Use of strain and tissue velocity imaging for early detection of regional myocardial dysfunction in patients with beta thalassemia

Amal M. Hamdy*

Cardiology Department, Al-Zahraa University Hospital, Al-Azhar University, Cairo, Egypt

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**KEYWORDS**

Strain imaging; Tissue velocity imaging; Beta thalassemia; Myocardial function

**Abstract**

**Background and aim of study:** Iron overload contributes to cardiac dysfunction in patients with beta thalassemia (Th). Tissue velocity and strain imaging (TVI and SI) might prove useful in early detection of regional myocardial dysfunction in these patients. The aim of this study is to clarify the value of TVI and SI in early detection of regional myocardial dysfunction in thalassemia patients.

**Methods and results:** This study included two age-matched groups; G1: 27 Th patients and G2: 14 normal subjects. Conventional echo-Doppler measures of LV and RV dimensions and function were obtained. TVI measures included systolic and diastolic myocardial velocities (Sm, Em, Am and Em/Am) of the basal segments of septal wall, lateral LV and RV free walls. Systolic strain values were measured in the same basal segments and included S-septal, S-LV and S-RV. Strain and TVI data were compared in the two groups. Sm and strain values were compared in the different walls (LV, RV and septum) in each group separately. S-LV was lower in G1 than G2 (20.9 ± 6.8 vs 27.2 ± 4.3, p < 0.001), while S-septal was higher in G1 than G2 (31.1 ± 8.3 vs 25.1 ± 3.8, p < 0.01). TVI measures of diastolic performance of the septal and RV walls were different in G1 compared to G2. Septal-Em was lower, septal-Am was higher and septal-Em/Am was lower in G1 compared to G2. RV-Am was higher and RV-Em/Am was lower in G1 compared to G2. Other SI and TVI measures were not significantly different in G1 from G2. Sm and strain values were lower in the lateral LV wall compared to septal wall in G1 but not in G2, while the corresponding values of the RV wall were higher than those of the septal and LV walls in both groups (G1 and G2).

**Conclusion:** Thalassemia patients have regional systolic dysfunction in the lateral LV wall and regional diastolic dysfunction in the septal and RV wall. TVI and the
**Introduction and aim of study**

Patients with beta thalassemia have extravasal hemolysis and ineffective erythropoiesis resulting in severe anemia. The regular transfusion program required for sustenance of life and the increased gastrointestinal absorption of iron lead to iron overload and iron toxicity in many organs including the heart.\(^1\)\(^-\)\(^3\)

Congestive heart failure is the main cause of death in patients with beta thalassemia major, occurring during the second decade of life and is traditionally attributed to iron overload.\(^4\)\(^,\)\(^5\) Aggressive chelation therapy may prevent, delay or even reverse myocardial dysfunction, but once overt heart failure is present, only 50% of patients survive.\(^6\) So, early recognition of cardiac disease may be useful in modifying therapy.\(^7\) However, early recognition of patients at risk of heart failure has been difficult because global ventricular function and exercise capacity in chronically transfused patients with iron overload may remain normal until late in the disease process.\(^6\)

Echocardiography is an imaging modality of choice for detection and quantification of ventricular function; however, the conventional echo-Doppler parameters are usually altered in the presence of overt ventricular dysfunction. The recent tissue Doppler imaging (TDI) modalities including tissue velocity imaging (TVI) and strain imaging (SI) may prove useful in early detection of regional myocardial dysfunction before the occurrence of abnormal indices of global ventricular function.

The aim of this study is to clarify the value of TVI and SI in early detection of regional myocardial dysfunction in thalassemia patients.

