patient) to identify patients at greatest risk of cardiac decompensation. Here we report
the outcome of this approach using sequential quantitative LVEF monitoring in 81 thalassemia major patients with no previous cardiac history.

**Methods**

**Study design**

The predictive value of sequential quantitative LVEF monitoring by MUGA for subsequent cardiac morbidity and mortality has been examined in 81 patients with β-thalassemia major born between 1957 and 1987. Between March 1981 and February 2001 a strategy was adopted at University College London Hospitals for yearly monitoring of LVEF by MUGA. Data from MUGA are available from 85 of 103 patients from this clinic in whom survival data have been previously reported. 81 of the 85 patients had no previous cardiac history at the time of entry into the study and are therefore those in whom the predictive value of MUGA monitoring is analyzed. 39 patients were male and 42 were female and the median age at which MUGA was initially performed was 19 years (inter-quartile range: 16-23 years). All patients were regularly transfused to maintain pre-transfusion hemoglobin levels of >10.5 g/dl prior to 1995 and >9.5g/dl thereafter.

Routine cardiac evaluation consisted of a detailed clinical history, physical examination, resting and exercise electrocardiography (ECG), echocardiography and MUGA. 24-hour Holter monitoring was performed in patients with palpitations or in patients with arrhythmias demonstrated by clinical examination and/or on routine ECG. Impaired left ventricular (LV) function was defined as a fall in the resting LVEF either to a value below the lower reference limit of 45% or by >10 percentage units between two consecutive measurements, regardless of
the LVEF value. 34 patients showed evidence of LV dysfunction on at least one occasion during
the period of observation (LVEF <45% in 28 and drop by >10 percentage units in 6).

Chelation therapy was exclusively with deferoxamine mesylate (DFO), which in the
absence of high-risk clinical features, consisted of a standard regimen (30-50mg/kg/d by
subcutaneous infusion 8-12h/d, 5-7d/wk). DFO treatment was intensified in the event of
objective evidence of asymptomatic LV dysfunction at rest, in an attempt to prevent progression
to frank CHF. Treatment intensification was with one of three modalities. The first was
continuous intravenous DFO through an indwelling line at a dose of (50-100 mg/kg/24h) as
previously described in 17 patients,\textsuperscript{15} 11 of whom were eligible for inclusion in this paper, as they
had no pre-existing cardiac disease. Data from 2 additional patients have also been included. The
second was improvement in the subcutaneous DFO regimen, achieved by increasing the
frequency, duration or dose of administration. In early years of the study, a maximum of 12-hour
infusions were possible through mechanical pumps (up to 60mg/kg/day). After 1994,
subcutaneous DFO was given through 24-hour disposable balloon infusers\textsuperscript{22} at doses of 40-
60mg/kg/24h up to 7 days a week. The third was continuous 24-hour intravenous infusion of
DFO (100mg/kg) diluted in 500-1000mls of normal saline and delivered though a peripheral vein
on an inpatient basis for up to 1 week at a time, to supplement ongoing subcutaneous treatment.
Intensification dosing was reduced as serum ferritin values fell in line with the therapeutic index,
as previously described.\textsuperscript{15} The decision about which approach to adopt was made on the basis of
extended interviews between the lead clinician with the patient and on the practicalities of each
option; option 1 being our preferred approach.

In addition, after 1995, this included interviews with a clinical psychologist, where
underlying psychological issues pertinent to poor compliance were explored and rectified.
Results of subsequent LVEF or serum ferritin were fed back to each patient as part of a sustained
follow up program. Compliance was monitored by patient interview with the mean number of infusions/week being used as a compliance endpoint.²³

