Evaluation of cardiac functions in patients with thalassemia major

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It is known that a blood transfusion is necessary for survival in patients with thalassemia, but it may cause myocardial dysfunction due to myocardial siderosis as in other organs. The aim of this study was to evaluate myocardial perfusion by means of stress thallium scanning (MPS) and left ventricular functions by rest radionuclide ventriculography (RNV).

Twenty-one patients at ages 9–16 (mean 12.1 ± 3.2) who have been diagnosed with thalassemia for 4–15 years (mean 12.7 ± 4.8) were included in the study. They had blood transfusions 78–318 times (mean 162.1 ± 71). MPS and RNV was performed within two days after the any transfusion.

MPS showed ischemia in 3 patients and normal perfusion in 18 patients. RNV revealed normal systolic parameters (wall motion, EF, PER, TPE) but diminished diastolic parameters (TPF, PFR) compared with normal values ($p < 0.05$).

We conclude that ischemia or fixed defects may be seen in stress MPS as a result of cardiac involvement in patients with thalassemia. But, RNV is an important and preferable test for the early detection of subclinic cardiomyopathy. RNV may therefore show diastolic abnormalities before the systolic abnormalities show up.

Key words: thalassemia, radionuclide ventriculography, myocardial perfusion siderosis

INTRODUCTION

BLOOD TRANSFUSIONS done after diagnosing Thalassemia Major (TM) are of great importance in relation to survival. But these transfusions lead to siderosis in the myocardium, as well as in other organs, and cardiac dysfunctions have been reported, depending upon the number and period of the transfusions.[1]

Although the actual diagnosis of cardiac siderosis is made by myocardial biopsy, this is usually not preferred clinically, since biopsy is an invasive technique.[1,2] Clinically, the cardiac functions are usually evaluated by non-invasive methods as ECHO, Doppler ECHO, MRI, CT scan and radionuclide techniques.

The object of this study is the evaluation of cardiac functions and myocardial perfusion in cardiologically asymptomatic TM patients, by means of such techniques as ECHO, radionuclide ventriculography and Tl-201 myocardial perfusion scintigraphy. We believe that the data will be helpful in planning treatment of the patients.

MATERIALS AND METHODS

A total of 21 TM cases (13 males and 8 females) from Ankara University Medical Faculty Paediatric Haematology Department were included in the study. The mean age was 12.11 ± 3.2 years (ages between 9 and 16 years) and the mean follow-up period was 12.7 ± 4.8 (between 4 and 15 years). The mean number of transfusions was 162.17 ± 71.8 (between 78 and 318). Only 5 of the patients had received less than 100 blood transfusions, but 6 cases needed more than 200 blood transfusions.

In the control group, there were 20 healthy children (ages 4–18, mean age 12.3 ± 4.5; 12 males, 8 females) who had applied to the clinic for reasons other than TM and were cardiologically asymptomatic.

ECHO, stress myocardial perfusion scintigraphy and resting radionuclide ventriculography (RNV) were performed both in the cases and the control group. In patients with TM, these tests were performed within 2 days after transfusion. The myocardial perfusion SPECT study is evaluated both after injecting Tl-201 after maximal or submaximal effort (stress), and 2 hours later (resting study).

Patients exercised on a marquette Quinton 3000 treadmill according to the Bruce protocol. Each patient exercised to $\geq 85\%$ of the age predicted maximal heart

Table 1 MUGA findings

	EF	PFR	PER	TPFR	TPER
Thalassemia	58.6 ± 6.9	3.3 ± 0.5	3.1 ± 0.5	117.9 ± 51	121.3 ± 27
Control	60.1 ± 8.1	3.8 ± 0.5	3.7 ± 0.7	136.3 ± 21	109.1 ± 25
	$p > 0.05$	$p < 0.05$	$p > 0.05$	$p < 0.05$	$p > 0.05$

EF: ejection fraction, PFR: peak filling rate, TPFR: time to peak filling rate,
PER: peak ejection rate, TPER: time to peak ejection rate