**Methods**

**Study population**

This study included two groups; G1: 27 patients with beta thalassemia major (mean age 12.3 ± 5.0 years), and G2: 14 age-matched normal subjects (mean age 13.6 ± 6.3 years). Patients with congenital or rheumatic heart disease as well as patients with present or past history of heart failure were excluded from the study. Routine laboratory investigations and work-up for thalassemic patients including serum ferritin levels were performed in the context of clinical evaluation. All thalassemic patients were under chelation therapy with subcutaneous desferrioxamine and regular blood transfusions every 2–4 weeks. All cases were subjected to thorough clinical examination to exclude patients with any overt sign of heart failure.

**Echo-Doppler studies**

Echo-Doppler examination was performed for all study cases using General Electric (GE, Vivid-7) system with a matrix probe M3S, having tissue velocity imaging and strain imaging capabilities. Conventional echo-Doppler measures, tissue velocity imaging measures and strain imaging measures were obtained.

**Conventional echo-Doppler measures**

Conventional echo-Doppler measures included left ventricular end-diastolic and end-systolic dimensions (LVEDD and LVESD, respectively), right ventricular end-diastolic and end-systolic dimensions (RVEDD and RVESD, respectively), interventricular septal thickness (IVST) and left ventricular posterior wall thickness (LVPWT) both measured at end diastole. These echo parameters were measured from M-mode echo derived from the parasternal short axis view at the mitral chordal level for LV parameters and at basal level for RV parameters. Left ventricular fractional shortening (LVFS) as well as right ventricular fractional shortening (RVFS) were calculated. Left ventricular ejection fraction (LVEF) was also calculated from M-mode echo according to Teichholz method.\(^8\) Conventional Doppler measures included early and late transmitral diastolic velocities (E\(_{\text{vel}}\) and A\(_{\text{vel}}\)) and their ratio (E/A), early deceleration time (EDT) of the transmitral diastolic flow and peak filling rate normalized to mitral valve stroke volume (PFR-n) measured as E\(_{\text{vel}}\) divided by the total mitral flow velocity integral and expressed in stroke volume/s (sv/s), as described by Bowman et al.\(^9\) In cases having tricuspid regurgitation
(TR), the RV systolic pressure (RVSP) was estimated from the peak TR velocity.

**Tissue velocity imaging (TVI) measures**

Tissue velocity imaging (TVI) measures included systolic myocardial velocities at the basal segments of the lateral LV wall, septal wall and RV free walls (LV-Sm, septal-Sm and RV-Sm, respectively), early and late diastolic myocardial velocities and their ratio (Em, Am and Em/Am, respectively) of the same basal segments (i.e. LV-Em, LV-Am and LV-Em/Am for the basal lateral LV segment; septal-Em, septal-Am and septal-Em/Am for the basal septal segment; and RV-Em, RV-Am and RV-Em/Am for the basal RV segment).

**Strain imaging (SI) measures**

Strain imaging (SI) measures included systolic strain at the basal segment of lateral LV wall (S-LV), systolic strain at the basal segment of septal wall (S-septal) and systolic strain at the basal segment of RV free wall (S-RV).

Both TVI measures and strain imaging measures were obtained from off-line analysis of stored loops in order to get the measured values of all basal segments from the same cardiac cycle. The sector angle was adjusted to allow simultaneous visualization of both LV and RV and the frame rates ranged from 98 to 144 fps. The strain data were expressed as negative %values and measured from systolic strain curves in both normal subjects and thalassemia patients (Fig. 1a, b).

**Statistical analysis**

Data were expressed as means (±SD). All measures in G1 patients were compared to those of G2 subjects. Sm and strain values were compared in LV vs septal, RV vs septal and LV vs RV segments in each group separately. Comparisons were made using the Mann—Whitney or Wilcoxon two-sample test (Kruskal Wallis test for two groups), and a p-value less than 0.05 was considered statistically significant. The tests used in statistical analysis were performed using the computer software Epi-Info which is a public domain software produced by Epidemiology Program Office, Center for Disease Control (Atlanta, Georgia) and the Global Program on AIDS, World Health Organization (Geneva, Switzerland).