**MUGA assessment**

All LVEF studies were performed in the left anterior oblique position using IGE Portacamera/Informatek Simis III and IGE Optima/Star 4000I configurations as previously described.¹⁵ The red cell labeling method¹⁵ had an efficiency of 98%. Image processing was carried out on the Portacamera/Informatek system as follows: after smoothing the raw data, Fourier phase and amplitude images as well as the end-diastolic and end-systolic images were displayed. A region of interest around the left ventricle was then assigned manually on the end-diastolic frame, always taking into account the end-systolic phase and amplitude image limits. Following background correction of the region of interest using the method of Goris,²⁴ ventricular time-activity curves were generated and LVEFs calculated. Data processing software was supplied by Informatek, Buc, France. Data analysis on the Optima/Star configuration was broadly similar to the method described above, except that SAGE software was used to determine the ventricular center (automatically) and edge (semi-automatically). The SAGE software was supplied by the manufacturers (GE Medical Systems, WI) and used unmodified.

The reproducibility of LVEF measurements was assessed on the two configurations used during the study. On the IGE Portacamera/Informatek configuration, the inter-observer correlation coefficient for a range of LVEF values (n=60 patients) between 7-71% was 0.99 (p = 0.001), with a standard error of 2.79% between the results of two observers. Intra-observer reproducibility for a range of LVEF values (n=66 patients) between 7-71% gave a correlation coefficient of 1.00 (p=0.001), with a standard error of 2.57% between the results. On the IGE Optima/Star configuration, LVEF values calculated from three acquisitions carried out by the
same observer on a range of values from 22-79% (n=75 patients) gave a correlation coefficient of 0.98 (p<0.001) with a standard error between the results of 2%. LVEF values calculated from three acquisitions by two independent observers at two different times on the same patients also showed a high correlation (r=0.99) with a standard error of 1.8% between the results. Thus, there was no appreciable difference in reproducibility between the two systems. Changeover from the Portacamera/Informatek to the Optima/Star was effected in 1993-1994, with no systematic difference for LVEF values among approximately 50 non-thalassemic subjects studied on both configurations.

The reference range for the resting LVEF by MUGA in non-thalassemic patients at our institution was 50-70%, with a 95% confidence interval for the lower value of 45-55%. The limits of reproducibility for the resting LVEF was 5 percentage units; thus a change of >5 percentage units between serial measurements was defined as clinically significant. However, in this study, a change in the resting LVEF by >10 percentage units between serial measurements was used as the trigger for treatment intensification as this is the limit of biological variability in normal subjects. Additionally, absolute LVEF values <45% were considered to be abnormal and a trigger for treatment intensification.

For exercise stress tests, LVEF measurements were obtained at rest, then following dynamic exercise in the supine position on a mechanically-braked bicycle. Chest movements during exercise were minimized by the use of shoulder restraints, chest straps and handgrips. Starting at 25 watts, the load was increased in 25-watt stages, each stage lasting three minutes, with continuous ECG monitoring using lead II and measurement of the pulse rate and blood pressure at the end of each stage. Exercise was continued until maximum workload was achieved, or the patient developed fatigue, angina, dyspnoea, significant hypotension, or ventricular
arrhythmia. Data were acquired for the final two minutes of each stage. A normal response to dynamic exercise was defined as a rise in LVEF by >5 percentage units at maximal exercise.

Serum ferritin measurements were generally measured monthly as previously described.\textsuperscript{15}

Outcome measures and statistical analysis

The outcome measures were CHF or arrhythmia requiring cardiac medication, and cardiac death attributable to iron overload. CHF was defined by the criteria of the Task Force on Heart Failure of the European Society of Cardiology.\textsuperscript{25} The period of follow up began on the date of an individual’s first MUGA, and the cut-off point for follow up was February 28 2001. Patients leaving the study center for treatment abroad or in other centers were censored for analysis at the point of exit. The median follow-up period for the 81 patients was 5.8 years, with an interquartile range of 2.4-11.7 years and a maximum of 20 years.

