Age, gender, and iron overload effects on cardiac systolic and diastolic function in thalassemia major

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Introduction: Patients with thalassemia major develop cardiac iron toxicity from chronic transfusion therapy. Thalassemia patients also have abnormal cardiac preload and afterload from their chronic anemia, complicating the recognition of pre-clinical iron myocardial dysfunction. Systolic and diastolic functional parameters vary with age and gender in normal individuals but this relationship has not been explored in thalassemia patients. To clarify, the interplay between age, gender and iron, we retrospectively evaluated cardiac dimensions, cardiac output and mitral inflow patterns by cardiac MRI in 65 adults with thalassemia major.

Methods: Patients were referred for clinical assessment of cardiac and liver iron or were participating in the Early Detection of Iron Cardiomyopathy Trial (EDICT). All patients were scanned on a 1.5 T General Electric CVi system using a phased-array torso coil. Cardiac and liver iron were measured using a multiecho, gradient echo sequence. Quantitative iron estimates were obtained from the gradient echo images using custom MATLAB reconstruction routines and calibration curves described elsewhere (1,2). Left and right ventricular diastolic volumes (LVEDVI, RVEDVI), systolic volumes (LVESVI, RVESVI), ejection fraction (LVEF, RVEF) and left ventricular mass (LV Mass) were assessed using short-axis steady state free precession images. Cardiac index (CI) and mitral inflow (E-wave, A-wave, E/A ratio) were assessed using phase contrast velocity measurements from the aortic root and from the atrioventricular ring. All volumes and flows were indexed to body surface area. Systolic (SBP), diastolic (DBP), and mean blood pressure (MBP) were measured by automated cuff at the completion of the MRI scan. Total vascular resistance index (TVRI) was calculated as the ratio of mean blood pressure to cardiac index.

Results: 65 patients (24M, 41F) aged 18.1 to 46.7 years (28.0 ± 7.1 years) were studied. Age range and cardiac/liver iron burdens were similar in males and females. Systolic blood pressure, diastolic blood pressure, mean blood pressure, and heart rate were also not significantly different. However, males had larger end systolic volumes, end-diastolic volumes, cardiac index and cardiac mass, but lower ejection fractions and lower total vascular resistance (Table 1). There were no gender difference in E/A ratio.

Cardiac dimensions and cardiac output were age-independent. Diastolic and mean blood pressures increased with age (Table 2). There was a trend toward increased total vascular resistance with age. Mitral inflows demonstrated significant decline in E/A ratio, suggesting decreased ventricular compliance. Four patients with cardiac siderosis demonstrated restrictive filling patterns.

Cardiac iron overload did not change blood pressure or heart rate. Nonetheless, cardiac R2* was correlated with increased total vascular resistance index and decreased cardiac index. Cardiac volumes decreased with increasing cardiac R2*. Overt LV dysfunction was demonstrated in 3 patients with heavy cardiac iron burden (R2* > 100 Hz) but there was no significant continuous relationship between cardiac R2* and right or left ventricular ejection fractions.

Table 1: Gender Differences

Parameter	Men	Women	p
LVEDVI	97.6 ± 18.3	86.7 ± 20.7	0.03
LVESVI	39.8 ± 9.9	32.0 ± 10.3	0.005
LVEF	59.5 ± 4.3	63.2 ± 6.5	0.01
LV Mass	119.5 28.6	98.5 21.8	0.004
RVEDVI	95.3 ± 15.3	84.0 ± 19.5	0.01
RVESVI	40.4 8.1	32.7 10.1	0.002
RVEF	57.7 ± 4.2	61.3 ± 6.7	0.01
TVRI	20.8 ± 4.0	24.3 ± 5.5	0.007
CI	4.0 ± 0.8	3.6 ± 0.8	0.03

Table 2: Correlations with Age

Parameter	Slope (year)	r	p
Diastolic BP	0.34 mmHg/yr	0.22	0.05
Mean BP	0.37 mmHg/yr	0.29	0.013
TVR	0.16 RU/yr	0.19	0.08
E/A ratio	0.046/yr	0.55	0.0001

Table 3: Correlations with cardiac R2*

Parameter	Slope (log (R2*))	r	p
TVRI	2.16 RU/log(Hz)	0.28	0.02
CI	-0.4 L/min/m^2/log(Hz)	0.33	0.007
LVEDVI	-10.2 ml/log(Hz)	0.37	0.002
LVESVI	-4.2 ml/log(Hz)	0.26	0.02
RVEDVI	-10.2 ml/log(Hz)	0.39	0.007
RVESVI	-3.6 ml/log(Hz)	0.27	0.02
LV Mass	-11.2 g/log(Hz)	0.29	0.02

Discussion: The present data demonstrate the complex interplay between cardiac function and gender, age, and cardiac iron burden in thalassemia major patients. Cardiac volumes and mass are increased in the thalassemia major population, compensating for chronic anemia. The increased cardiac volumes observed in males are consistent with the decreased TVRI and increase CI observed. However, lower ejection fraction is counterintuitive given the decreased afterload and may reflect increase vulnerability to iron (3).

Cardiac dimensions and systolic function were stable over the relative narrow time window (18-47 years old) but diastolic function worsened with age, independent of cardiac R2*, similar to trends in normal individuals. Restrictive physiology was specific for heavy cardiac iron burden but insensitive, consistent with prior observations (4). Cardiac iron was paradoxically associated with decreased cardiac volumes except in the three patients who progressed to dilated cardiomyopathy, indicating that peripheral vascular effects (↑TVRI) of iron *precede* cardiac decompensation.

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