Table 2 The findings of TM patients

Case No.	EF (%)	PFR	TPF	PER	TER	Tl-201
1	52	3.13	111	2.59	130	%8 effort, N
2	64	3.54	93	3.39	170	%70 effort, N
3	66	4.06	104	3.73	91	%60 effort, N
4	49	492	93	2.29	108	%100 effort, N
5	47	2.82	160	2.56	144	%100 effort, N
6	61	4.19	125	4.07	88	%80 effort, N
7	71	3.90	90	3.51	105	%80 effort, N
8	55	2.41	140	2.68	158	%85 effort, N
9	54	3.46	76	3.39	133	%100 effor, N
10	57	3.17	308	3.38	98	%85 effort, N
11	64	3.13	148	3.54	130	%85 effort, N
12	55	3.56	96	3.88	144	%100 effort, N
13	55	3.57	90	3.23	75	%100 effort, anteroseptal ischemia
14	66	4.98	124	3.10	108	%85 effort, N
15	51	2.93	50	2.48	88	%90 effort, N
16	67	3.52	102	3.99	118	%85 effort, anterolateral ischemia
17	50	2.36	110	3.32	165	%85 effort, N
18	57	2.99	105	2.70	123	%85 effort, N
19	60	3.29	88	2.98	154	%85 effort, N
20	67	3.88	108	3.48	126	%85 effort, N
21	64	3.92	156	4.07	91	%90 effort, inferolateral ischemia

rate or until the onset of limiting symptoms or ST depression 1.4 mm, or until the appearence of a decrease in systolic blood pressure to 10 mmHg below peak value at a prior stage of exercise. The stress acquisitions were started within a few minutes of stress injection of Tl-201 with a GE starcam 4000I or GE camstar 3200 XRT equipped with high resolution, low energy collimators.

The images were acquired for 40 seconds in 32 steps between the right anterior 45° and left posterior 45° positions, then stored in a 64 × 64 matrix. For all cases, a Butterworth filter was used for filtered backprojection with a cutoff frequency of 0.45, order 5.

The reconstructed transaxial slices were reoriented according to the long axis of the heart. Paired images of stress and rest short axis and vertical and horizontal long axis slices were generated for visual analysis. The tracer distributions in the vascular territory were classified in individual cases as: (a) normal; (b) stress-induced perfusion defect with complete normalization at rest (reversible defect); (c) stress-induced perfusion defect with incomplete normalization at rest (partially reversible defect); and (d) perfusion defect at stress without significant improvement at rest (persistent defect) by the con-

sensus of three experienced readers.

Radionuclide data acquisition; In vivo red blood cell labeling[8] was performed with 925 MBq (25 mCi) of technetium-99m pertechnetate. The patient was placed in the left anterior oblique position. The cardiac cycle was divided into 32 frames and counts were collected beginning on the upslope of the baseline RR interval, resulting in rejection of the following cycles until the RR interval returned to the preselected range.