Summary data are presented either as median or mean ± 1 standard deviation. Pearson’s chi squared and Fisher’s exact tests have been used to test the relationship between categorical variables. Differences between means of samples have been analyzed using paired t-tests. Survival has been calculated using Kaplan-Meier survival analysis and differences in survival between different groups of patients compared using the log rank test. A logistic regression model, adjusted for serial tests on patients, was used to investigate the association between exercise response and subsequent CHF. All statistical analyses were performed using Stata software, version 7 (Stata Corporation, TX).
Results

1. Initial evaluation of MUGA for LVEF monitoring.

Effect of blood transfusion on LVEF

To determine whether it was necessary to stipulate the point in the blood transfusion cycle when MUGA was performed, paired measurements of LVEF were undertaken in 10 patients immediately pre- and 24 hours post-transfusion. Mean pre- and post-transfusion hemoglobin concentrations were $11.56 \pm 1.16$ g/dl and $15.0 \pm 1.61$ g/dl ($p<0.0001$), with mean hematocrits of $0.34 \pm 0.03$ and $0.46 \pm 0.06$ ($p<0.0001$). There was no significant difference between resting LVEF pre ($52 \pm 14\%$) and 24 hours post ($51 \pm 15\%$) blood transfusion ($p=0.36$) (Figure 1). The relatively high ‘pre-transfusion’ mean hemoglobin value partly reflects the transfusion policy used at the time (to keep pre-transfusion hemoglobin $>10.5$ g/dl) and partly that some patients in this study were transfused mid-cycle. There was no relationship between the change in LVEF pre- and post-transfusion and either the hemoglobin increment with transfusion or the pre-transfusion hemoglobin value.

Effect of dynamic exercise on LVEF

A total of 60 paired LVEF exercise studies were performed sequentially on 27 thalassemia major patients over a 5-year period. Fatigue and dyspnoea were the reasons for termination of the exercise and there was a failure to achieve $85\%$ of the predicted heart rate post-exercise in over half of these. In those with normal resting LVEF, the mean peak exercise load
achieved was 78 ± 21 watts. By contrast, the mean peak exercise level attained in 25 control subjects, comprising 4 healthy volunteers and 21 patients with angiographically normal hearts, was 155 watts (range 125-200 watts), with only 5 of the 25 subjects failing to achieve the desired hemodynamic response. 40 tests showed an abnormal response (with failure to show an increased LVEF of >5 percentage units) and 20 had a normal response.

In all 27 thalassaemia patients, there was no significant difference between LVEF values pre- and post-exercise (52 ± 8% and 53 ± 11%; p=0.47) (Figure 2). Exercise-induced changes in the subgroup of patients with normal resting LVEF (n=19) again showed no difference between pre- and post-exercise LVEF (54 ± 7% versus 54 ± 12%; p=0.91). In the 25 control subjects, the mean LVEF increased from 64 ± 10% to 73 ± 8% (p<0.01).

Investigation of cardiac outcome following each of the 60 studies in the 27 patients, using logistic regression adjusted for serial tests on patients, provided no evidence to support an added prognostic value of exercise testing. Exercise response was not significantly associated with subsequent heart failure, even after adjusting for peak exercise load.

2. Value of LVEF in prediction and management of cardiac disease.

Relationship between impaired LVEF and long-term survival (Table 1).

The Kaplan-Meier estimate of survival beyond 40 years of age is 83%, in the entire cohort of 81 patients monitored regularly with resting MUGA for LVEF (Figure 3a). Where LV dysfunction was demonstrated by MUGA, subsequent symptomatic heart disease and cardiac death were more frequent. Thus, in patients with asymptomatic LVEF changes, as defined in methods, the odds of subsequent heart disease were 25 times those of patients with normal LVEF
Only 1 out of 47 patients who never recorded a drop in LVEF experienced a cardiac event. There was also a significant difference in the frequency of cardiac death between the groups with and without asymptomatic LVEF changes (p=0.001). The median time interval between the first abnormal LVEF and development of symptomatic heart disease was 3.5 years (range: 1.7-10.9 years) and 7 of these died after a median of 3.8 years (range: 2.9-9.3 years) from the time of initial LVEF drop. These findings show that LVEF changes identified with sequential quantitative monitoring generally precede and predict subsequent significant clinical cardiac decompensation by a sufficient period to allow treatment intensification. Although all treatment decisions were made on the basis of either LVEF <45% or fall of >10 percentage units, we have also retrospectively examined the relative importance of absolute LVEF <45% compared with a decrement of >10 percentage units to subsequent survival and cardiac complications. This showed that whereas there were no deaths or cardiac disease among patients who dropped LVEF >10 percentage units while maintaining absolute values >45%, only 57% of patients in whom LVEF fell below this value had no cardiac disease, with only 75% surviving long-term.