**Results**

The study cases included G1: 27 patients with beta thalassemia major (14 females and 13 males), and G2: 14 normal subjects (10 females and 4 males). The mean age of thalassemic patients was not significantly different from that of normal subjects. Only one patient from G1 had NYHA functional class II, while other study cases had no cardiac symptoms. None of the study patients had clinical evidence of overt congestive heart failure. All of thalassemic patients had serum ferritin level >500 μg/L with nine of them having their serum ferritin level >2000 μg/L. Among G1, splenectomy was done in 17 patients and 10 patients had splenomegaly.

**Conventional echo-Doppler parameters**

Comparison of the mean values of conventional echo-Doppler parameters between the two groups (G1 and G2) is shown in Table 1. LVEDD, RVEDD and RVESD were higher in G1 compared to G2, while IVST, LVPWT, LVESD, LVEF, LVFS and RVFS did not significantly differ in the two groups. Both E\(_{vel}\) and A\(_{vel}\) were higher in G1 than G2, while E/A was lower in G1 than G2. There was no significant difference between the two groups as regards EDT or PFR-n. Variable degrees of TR were detected in 17 thalassemic patients and trivial TR was found in 12 normal subjects. The estimated RVSP or pulmonary artery pressure (PAP) in thalassemic patients ranged from 23 to 85 mm Hg and its mean value was significantly higher as compared to normal values (p < 0.05).

**TVI parameters**

Table 2 illustrates comparison between G1 and G2 as regards the systolic and diastolic myocardial velocities of the basal segments of LV, septal and RV walls. The LV-Sm and septal-Sm in G1 were not significantly different from those in G2, while RV-Sm was higher in G1 than G2 (p < 0.05). Early and late diastolic myocardial velocities of the lateral LV wall and their ratio (LV-Em, LV-Am and LV-Em/Am) were not significantly different in G1 compared to G2. In contrast, the TVI parameters of diastolic performance of the septal and RV walls were different in G1 compared to G2. Both septal-Em and septal-Em/Am were significantly lower in G1 compared to G2 (p < 0.01 and p < 0.0001, respectively), and septal-Am was higher in G1 than G2 (p < 0.005). RV-Am was higher (p < 0.0001) and RV-Em/Am was lower (p < 0.005) in G1 compared to G2, but RV-Em was not different in G1 from G2.

Comparison of the mean values of myocardial systolic velocities between the different walls (i.e. LV, septum and RV), in each group revealed
a significantly lower LV-Sm than septal-Sm in thalassemic group ($p < 0.05$), but not in normal subjects, while the RV-Sm was significantly higher than LV-Sm ($p < 0.0001$) and septal-Sm ($p < 0.0001$) in both groups.

**Strain imaging measures**

The systolic strain values at the basal segments of the LV, septal and RV walls in G1 compared to those in G2 are shown in Table 3. Systolic strain at the lateral LV wall (S-LV) was lower in G1 than G2 ($p < 0.001$), S-septal was higher in G1 than G2 ($p < 0.01$) and S-RV was not significantly different in G1 from G2 (Fig. 2). The lateral LV wall strain was significantly lower than septal strain in thalassemic patients ($p < 0.0001$), but not in normal subjects. The RV strain was significantly higher than LV strain and septal strain in G1 ($p < 0.0001$ and $p < 0.05$, respectively) and were also higher.
Table 1 | Comparison of conventional echo-Doppler measures between thalassemic patients (G1) and normal subjects (G2)