Completely automatic left ventricular analysis was performed with a standard program that transforms these data to the frequency domain, retaining the first three harmonics and the diastolic image. The left ventricular region of interest was used to create a 100 point volume curve. From this curve and its first derivative the program determines the time of end-diastole (maximal counts), the time of end-systole (minimal counts), the normalized peak filling rate (maximal slope of the first derivative of the early filling portion), time of the normalized early peak filling rate and time to the peak filling rate from end-diastole and end-systole. The fraction of diastolic filling occurring during the early or rapid filling period and during atrial systole was also determined.
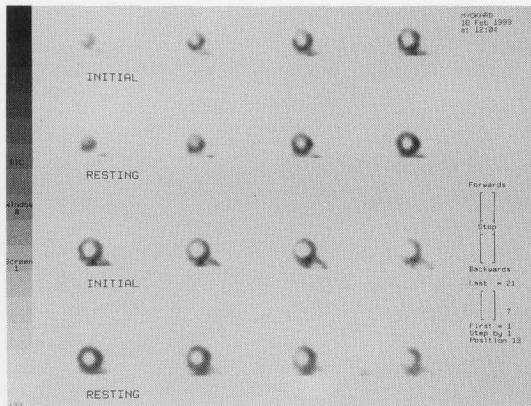
Fig. 1 Tl-201 myocardial perfusion short axis images in TM patient (anteroseptal ischemia).
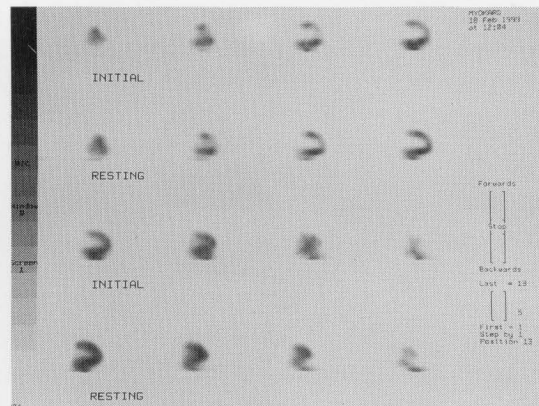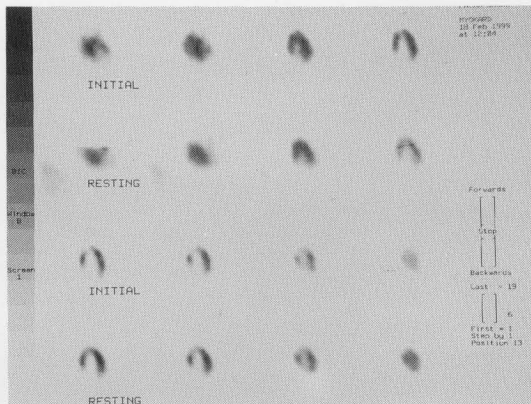

Fig. 2 Horizontal images.

Fig. 3 Vertical images.

The tissue parameters and the changes in the wall movements are evaluated in the ECHO study (Toshiba SSS-140A instrument; 3.75 and 2.1 MHz transducer). Left ventricular systolic functions are evaluated by measuring left ventricle posterior wall and septal thickness' in M Mode echocardiography by the Teichholz method.[21]

RESULTS

No cardiac pathology was found in cardiac examination or ECG recordings in any of the TM patients. The ferritin levels were in the normal range (< 8 mg/dl) in all cases.

In myocardial perfusion scintigraphy, perfusion was normal in all but 3 of the patients. One of these three had anterolateral, one had inferolateral, and the other had anteroseptal ischemia. It is worth noting that these 3 patients had each received more than 250 blood transfusions.

The results of the ECHO study showed that the differences between the study group and control group were not statistically significant.

The RNV study showed that while the EF (ejection fraction) value did not significantly differ from that of a similar age group, the TPFR (time to peak filling rate) and PFR (peak filling rate) were significantly different from the control group (p < 0.05). Although not statistically significant, the changes were more notable in the TM patients with a history of more than 200 transfusions, compared to the cases with fewer transfusions (p > 0.05).

DISCUSSION

Chronic serious anemia and the siderosis related to recurrent blood transfusions to treat this anemia take first place in the list of reasons for cardiac problems in patients with TM.[14,16,17] The cardiac insufficiency which is the main clinical problem in these cases is the reason for most of the deaths, especially in the 2nd decade.[6,7] In a study, Lombarda et al.[1] showed that myocardial hemochromatosis may progress without clinical symptoms and this condition cannot be recognised by non-invasive indirect methods; and they reported that a high ferritin level may be an indicator of this condition. The ferritin level did not reach the pathological level in any of our cases.

