

Lack of correlation between iron overload cardiac dysfunction and needle liver biopsy iron concentration

In 58 patients with transfusion dependent anaemia, we compared cardiac function, as assessed by gated pooled cardiac scan at rest and during exercise stress, with liver iron concentrations (LIC) as determined by adequate biopsy samples. There was no relationship between LIC and cardiac function and deaths occurred in patients with LIC levels below those that are usually associated with cardiac death. LIC should not be used as a surrogate to determine risk of cardiac complications but purely for management of the hepatic iron load. Other methods, particularly magnetic resonance imaging, should be used to assess cardiac iron overload.

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In transfused thalassemia patients, liver iron concentration (LIC) is said to reflect total iron body load.¹ Assessments by liver biopsy were regarded as the gold standard, despite problems with heterogeneity of iron distribution and the small size of samples. LIC levels between 7-15 mg/g dry weight are reported to indicate an increased risk of iron related toxicity and levels >15 mg/g dry weight a significant risk of fatal cardiomyopathy.² A table has been proposed to indicate these risks.³

Radionuclide ventriculography (MUGA scan) is a reproducible and accurate technique that measures resting left ventricular ejection fraction (LVEFrest), and left ventricular function during exercise (LVEFex). It is a valuable tool in the assessment of cardiac dysfunction, particularly sub-clinical forms.⁴ In 58 transfusion-dependent patients, we assessed whether LIC, measured on needle biopsy samples, can predict subclinical cardiac dysfunction assessed by MUGA scan. The patients were aged between 10-45 years (mean 22.6±6.5 years). There were 53 patients with thalassemia major, 3 with sickle cell disease and 2 with Diamond-Blackfan anemia. All were on similar transfusion regimes and received iron chelation therapy with desferrioxamine 40-50 mg/kg/infusion 5 days per week. Compliance was variable. Each patient had radionuclide gated pooled cardiac studies performed at rest and 55 were able to perform a semi-supine bicycle test to maximum exercise stress as described previously by our unit.^{5,6}

Liver iron concentration was measured on core needle biopsies performed within 6 months before or after the cardiac test. The dry weight of all biopsies exceeded 1g and all were at least 2 cm in total length. The hepatologist used a Menghini 1.6 mm needle and did not stop taking samples until satisfied that they were adequate. We have recently described our method of sample collection and assessments of LIC and degree of fibrosis.⁷

Table 1 shows the LVEFrest, LVEFex and change in ejection fraction (Δ LVEF) grouped according to LIC and in all patients; the same table also presents the number of

Table 1. Ejection fraction results grouped according to liver iron concentration.

	N	Minimum	Maximum	Mean	S.D.
Group 1 LIC <7 mg/g dry weight					
resting LVEF	19	48	72	61	6.7
exercise LVEF	17	53	82	68	9.0
Δ LVEF	17	-8	23	7	7.9
*biopsy LIC (mg/g)	19	1.200	6.800	4.238	1.606
abnormal at rest	1				
abnormal with exercise	3				
percentage abnormal	30				
Group 2 LIC \geq7 mg/g and <15 mg/g dry weight					
resting LVEF	25	40	70	57.3	7.8
exercise LVEF	25	35	82	64.5	11.2
Δ LVEF	25	-7	24	7.2	7.9
*biopsy LIC (mg/g)	25	7.030	14.400	10.422	2.234
abnormal at rest	5*				
abnormal with Exercise	2				
percentage abnormal	25				
Group 3 LIC \geq15 mg/g dry weight of liver					
resting LVEF	14	30	72	58.9	9.9
exercise LVEF	13	57	81	69.7	7.9
Δ LVEF	13	-5	22	8.8	7.9
*biopsy LIC (mg/g)	14	17.000	62.000	32.417	15.076
abnormal at rest	1*				
abnormal with exercise	2				
percentage abnormal	21				
All patients					
resting LVEF	58	30	72	58.6	8.2
exercise LVEF	55	35	81	66.5	10.1
Δ LVEF	55	-8	24	7.5	7.9
*biopsy LIC (mg/g)	58	1.200	62.000	13.705	13.242
abnormal at rest	7				
abnormal with exercise	16 (7 significantly)				
percentage abnormal	28				

*Two from group 2 and one patient from group 1 died. (descriptive statistics and regression analysis using Microsoft® Excel 2000.). Normal LVEFrest \geq 52%. Δ LVEF > 10% of LVEFrest – i.e. if LVEFrest is 60% the Δ LVEF should be \leq 6%. A significant reduction in Δ LVEF is \leq 0. If the LVEFrest \geq 70% a rise not expected as it considered that the patient was stressed even at rest in those circumstances; a fall in LVEFex was regarded as abnormal but only significant if \geq 5%.

patients with abnormal cardiac studies. There were no significant relationships between the patients' ages and LVEFrest ($p=0.75$), LVEFex ($p=0.2$) or Δ LVEF ($p=0.09$), as evaluated by the t-test for independent samples using SPSS for Windows (version 8.0.0)