<table>
<thead>
<tr>
<th></th>
<th>G1 (thalassemia)</th>
<th>G2 (normal)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD (cm)</td>
<td>4.5 ± 0.6</td>
<td>4.1 ± 0.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>2.8 ± 0.5</td>
<td>2.6 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>RVESD (cm)</td>
<td>1.9 ± 0.4</td>
<td>1.6 ± 0.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IVST (cm)</td>
<td>1.5 ± 0.4</td>
<td>1.3 ± 0.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVPWT (cm)</td>
<td>0.82 ± 0.14</td>
<td>0.79 ± 0.09</td>
<td>NS</td>
</tr>
<tr>
<td>LVFS (%)</td>
<td>0.79 ± 0.13</td>
<td>0.75 ± 0.09</td>
<td>NS</td>
</tr>
<tr>
<td>RVFS (%)</td>
<td>20.3 ± 7.6</td>
<td>23.9 ± 6.9</td>
<td>NS</td>
</tr>
<tr>
<td>Erel (m/s)</td>
<td>1.07 ± 0.13</td>
<td>0.98 ± 0.11</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Avel (m/s)</td>
<td>0.66 ± 0.12</td>
<td>0.52 ± 0.08</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.66 ± 0.30</td>
<td>1.92 ± 0.33</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>EDT (ms)</td>
<td>169.6 ± 28.1</td>
<td>168.3 ± 25.3</td>
<td>NS</td>
</tr>
<tr>
<td>PFR-n (sv/s)</td>
<td>5.89 ± 1.13</td>
<td>5.45 ± 0.85</td>
<td>NS</td>
</tr>
<tr>
<td>RVSP (mm Hg)</td>
<td>34.6 ± 14.8</td>
<td>25.2 ± 3.6</td>
<td>&lt;0.05</td>
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</tbody>
</table>

NS = nonsignificant. Other abbreviations are mentioned in the text.

Table 2 | Comparison of TVI measures between G1 and G2

<table>
<thead>
<tr>
<th></th>
<th>G1 (thalassemia)</th>
<th>G2 (normal)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV-Sm (cm/s)</td>
<td>5.9 ± 1.2</td>
<td>6.2 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Septal-Sm (cm/s)</td>
<td>6.5 ± 0.8</td>
<td>6.2 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>RV-Sm (cm/s)</td>
<td>10.8 ± 1.7</td>
<td>9.5 ± 2.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LV-Em (cm/s)</td>
<td>14.2 ± 1.9</td>
<td>14.4 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>LV-Am (cm/s)</td>
<td>4.2 ± 1.5</td>
<td>3.7 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td>LV-Em/Am</td>
<td>3.8 ± 1.5</td>
<td>5.2 ± 3.2</td>
<td>NS</td>
</tr>
<tr>
<td>Septal-Em (cm/s)</td>
<td>10.2 ± 1.9</td>
<td>11.8 ± 1.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Septal-Am (cm/s)</td>
<td>5.2 ± 2.1</td>
<td>3.6 ± 1.0</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Septal-Em/Am</td>
<td>2.2 ± 0.8</td>
<td>3.6 ± 1.2</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>RV-Em (cm/s)</td>
<td>12.4 ± 2.1</td>
<td>11.7 ± 3.0</td>
<td>NS</td>
</tr>
<tr>
<td>RV-Am (cm/s)</td>
<td>8.8 ± 2.1</td>
<td>4.7 ± 2.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV-Em/Am</td>
<td>1.5 ± 0.4</td>
<td>3.9 ± 3.1</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

been suggested in the development of cardiac dysfunction in thalassemic patients including myocarditis, and iron overload in the heart, leading to LV dysfunction, and iron overload in the lungs leading to elevated pulmonary arteriolar resistance, RV dilatation and dysfunction. However, congestive heart failure develops late in the disease process of these patients.4

Because congestive heart failure is the main cause of death in these patients, early recognition of cardiac dysfunction may be useful in modifying therapy. Echocardiography provides a relatively cheap and fast bedside method to study the heart function; however, the conventional echo-Doppler technique has its limitation in the quantitative assessment of regional myocardial function. There is evidence that long axis function is a more sensitive index of myocardial contractility than conventional echocardiographic parameters, and impairment of longitudinal fiber motion is a sensitive marker of early myocardial dysfunction. Therefore, the new promising modality, tissue velocity imaging (TVI), can be applied in the quantitative assessment of regional myocardial function. Myocardial strain imaging (SI) is a dimensionless index of change in myocardial length in response to applied force. It is a new quantitative parameter of intrinsic cardiac deformation having a theoretic advantage over TVI because of its independence of cardiac translation motion and tethering effect of adjacent segments. So, it is suggested that SI may be an optimal method for objective, quantitative assessment of regional myocardial function.