For the siderosis-related changes in ECG, it is reported that there may be findings only after changes related to serious cardiomyopathy. As a result, this method is not suitable for the follow-up of siderosis in the early stage.[5]

ECHO is now a frequently-used method. The ECHO and Doppler studies[14] made in the TM cases showed that pathological changes happen in filling parameters, ventricular dilatation and a decrease in EF.[2,4] It's reported that the changes in the ECHO show a correlation with the ferritin level, enlargement of the heart chambers and the ventricular dysfunction is more significant when ferritin levels are above 8 mg/dl.[12]

For MRI studies, no quantification method is found to be completely related with siderosis.[8]

Using myocardial perfusion scintigraphies, RNV and ECHO, we evaluated the cardiac functions of asymptomatic TM cases whose ferritin levels are within normal limits and who have no ECG findings. In myocardial perfusion scintigraphies, we found ischemia in only 3

cases and it was found that the number of transfusions received in these cases were above average. These data are in keeping with previous hemodynamic studies of chronic anemia which show that peripheral resistance falls as a consequence of tissue hypoxia, whereas venuos return stroke volume and cardiac output increase and the A.V. oxygen difference widens.[22] During exercise there may be a further increase in myocardiac contractility, and cardiac output increases without changes in left ventricle end diastolic volume or pressure.[23]

Coronary blood flow increases in relation to the increased cardiac output and supplies the additional myocardial oxygen demand.[24] Ventricular enlargement and hypertrophy are mechanisms which compensate for the volume overload and do not necessarily imply impaired myocardial contractility.

In the RNV study we found differences between TM cases and the controls in TPF and PFR values. We were not able to investigate the effects of different numbers of transfusions because we had too few patients. On the other hand, there was no significant difference in the ECHO study.

The number and period of blood transfusions are important factors related to cardiac functions, and it was observed that cardiac changes became more significant as the number of transfusions increased.[3,18] The changes in the RNV in the early phase are believed to be of importance in the patients' follow-up.[9,11,19] Leon et al. have also reported changes in PFR values in RNV in TM patients.[15] Our findings agree with those of their study. It was concluded that it is especially useful to study groups that have received different numbers of transfusions in different periods.

In conclusion, cardiac involvement may show itself as ischemia in MPS, whereas RNV may act as a guide detecting cardiomyopathy in asymptomatic cases and, PFR is especially affected in the early phase. It is worth noting that the changes were more significant in patients who have been followed up for more than 8 years and who have received over 200 transfusions. In these cases, RNV and MPS may be helpful in detecting and following up the changes related to cardiac siderosis in the early stage. It should be useful to repeat these studies in patients with different ferritin levels and in larger patient groups.