**Interventional treatment with DFO based on LVEF and long-term survival.**

Patients were categorized into those with a resting LVEF <45% or >10 percentage unit drop (category 1) or >45% (category 2) in line with pre-determined criteria for DFO intensification (see Methods). When survival is compared between category 1 and category 2 patients based on LVEF, it can be seen that all deaths occurred in category 1 patients (Table 1)(Figure 3b). Figure 3c shows that among the 34 category 1 patients, all deaths (n=7) occurred in those who failed to sustain an improvement in compliance with intensified DFO after the LVEF abnormality had been identified. Median survival in this group with abnormal LVEF plus poor sustained compliance to intensification was only 3.8 years from the initial deterioration in
resting LVEF. This contrasts with those patients who adhered to sustained intervention with DFO (n=27), none of whom have died with a follow up period of up to 20 years (median 11.7 years) after the initial fall in LVEF.

The influence of the route of DFO used for intensification (subcutaneous or intravenous) on outcome among the 34 category 1 patients was also examined (Table 2). As previously reported, there is a significant improvement in LVEF following intravenous DFO through Port-a-Cath. However it is also clear from Table 2 that there is significant improvement in LVEF following subcutaneous DFO intensification. These findings show that sustained response can be achieved with either route, provided compliance is maintained.

Among the 27 surviving patients who received treatment intensification on the basis of LVEF, the cumulative DFO dose to the point when their cardiac function stabilized was estimated in 22 in whom adequate records are available. The median cumulative DFO dose was 36g/kg body weight (range: 16-139g/kg) over a median of 3 years (range: 1.3-8 years). When the cumulative dose for each patient was calculated on a daily basis, the median value was 43mg/kg/day, suggesting that conventional doses of DFO are efficacious both in preventing and reversing LV dysfunction, provided there is sustained patient compliance to the prescribed regimen.

3. Relationship between other risk factors and cardiac complications.

Age of commencement of standard subcutaneous DFO, and serum ferritin levels have been previously identified as predictors of cardiac risk in patients with thalassemia major. We therefore examined their predictive value for cardiac risk in relation to that of sequential LVEF monitoring. While myocarditis has been identified as a precipitant of heart failure in a small
portion of thalassemia patients, no patients in this study had evidence of myocarditis as a precipitant of cardiac decompensation.28

**Effect of age at subcutaneous DFO commencement on cardiac risk (Table 1).**

78 patients had evaluable data with respect to age of DFO commencement. 42 of these patients had started therapy at <10 years of age and 36 patients at >10 years of age. Symptomatic heart disease occurred more frequently in patients commencing subcutaneous DFO >10 years of age than in those in whom this treatment was started at an earlier age (odds ratio: 5.0, p=0.005). This was also true of death from cardiac causes (odds ratio: 7.0, p=0.01)

**Serum ferritin and cardiac risk.**

To examine the relationship between serum ferritin concentration and cardiac risk, we divided the study cohort into two groups using the risk stratification criteria identified by Olivieri.27 This analysis examines the effect of consistently high ferritin values (>2500µg/L) on at least 2/3 of occasions on survival. Table 1 shows that cardiac outcome was significantly better in those patients who maintained serum ferritin values <2500µg/L on at least 2/3 of occasions. The odds for cardiac complications in patients who failed to maintain ferritin <2500µg/L on at least 2/3 of occasions was 3.25 (p=0.05). The risk of dying from iron overload was also significantly increased in this group (p=0.002).