In beta thalassemia patients wall motion abnormalities may represent an early sign of cardiac disease despite preserved global ventricular function. Visual assessment of wall motion abnormalities is rather subjective and may miss subtle changes in segmental wall motion. Based on this concept, this study aimed at clarifying the value of TVI and SI in early detection of regional myocardial dysfunction in thalassemic patients before the development of overt cardiomyopathy. In the methodology of this study, myocardial velocities and strain values were measured in the basal segments of the LV, RV and interventricular septum as...
representatives of regional function of the related walls. The basal segments only were selected on the basis of the reported findings that in healthy individuals, longitudinal velocities progressively decrease from base to apex, while strain values remain uniform in all segments.16

In this study the LVEDD, RVEDD and RVESD were increased in the group of thalassemia (G1), compared to the normal subjects (G2). These findings are in accordance with the previous studies that showed increase in LV dimensions,5,7,17 and increase in RV dimensions7 in thalassemic patients. The increase in left and right ventricular diameters is attributed to the high cardiac output state secondary to the chronic anemia in these patients. Although one would expect an increase in LVEF or % fractional shortening in response to high cardiac output and increased preload secondary to chronic anemia in these patients, the absence of this response in the current study might reflect an early marker of systolic alteration. Supporting this hypothesis is the tendency toward concomitant increase in end-systolic dimensions in the thalassemia group. The transmitral Doppler parameters in the present study revealed increased E and A velocities reflecting an increase in the preload state due to the chronic anemia, thus matching the previous reports.18–20 The transmitral early deceleration time and peak filling rate in thalassemic patients of the current study were not significantly different from those of the normal subjects indicating absence of overt global LV diastolic dysfunction early in the disease process of such patients. This is in accordance with what has been reported by Kremastinos et al.21 who found that global LV diastolic function might be preserved well until the final stages of the disease.

The conventional echo parameters of systolic function, mainly the percent fractional shortening of the LV and RV and the LVEF in all of the study patients were normal and not significantly different from those in the group of normal subjects. None of the study patients had overt congestive heart failure, thus it is expected not to find altered parameters of global systolic dysfunction. This is in agreement with the previous studies on thalassemic patients with, and without clinical evidence of cardiomyopathy where parameters of global systolic function were altered only in patients with congestive heart failure which usually develops late in the disease process in patients with beta thalassemia.4,22 However, early myocardial dysfunction especially regional dysfunction occurs in such patients and can be detected by other modalities such as tissue Doppler imaging, magnetic resonance imaging,6 or acoustic densitometry using ultrasonic backscatter techniques.23 The new deformation indices, strain and strain rate, also allow early detection of myocardial dysfunction and may be the optimal method for quantitative assessment of regional myocardial dysfunction.13–15 Thalassemic patients of the present study who had no overt clinical cardiac dysfunction showed abnormal TVI and SI parameters indicating the early myocardial involvement in such patients.

The systolic myocardial velocities of the lateral LV basal segment (LV-Sm) was slightly lower in thalassemic patients compared to normal subjects in this study, however, the difference was not statistically significant. On the other hand, comparison of this parameter (LV-Sm) with its equivalent of the interventricular septum (septal-Sm) in each group separately, revealed significantly lower values of LV-Sm than septal-Sm in thalassemic but not in normal subjects suggesting systolic involvement of the lateral LV wall in such patients. A supporting evidence of this suggestion is the presence of significantly lower systolic strain values of the same segment (S-LV) in thalassemic patients as compared to normal subjects and lower LV strain than septal strain in thalassemic but not in normal subjects. These findings also indicate the superiority of SI over TVI in early detection of systolic dysfunction.