REFERENCES

1. Lombardo T, Tamburio C, Bartoloni G, Morrone ML, Frontini V, Italia F, et al. Cardiac iron overload in thalassemic patients: an endomyocardial biopsy study. *Ann Hematol* 71 (3): 135–141, 1995.
2. Intragumtornchai T, Minaphinant K, Wanichsawat C, Somabutr C, Posayachinda M, Watananukul P, et al. Echocardiographic features in patients with beta thalassemia/hemoglobin E: a combining effect of anemia and iron load. *J Med Assoc Thai* 77 (2): 57–65, 1994.
3. Oliviere NF, Liu PP, Sher GD, Daly PA, Greig PD, McCurker PJ, et al. Brief report: combined liver and heart transplantation for end-stage iron-induced organ failure in and adult with homozygous beta-thalassemia. *N Engl J Med* 330 (16): 1125–1127, 1994.
4. Kremastinos DT, Rentoukas E, Mavrogeni S, Kyriakides ZS, Politis C, Toutouzas P. Left ventricular filling pattern in beta-thalassaemia major—a Doppler echocardiographic study. *Eur Heart J* 14 (3): 351–357, 1993.
5. Oreto G, Luzza F, Donato A, Satullo G, Calabro MP, Consolo A, et al. Electrocardiographic changes associated with haematocric variations. *Eur Heart J* 13 (5): 634–637, 1992.
6. Wielopolski L, Zaino EC. Noninvasive *in-vivo* measurement of hepatic and cardiac iron. *J Nucl Med* 33 (7): 1278–1282, 1992.
7. Olivieri NF, Koren G, Matsui D, Liu PP, Blendis L, Cameron R, et al. Reduction of tissue iron stores and normalization of serum ferritin during treatment with the oral iron chelator L1 in thalassemia intermedia. *Blood* 79 (10): 2741–2748, 1992.
8. Perrimond H, Chagnon C, Moulanier I, Michel G, Guidicelli H, Bernard PJ. The value of nuclear magnetic resonance in the study of iron overload in thalassemia patients. *Ann Pediatr (Paris)* 38 (3): 175–184, 1991.
9. Akagi T, Green M. Evaluation of ventricular diastolic fonction in normal children using equilibrium angiography. *Nucl Med Commun* 13: 609–613, 1992.
10. Basil S, Lewis, Elieze A. Left ventricular function in beta thalassemia and the effect of multiple transfusion. *Am Heart J* 96 (5): 636–655, 1978.
11. Scapinaro F, Banci M, Vania A. Radioisotope assessment of heart damage in hypoperfused thalassemic patients. *Eur J Nucl Med* 20 (7): 603–608, 1993.
12. Spirito P, Gabriele L. Restrictive diastolic abnormalities identified by Doppler ECHO in patients with Thalassemia major. *Circulation* 82: 88–94, 1990.
13. Nienhuis AW, Friffith P, Strawezynski H, Henry W, Borer J, Leon M, et al. Evaluation of cardiac function in patients with thalassemia major. *Ann NY Acad Sci* 344: 377–396, 1980.
14. Enlers K, Levin AR, Makerson AL, Marcus JR, Klein AA, Hilgarten MW, et al. Longitudinal study of cardiac function in thalassemia major. *Ann NY Acad Sci* 344: 397–404, 1980.
15. Leon MB, Borer JS, Bacharach SL, Green MS, Benz EJ, Griffith RN, et al. Detection of early cardiac dysfunction in patients with severe beta-thalassemia and chronic iron overload. *N Engl J Med* 22: 1143–1148, 1979.
16. Lewis BS, Rachmilewitz EA. Amitasi N, Halon DA, Gotsman MS. Left ventricular function in beta-thalassemia and the effect of multiple transfusions. *Am Heart J* 96: 636–645, 1978.
17. Freeman AP, Giles RW, Berdoukas V, Walsh WF, Chay D, Murray PC. Early left ventricular dysfunction and chelation therapy in thalassemia. *Ann Intern Med* 99: 450–454, 1983.
18. Marni E, Borgna-Pignatti C, De Stefano P, Dell'Acqua S, Noe GP, Barzina F, et al. Evaluation of cardiac status in thalassaemia major: a study of 32 patients. *Hematologica* 68: 517–522, 1983.
19. Friedman BJ, Drinkovic N, Miles H, et al. Assessment of left ventricular diastolic function: comparison of Doppler echocardiography and gated blood pool scintigraphy. *J Am*

Coll Cardiol 8: 1348–1354, 1986.

20. Teichholtz LE, Kreulen T, Herman MW, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic angiographic correlations in the presence or absence of asynergy. *Am J Cardiol* 37: 7311, 1976.

21. Escobar E, Jones NL, Rapaport E, Murray JF. Ventricular performance in acute normovolemic anemia and effects of beta blockade. *Am J Physiol* 211: 877, 1966.

22. Fowler NO, Holmes JC. Ventricular function in anemia. *J Appl Physiol* 31: 260, 1971.

23. Rodriguez JA, Chamorro GA, Rapaport E. Effect of isovolemic anemia on ventricular performance at rest and during exercise. *J Appl Physiol* 36: 28, 1974.

24. Bhatia ML, Manchanda SC, Roy SB. Coronary haemodynamic studies in chronic severe anemia. *Br Heart J* 31: 365, 1969.