Survival was significantly worse in the group with chronically elevated serum ferritin values (p=0.02) (not shown). This was also true in the subgroup of patients in whom a fall in LVEF had been recorded (n=34), where deaths from cardiac disease (n=7) only occurred in subjects who failed to maintain ferritin values <2500µg/L on at least 2/3 of occasions. No deaths
were seen in those patients with LVEF decrements, in whom ferritin values were maintained at <2500µg/L on at least 2/3 of occasions.

**Discussion**

Although resting and exercise response of LVEF using MUGA have been previously described in follow-up of small groups of thalassaemia patients for periods up to 4 years, this is the first study to investigate the long-term prognostic value of monitoring for asymptomatic LV dysfunction in a large group of thalassemia patients with unlimited access to DFO chelation therapy. In our group of patients, LVEF performed by MUGA and serum ferritin were the regularly used tools for monitoring and adjustment of therapy. Whilst this approach was adopted in all patients since the early 1980s, this was not set up as a formal prospective study and consequently there is heterogeneity in patients’ follow up time and prior chelation history. It is clear, however, that the overall survival is excellent (83% at 40 years) and indeed is the best so far reported, suggesting that this approach is useful. Our findings show that a fall in LVEF by MUGA of >10 percentage units or to an absolute value below the reference range is associated with progression to clinical heart failure within a median period of 3.5 years and death within a median of 3.8 years if DFO intensification is not achieved. Further analysis of the data suggested that under the conditions of observation and intervention adopted in this study, a fall to an absolute value of <45% is more discriminatory for survival than a relative decrement of >10 percentage units.

Previous studies in thalassemia major using MUGA suggested that systolic dysfunction may precede frank CHF and that a successful clinical outcome may be achieved with appropriate intensification of DFO therapy. In this paper, we have observed LVEF changes over a median period of 6 years, with 25% of the patients being observed for between 12-20 years. It is
clear that detectable changes in systolic function precede development of clinical heart failure sufficiently early for a useful intervention strategy to be adopted. After an initial rapid improvement in systolic function with intensification of DFO as previously described, there was characteristically a more gradual improvement that took several years of sustained treatment for maximal effect (data not shown). In all but one patient in the present study, LVEF changes were demonstrable prior to the development of cardiac symptoms.

Our findings may underestimate the effectiveness of the strategy used for LVEF monitoring and treatment intensification because in the older patients, ‘baseline’ LVEF values were not obtained in childhood or in early teenage years. Thus, a fall of LVEF of 10 percentage units or more from the true baseline value could have been missed and intensification delayed. Indeed, survival among patients born after 1975, who were exposed to DFO early in life and have been monitored from an earlier age, shows 100% survival at 25 years. These data compare strikingly with survival of patients in the United Kingdom as a whole where survival is only 50% by the age of 35 years, and reflect the effectiveness of DFO therapy if used in a center where monitoring and intervention such as described in this paper are considered a high priority. However, the optimal age at which monitoring of ventricular function should be commenced remains unclear. In Engle’s pre-chelation era study, the first signs of cardiac involvement emerged at about 10 years of age, with patients becoming symptomatic in mid- to late teens. In our study, one patient already had a reduced LVEF of 39% when her initial MUGA was performed at 13 years of age, although she was clinically asymptomatic at the time. We suggest that yearly quantitative LVEF monitoring of patients should begin ideally by 10 years of age.