In the current study, the systolic TVI and SI parameters of the basal RV and basal septum indicated absent early systolic derangement of these walls in patients with thalassemia, while diastolic TVI parameters revealed regional diastolic dysfunction of RV and interventricular septum but not lateral LV wall. So, the results of this study indicate a differential behavior of the two ventricles as regard the regional ventricular function (i.e. altered systolic function of the lateral LV wall and altered diastolic function of the RV wall and interventricular septum). These findings are consistent with the results of previous studies.6,7 Hahalis et al.7 reported an abnormal relaxation
pattern of the RV while LV filling characteristics indicated increased preload without abnormal alteration. They reported also deterioration of LV systolic function in a follow-up echocardiographic study in 35 asymptomatic patients with beta thalassemia. Another study conducted by Vogel et al.6 revealed a reduction in systolic myocardial velocity in thalassemic patients compared to normal subjects, that was more pronounced in the LV rather than the RV. The same study also revealed prolongation of the isovolumic relaxation time in the RV segments but not in the LV segments, supporting the concept of the presence of differential regional impairment of systolic and diastolic function of both LV and RV in thalassemic patients.

The differential effects of thalassemia on the two ventricles might be potentially explained by the pattern and sequence of iron deposition in the different tissues including the lung leading to pulmonary hypertension and the heart muscle leading to myopathic changes. On the other hand, thinking on a molecular basis, there are structural, ultrastructural and mechanical differences in the myocardium of the two ventricles, which might be related to the relative proportion of V1 isoform of myosin heavy chain (α-MHC) with its higher shortening velocity and ATPase activity and V3 isoform (β-MHC) with its slower shortening velocity and less ATPase activity.24–26 The differences in structural and mechanical properties of the ventricles may explain the differential response to the different components of the hemodynamic burden associating thalassemia including iron overload, volume overload due to the chronic anemia and RV pressure overload due to elevated pulmonary artery pressure.

In the present study, the higher PAP in thalassemic patients might be responsible for the presence of early markers of diastolic impairment of the RV, whereas systolic impairment might be delayed or masked by the effect of volume overload of the chronic anemia on the thin-walled RV leading to increase velocity of shortening as a consequence of myocardial stretch (Frank-Starling mechanism). Again, the presence of RV pressure overload may be another factor delaying its systolic impairment. Supporting this hypothesis is the demonstration in a previous study,27 of progressive reactivation of the fetal iso-gene pattern (α-MHC, with its higher velocity of shortening) in the right ventricular myocardium in response to pressure overload of pulmonary hypertension.

On the other hand, the effect of iron deposition in the myocardium of the left ventricle with its slower shortening velocity may be more pronounced and appear earlier in the LV than the RV. Further studies are recommended to highlight the molecular aspects of structural differences between the two ventricles in thalassemic patients. It is also suggested that with the progress of the disease duration, the progressive iron deposition in the left ventricular myocardium would affect its diastolic properties with alteration of diastolic performance, and the progressive hemodynamic burden on the right ventricle would alter its systolic performance. Follow-up of patients in longitudinal studies would support this hypothesis, if progressive reduction of systolic and early diastolic velocities occurs in both RV and LV. However, the therapeutic effect and intensity of the different treatment modalities should be considered.

Conclusion

The current study points to the pattern of early changes in myocardial function and indicates that thalassemia patients who have no overt heart failure, have early regional systolic dysfunction in the lateral LV wall and regional diastolic dysfunction in the septal and RV walls. TVI and the newer modality SI are promising tools for quantitative assessment of myocardial function and early detection of regional systolic or diastolic dysfunction of either ventricle. SI seems to be more superior to TVI in early detection of regional myocardial systolic dysfunction.

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References

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