Figure 1 shows LIC in relation to LVEFrest, LVEFex and Δ LVEF, illustrating that there are no significant relationships between the LIC and any of the LVEF results. No patient with only an abnormal Δ LVEF died, but three subsequently developed abnormal LVEFrest and were treated with intensified chelation therapy with improvement in

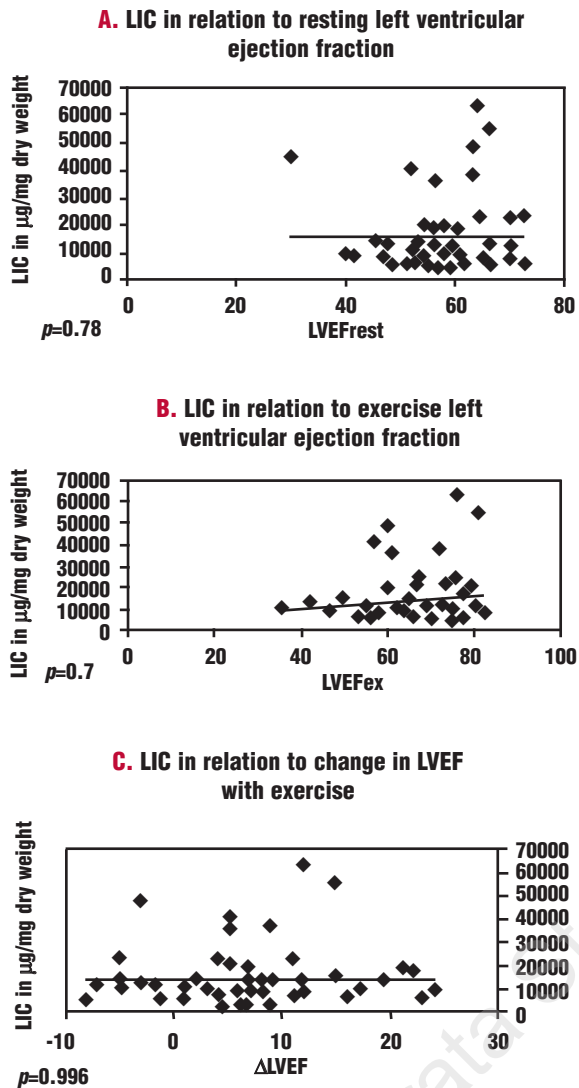


Figure 1. A. LIC in relation to the LVEFrest and the regression analysis. The grey line is the line of best fit; $r=0.04$ and $r^2=0.001$. B. LIC and LVEFex and regression analysis. The grey line is the line of best fit; $r=0.1$ and $r^2=0.01$. C. LIC in relation to the ΔLVEF and regression analysis. The grey line is the line of best fit. The r and r^2 are almost zero indicating that the line of best fit is almost horizontal.

their cardiac function. The LVEF results in patients from group 3 (LIC ≥ 15 mg/g dry weight) were compared with those in group 1 (LIC < 7 mg/g dry weight) and group 2 (LIC ≥ 7 mg/g to < 15 mg/g dry weight) combined and the results in groups 2 and 3 were compared with those in group 1: no statistically significant difference was found (assessed by the t-test for equality of means-SPSS). A Pearson 2-tailed correlation (SPSS) analyzing the LVEF results and LIC showed no significant correlation between any cardiac measure and liver iron.

There were two deaths in group 2 and one in group 1. The percentage of patients with abnormal cardiac function in each group as well as the number of deaths do not support the threshold values proposed by Olivieri and Brittenham.²³ In 15 patients with a LIC in the range in which one might expect serious problems from iron over-

load, only one had an abnormal resting LVEF and only two had a significant reduction in their ΔLVEF . Magnetic resonance imaging (MRI) techniques can now provide an assessment of the myocardial iron load and accurate and reproducible evaluation of cardiac function.⁸⁻¹⁰ Studies have shown that liver iron concentration in chelated patients is a poor predictor of the amount of iron accumulated in the heart or of the risk of developing cardiomyopathy and that severe cardiac iron loading affects cardiac function negatively. In conclusion, there is no relationship between LIC by biopsy and cardiac function by MUGA. This analysis suggests that: (i) it is not useful to perform liver biopsies regularly to determine the risk of developing cardiomyopathy; (ii) cardiac risk should be assessed by echocardiography, MRI T2* and/or MUGA at rest and during exercise stress testing, if available; (iii) liver biopsies should be performed only to determine LIC and fibrosis for making appropriate clinical decisions related to the liver itself. The reasons why some patients who have complied very well with therapy and who maintain what is regarded as an acceptable LIC nevertheless have significant cardiac dysfunction, and why other patients who are poorly compliant and have a high LIC manifest little evidence of cardiomyopathy, remain to be clarified.

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