Longitudinal monitoring of LV systolic function in thalassemia was traditionally considered to be of limited value because changes were only demonstrable as late events using echocardiography. However, the limitations of echocardiography for sequential quantitative
LVEF measurement are well-recognized: the technique is heavily reliant on operator skill and assumptions have to be made about ventricular geometry, resulting in greater inter-observer variability for LVEF,\textsuperscript{35} more so in severely impaired ventricles. Indeed, early studies in thalassemia major showed that MUGA was a more sensitive indicator of declining cardiac function than M-mode echocardiography, both at rest and on exercise.\textsuperscript{7} Also, the echocardiographic studies were conducted before current standard subcutaneous and intensive intravenous DFO regimens were available, and used either no chelation, or sub-therapeutic doses of DFO.\textsuperscript{6,8,9,12} Thus, there was no effective salvage therapy for patients with deteriorating ventricular function and mortality was high. Doppler echocardiography has been used to evaluate diastolic function,\textsuperscript{3,36} and more recently for examining regional wall motion.\textsuperscript{37} While abnormalities in diastolic function and regional wall motion can be identified before those of systolic dysfunction, there have been no studies of how these affect prognosis or how these might be used as a trigger for treatment intensification. Unlike echocardiography, MUGA does not require any geometric assumptions about ventricular shape; it is thus highly reproducible for quantification of LVEF, even for abnormal hearts. The recognized reliability of MUGA in the assessment of ventricular function is demonstrated by its selection as the method of choice for several major cardiac intervention studies in the 1980s and 1990s.\textsuperscript{38-41} The intra- and inter-observer reproducibility of <3\% for resting LVEF in our hands is comparable to that reported by other workers.\textsuperscript{18,19,21} While MUGA was the tool available for sequential quantitative monitoring from the early 1980s, quantitative monitoring of LVEF is now possible with MRI,\textsuperscript{42-44} which also has excellent reproducibility. Recently, MRI techniques have been also used to estimate myocardial iron and by inference cardiac risk.\textsuperscript{45,46} However, the long-term prognostic significance of this modality has yet to be verified and it is presently unclear how chelation treatment should be stratified based on such a measurement. Our study, on the other hand, shows that LVEF can
be used as an easily available and effective tool for treatment stratification and intervention with a demonstrable impact on cardiac disease and survival.

Our findings show that the excellent reproducibility achieved with MUGA is unaffected by blood transfusion under the conditions of this study. A mean pre-transfusion hemoglobin of >10.5g/dl, was policy at the time of the paired measurements and was relatively high compared to current transfusion practice. However, analysis of the individual changes in LVEF with transfusion shows that these are unaffected by the variability in pre-transfusion hemoglobin values seen in this study. These findings are in keeping with those observed by Henry et al using echocardiography, who found no change in LVEF 2-4 hours after transfusion in thalassemia major patients, where pre-transfusion values were lower than in our patient group.

Exercise stressing appeared to be of limited additional value in our patient group. LVEF by MUGA was originally reported to be abnormal in a higher proportion of hitherto unchelated thalassemia patients following exercise than at rest, with an invariable rise in LVEF noted in control subjects. However, subsequent work showed a wide variation in exercise responses in normal individuals and exercise-induced increments are not invariably seen. Furthermore, a wide overlap between LVEF responses of subjects with angiographically normal hearts and those with coronary artery disease is now recognized, whereas invariable increases in LVEF had been reported initially. Exercise LVEF testing using MUGA with follow up of 1-4 years was reported by Freeman et al in 23 thalassemia major patients receiving subcutaneous DFO. Whereas a minority of patients had abnormal resting LVEF, the majority showed an abnormal exercise response, suggesting an increased sensitivity of exercise compared with resting LVEF. However, neither increased specificity nor prognostic significance was demonstrated. In our own study, subsequent clinical heart failure or cardiac death, were no more common in those with abnormalities demonstrated with exercise compared with those at rest. A confounding factor in
our study was that peak exercise load, an independent determinant of the exercise response,\textsuperscript{47} was variable both between and within patients. Since exercise testing was undertaken at variable points in the transfusion cycle, in principle this could have contributed to the variation in exercise tolerance. In practice, however, this is unlikely as pre-transfusion values were typically >10.5g/dl. It has been suggested that pharmacological stressing might reduce variability related to patient cooperation during exercise testing. In our hands, dobutamine at doses up to 40µg/kg/minute often led to unacceptable symptoms such as flushing and lightheadedness. Although low dose dobutamine (5µg/kg/minute) has been reported to expose underlying cardiomyopathy in thalassaemia patients using echocardiography,\textsuperscript{50} there are no peer-reviewed papers on its effects on LVEF in thalassemia patients using MUGA.

