Research paper

Left ventricular diastolic abnormalities and the impact of hepatitis C virus infection in multitransfused Egyptian children

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Abstract

Introduction: The aim of the study was to evaluate left ventricular cardiac systolic and diastolic functions by echocardiography in multitransfused children and the possible risk of *hepatitis C* virus infection as an additional factor impairing cardiac functions in these patients.
Material and methods: Echocardiographic studies of left ventricular function in 80 multitransfused patients aged 3 to 15 years with no clinical evidence of heart failure were included in our study. Anti-hepatitis C virus antibody was present in the sera of 25 of them. Twenty age and sex matched normal subjects were studied as a control.
Results: Results showed left ventricular systolic abnormalities in 15 cases (18%). Nine cases were HCV seropositive. Dilatation of left ventricle and impaired systolic function guided by FS (fractional shortening) was significantly reduced compared to normal subjects' mean FS ($p < 0.01$). Systolic dysfunction is significantly observed in hepatitis C virus seropositive cases (mean FS 29 ±7.9 vs seronegative cases 31.4 ±10 ($p < 0.035$). Restrictive left ventricular diastolic abnormalities were detected in 45 patients (56.25%). Diastolic dysfunction was represented in prolonged isovolumic relaxation time in comparison to the control group ($p < 0.03$) and higher E wave ($p < 0.001$) also increased the ratio of early to late diastolic velocity (E/A ratio, 2.03 ±0.59 vs 1.6 ±0.27, $p < 0.05$). No significant difference in diastolic functions was found between HCV seropositive and seronegative groups. There is a weak negative correlation between left ventricular FS and serum ferritin level ($r = 0.77$, $p < 0.001$).
Conclusions: Multitransfused children are more liable to left ventricular diastolic dysfunction suggested by impaired relaxation probably due to iron overload and anaemia. *Hepatitis C* virus infection is an additional factor which might share in impairing left ventricular systolic function. Left ventricular performance is better preserved when chelation treatment is adjusted to maintain serum ferritin at <1000 ng/ml.

Key words: thalassaemia, Doppler, echocardiography, iron, cardiomyopathy.

Introduction

Multitransfused infants and children are those who have received two or more units of blood (Pineda *et al.*, 1987). Blood transfusion was the principal transmission route of HCV infection in children. In a random healthy Egyptian sample of children the prevalence of HCV antibody seropositivity was relatively high (up to 12%) and significantly higher (up to 44%) in patients with thalassaemia and multitransfusion (El-Nanawy *et al.*, 1995).

Waldes-Cruz *et al*. (1982) demonstrated abnormalities of left ventricular systolic and diastolic functions of asymptomatic children with β-thalassaemia. Rinz *et al*. (1999) and Francisco *et al*. (2006) found HCV replication in myocardial tissue of patients with myocarditis. Their study suggested that HCV infection may be involved in the development of an unusual form of idiopathic cardiomyopathy. Matsumori's (2001) study of idiopathic cardiomyopathy found that *hepatitis C* virus antibody was detected in 10.6% of patients with hypertrophic cardiomyopathy and in 6.3% with dilated ones. The present study aimed to evaluate left ventricular cardiac systolic and diastolic functions by echocardiography in multitransfused children and the possible risk of *hepatitis C* virus infection as an additional factor impairing cardiac functions in these patients.

Material and methods

This study was performed in the National Heart Institute in Cairo in 2003. Eighty Egyptian children from the health insurance clinic with history of multitransfusion were included. In 25 of them (patients), HCV antibody was detected. A sample of 20 normal children of the same age and sex were studied as a control group. Ninety percent of the multitransfused patients were diagnosed as having thalassaemia major and 10% with other blood disorders. These patients were subjected to a full history and thorough physical examination including weight, height, blood pressure and heart rate, duration of the disease and serum ferritin in the previous year.

All patients were screened for *hepatitis C* virus by HCV detection test ELISA (enzyme linked immunoassay) Atlas Link Biotech Co, Catalogue No. 921.

Table I. Demographic data of multitransfused patients and control group

Variable	Multitransfused (n = 80)	Control (n = 20)	P-value
Age [months] Mean ± SD	7.8 ±3.3[a]	7.5 +3.0[a]	NS
Sex (M/F)	48/32	12/8	
Weight [kg] Mean ± SD	23.3 ±10[a]	26.1 ±9.8[b]	< 0.01
Height [m] Mean ± SD	1.2 ±0.18[a]	1.45 ±0.1[b]	< 0.01
BSA (m^2) Mean ± SD	0.8 ±0.2[a]	0.95 ±0.2[b]	< 0.01
MBP Mean ± SD	70.0 ±6.9	90.0 ±6.0[b]	< 0.01
HR Mean ± SD	90.0 ±5.2	85.3 ±3.1[a]	NS

*NS – not significant. Results are expresses as mean ± standard deviation (SD). Letters not shared on each horizontal column show significance (*p ≤ 0.05) as analyzed by Student's test*

A complete cross-sectional echocardiographic imaging and Doppler examination of all the cardiac chambers was done to exclude left ventricular dysfunction by echocardiography Doppler examination. All echocardiographic measurements were done by the same operator and reported as the average of at least three cardiac cycles according to the criteria of the American Society of Echocardiography (Shan *et al*., 1978). Analysis of left ventricular systolic function detected from parasternal short axis and measuring the diastolic and end systolic diameters was performed. Posterior wall and septal wall thickness and fractional shortening (FS) were calculated. Analysis of left ventricular diastolic function was evaluated by pulsed Doppler sampling of the mitral inflow. The peak E (E) and A (A) wave velocities, the E/A ratio, deceleration time, and isovolumetric relaxation time (IVRT) were obtained.