Clearly there are a number of useful approaches to monitoring iron overload in thalassemia major, some of which have been shown to have prognostic value with DFO use, such as serum ferritin,\textsuperscript{27} liver iron\textsuperscript{51} and treatment compliance.\textsuperscript{23,51} Although our findings support a relationship between serum ferritin and outcome, we recognize the limitations of using serum ferritin, particularly as a single measurement at an arbitrary time point, as many factors other than body iron burden affect serum ferritin. It is of note that the association of ferritin with prognosis in both this study and the previous study of Olivieri\textsuperscript{27}, linked prognosis to sustained rises of serum ferritin over many years and not simply single ferritin measurements. The relationship of liver iron to prognosis has not been examined in this paper as this was not one of the determinants used for regular monitoring and thus for chelation stratification. Outcome however is likely to include a component of the duration of exposure to high liver iron levels as in the Brittenham analysis,\textsuperscript{51} where survival was examined in relation to the ratio between cumulative transfusional iron loading and DFO use over time.
In conclusion, it is clear that sequential quantitative monitoring of LVEF, combined with timely and sustained intensification of DFO where necessary, can be used to achieve excellent long-term prognosis in thalassemia major. Contrary to some traditional thinking, it is clear that changes can be identified sufficiently early to prevent further deterioration of LVEF, to reverse cardiac dysfunction and to achieve excellent long-term survival. For this approach to be effective, however, LVEF measurements need to be quantitative, highly reproducible and performed regularly (at least annually). Our data show that single measurements at arbitrary time points will have less prognostic value than those obtained by sequential analysis. We suggest that when either new or established monitoring tools are used to identify cardiac risk, the sequential changes of the marker in question, as well as the full transfusional and chelation history should be taken into account.

References


Table 1. Variables associated with long-term survival in thalassemia major

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of patients</th>
<th>CHF and/or Arrhythmia</th>
<th>Dead</th>
<th>Alive</th>
</tr>
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<tbody>
<tr>
<td>LVEF fell to absolute value below 45% or by more than 10%</td>
<td>34</td>
<td>12</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>LVEF never fell to absolute value below 45% or by more than 10%</td>
<td>47</td>
<td>1</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>81</td>
<td>13</td>
<td>68</td>
<td>7</td>
</tr>
<tr>
<td>Subcutaneous DFO commenced after 10 years of age</td>
<td>30</td>
<td>11</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>Subcutaneous DFO commenced before 10 years of age</td>
<td>48</td>
<td>5</td>
<td>43</td>
<td>2</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>78</td>
<td>16</td>
<td>62</td>
<td>9</td>
</tr>
<tr>
<td>Serum ferritin over 2500µg/l for at least a third of follow up time*</td>
<td>47</td>
<td>13</td>
<td>34</td>
<td>10</td>
</tr>
<tr>
<td>Serum ferritin over 2500µg/l for less than a third of follow up time</td>
<td>38</td>
<td>4</td>
<td>34</td>
<td>0</td>
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<tr>
<td>Total number of patients</td>
<td>85</td>
<td>17</td>
<td>68</td>
<td>10</td>
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</table>

Cardiac disease free survival is shown in patients as a function of LVEF, age of DFO commencement and serum ferritin. Subsequent development of heart disease (p<0.001) and death (p=0.001) were significantly more likely in those patients who displayed a LVEF <45% or drop by >10 percentage units. Symptomatic heart disease occurred more frequently in patients commencing subcutaneous DFO >10 years of age than in those in whom this treatment was started at an earlier age (p=0.005). This was also true of death from cardiac causes (p=0.01). Cardiac complications (p=0.05) and death (p=0.002) were significantly greater in patients who failed to maintain ferritin <2500µg/L on at least 2/3 of occasions.

*Serum ferritin data were available for a median period of 8 years (inter-quartile range: 4-16 years)
### Table 2. Outcomes among thalassemia major patients with asymptomatic left ventricular impairment treated with intensive deferoxamine therapy.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Subcutaneous n=21</th>
<th>Intravenous n=13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at first MUGA (years)</td>
<td>18 (9-27)*</td>
<td>18 (13-24)</td>
</tr>
<tr>
<td>Median follow up (years)</td>
<td>12 (3-20)</td>
<td>11 (5-18)</td>
</tr>
<tr>
<td>Median age at start of chelation therapy (years)</td>
<td>13 (2-24)</td>
<td>9 (2-18)</td>
</tr>
<tr>
<td>Mean (±SD) “baseline” LVEF (%)</td>
<td>55 ± 10</td>
<td>54 ± 12</td>
</tr>
<tr>
<td>Mean (±SD) LVEF pre-intensification (%)</td>
<td>43 ± 6</td>
<td>41 ± 5</td>
</tr>
<tr>
<td>Mean (±SD) maximum LVEF post intensification (%)</td>
<td>57 ± 7</td>
<td>55 ± 4</td>
</tr>
<tr>
<td>Number of patients alive</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Number of deceased patients</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

Outcomes among patients with asymptomatic LV impairment are shown in 34 patients receiving intravenous intensification with DFO (n=13) and those receiving DFO intensification by the subcutaneous route (n=21). There are no significant differences in outcome between subcutaneous and intravenous regimens but patients of higher risk generally received intravenous treatment. There is a fall in LVEF from baseline prior to commencement of intensification of DFO (p<0.0001). Post intensification maximum LVEF values are significantly higher than pre-intensification values in patients treated by both subcutaneous and intravenous DFO (p<0.0001).

*Ranges are in parentheses*
**Figure Legends.**

**Figure 1. Effect of blood transfusion on LVEF measurement by MUGA.** LVEF by MUGA at rest is shown in 10 thalassemia major patients pre- and 24 hours post blood transfusion. There is no significant difference between mean pre- and mean post-transfusion LVEF (p=0.36).

**Figure 2. Effect of dynamic exercise on LVEF measurement by MUGA.** LVEF is shown before and after fatigue-limited exercise in 60 paired observations in 27 patients. There is no significant difference in mean LVEF pre- and post-exercise (p=0.47).

**Figure 3. Survival in 81 thalassemia major patients monitored regularly with MUGA for LVEF.** Figure 3a shows that the Kaplan-Meier estimate of survival beyond 40 years of age is 83%, in the entire cohort of 81 patients monitored regularly with MUGA for LVEF. Kaplan-Meier estimates of survival in category 1 (n=34) and category 2 (n=47) are shown in figure 3b. It can be seen that all deaths (n=7) occurred in category 1 patients, namely, patients with demonstrable left ventricular dysfunction during the period of observation. In figure 3c, Kaplan-Meier estimates of survival are shown in 34 category 1 patients subdivided on the basis of compliance with intensification with deferoxamine. All deaths (n=7) occurred in patients who failed to sustain compliance with deferoxamine (log rank p< 0.0001).
Figure 1

- LVEF (%)
- Pre
- 24h post
- Mean = 52
- Mean = 51
- p = 0.36
Figure 2
Figure 3a
Figure 3b

The figure shows survival probability over years from the first MUGA (Magnetic Resonance Angiography) for patients with and without LVEF (Left Ventricular Ejection Fraction) impairment. The survival probability is indicated on the y-axis, ranging from 0.00 to 1.00. The x-axis represents years from the first MUGA, ranging from 0 to 30 years. The graph distinguishes between patients with no LVEF impairment and those with LVEF impairment.
Figure 3c
Value of sequential monitoring of left ventricular ejection fraction in the management of thalassemia major

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