Statistical analysis

Data are represented as mean (SD). Significant values were considered at a probability of $p < 0.05$. Linear regression analysis was tested between haematological and echocardiographic findings.

Results

Demographic data of the patients and healthy children are summarized in Table I. Weight, height and body surface area were significantly lower in the multitransfused group; furthermore, mean blood pressure was low, while heart rate showed a slight increase.

Table II comparing the multitransfused children who are HCV seropositive and HCV seronegative groups showed no significant difference between any of the parameters.

Table II. Demographic data of multitransfused patients with and without hepatitis C virus

Variable	Multitransfused (n = 80)	Control (n = 20)	P-value
Age [months] Mean ± SD	7.8 ±3.3[a]	7.8 +3.0[a]	NS
Sex (M/F)	(25/30)	(12/13)	NS
Weight [kg] Mean ± SD	23.0 ±10[a]	26.1 ±9.8[a]	NS
Height [m] Mean ± SD	1.2 ±0.18[a]	1.3 ±0.1[b]	NS
BSA (m^2) Mean ± SD	0.8 ±0.2[a]	0.95 ±0.2[b]	0.05
MBP Mean ± SD	70.0 ±6.9[a]	81.0 ±6.0[a]	NS
HR Mean ± SD	85.0 ±5.3[a]	85.0 ±5.1	NS

Values are mean (SD), BSA – body surface area, MBP – mean blood pressure, HR – heart rate

Table III. Haematological profile of the patients

Age at diagnosis	1.3 ±2.0
Haemoglobin* [g/dl]	7.5 ±0.3
Serum ferritin [ng/ml]**	1350 ±989
Iron chelating treatment (yes/no)	70/10
Compliance with chelation treatment (1/2)#	55/15
Number of transfusion per year	12.2

*Values are mean + SD, *Mean pretransfusional value of previous year **Mean value of previous year, #1 – good compliance (5-6 days/week), 2 – poor compliance (4 days/week)*

The haematological profile of the patients is shown in Table III. The mean pre-transfusion haemoglobin concentration was 7.5 ±0.3 g/dl and the average serum ferritin level was 1350 ±989 ng/ml. The majority of patients who had iron chelation showed good compliance with iron chelation treatment. Seventy percent of patients underwent splenectomy.

Among all haematological data considered in Table III, only serum ferritin concentration showed a weak negative correlation with left ventricular fractional shortening.

Discussion

This study shows interesting results concerning the abnormalities in systolic and diastolic function of the left ventricle in multitransfused Egyptian children without clinical cardiopulmonary involvement and a mean pre-transfusion haemoglobin concentration around 7.5 ±0.3 g/dl.

There is an increase in left ventricular volumes with decreased systolic and diastolic blood pressure. The increased volume load is a reflection of the Frank-Starling mechanism and an increase of heart rate. These findings are in agreement with those reported by others and are related to increased cardiac output caused by chronic anaemia (Kermastinos *et al*., 1993; Duke and Abelmann 1969).

The study shows a decrease in left ventricular systolic performance which is probably secondary to iron toxicity (Waldes *et al*., 1982; Christina *et al*., 2006). The results indicate significant left ventricular systolic dysfunction in HCV seropositive patients and this shows the implication of *hepatitis C* virus as an additional factor in cardiomyopathy. Matsumori (2001) suggested that *hepatitis C* virus is frequently found in patients with dilated cardiomyopathy (Bahl *et al*., 1998).

Reports concerning left ventricular diastolic function in patients with β-thalassaemia are somewhat conflicting (Spirito *et al*., 1990). In the study of Yaprak *et al*., 1998, 54% of patients having β-thalassaemia major had restrictive left ventricular diastolic abnormalities, and this correlates with our study, as a total of 56% of patients had diastolic dysfunction.

In the early phase of thalassaemia major before the appearance of systolic abnormalities with no symptoms of congestive heart failure, diastolic abnormalities were detected (Yapark *et al*., 1998; Iarussi *et al*., 2003; and Christina *et al*., 2006). Systolic dysfunction could be due to *hepatitis C* virus infection as reported by Matsumori and Sasayama (2000). In our study we found a weak but significant correlation between left ventricular fractional shortening and serum ferritin concentration, and this agreed with Bosi *et al*., 2003. In 1994 Oliveri *et al*. found that the cardiovascular prognosis in thalassaemic patients was excellent if serum ferritin concentration was maintained below 2500 ng/ml; this value was considered a safe concentration. However, Bosi *et al*. 2003 suggest that a serum ferritin value of less than 1000 ng/ml should be considered.

In conclusion, our study suggested that dilated cardiomyopathy in multitransfused children, especially thalassaemic patients, had several factors which could be involved in the pathogenesis. The first factor is the significant volume overload imposed by chronic anaemia. The second factor is *hepatitis C* virus infection, which could be an important causal agent. The third factor is iron toxicity, although the mechanism involved in this is not universally agreed. Cardiac examination and follow-up by Doppler echocardiography is an essential and important non-invasive safe tool for follow-up of these children. Chelation treatments and good compliance to maintain ferritin levels less than 1000 ng/ml give a good cardiovascular prognosis.

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