The Left Ventricular End-systolic Pressure-Dimension Relation in Patients with Thalassemia Major

A New Noninvasive Method for Assessing Contractile State

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SUMMARY Transfusion-dependent patients with thalassemia major (TM) are at an extremely high risk for cardiomyopathy. Traditional tests of left ventricular (LV) systolic function performed in these patients do not distinguish derangements in loading conditions from abnormalities in contractile state. In this study, we used the LV end-systolic pressure dimension ($P_{ES}$-$D_{ES}$) relation, which is independent of preload, incorporates afterload and is highly sensitive to contractile state, to assess LV performance in 20 asymptomatic, chronically transfused patients, ages 7–25 years, with TM. All patients had normal resting systolic time intervals and exercise duration on treadmill. Baseline resting percent fractional shortening ($\%\Delta D$) on M-mode echocardiography (echo) was normal in 14 patients (group 1) and abnormal in six patients (group 2). Echo and carotid pulse recordings were made at rest and during i.v. infusion of methoxamine to alter LV afterload. $D_{ES}$ was measured directly from echo; $P_{ES}$ was estimated from a calibrated carotid pulse tracing. The value for the slope of the $P_{ES}$-$D_{ES}$ line was calculated for each patient. Values more than 2 standard deviations below the mean for 14 control subjects, ages 8–25 years, were defined as abnormal. All group 2 patients and four of 14 group 1 patients had abnormal slopes. All patients younger than 13 years of age had normal slopes, while all seven patients 15 years or older had abnormal values. Three of seven patients ages 13–15 years had depressed slopes. On clinical follow-up (mean 12 ± 3 months), two of 10 patients with abnormal slopes developed overt signs of LV decompensation; all other patients remained asymptomatic.

The noninvasive determination of the LV $P_{ES}$-$D_{ES}$ relation in patients with TM appears to identify preclinical LV dysfunction not evident from resting or dynamic exercise studies. This test may be useful clinically for monitoring LV contractility in response to therapeutic interventions. Because of its insensitivity to loading conditions, it may have widespread clinical applicability for other patients at risk for cardiomyopathy, including those with chronic LV volume overload from valvular regurgitation.

ACCURATE assessment of left ventricular (LV) contractile state, especially using noninvasive techniques, is a complex and controversial problem. The most commonly used clinical measurements of contractility are the resting ejection fraction (EF) determined by contrast or radionuclide ventriculography and the percent fractional shortening ($\%\Delta D$) determined by echocardiography. Radionuclide ventriculographic determination of EF during dynamic exercise has been advocated as an even more sensitive index of LV contractility.1–3 None of these ejection fraction measurements of LV function, whether determined at rest or during exercise, can distinguish derangements in loading conditions from abnormalities of myocardial contractility.4–6 This is not surprising; the extent of LV fiber shortening is determined by the complex interaction between contractile state, preload and afterload. The LV end-systolic pressure-dimension ($P_{ES}$-$D_{ES}$) relation, which is independent of preload, incorporates afterload and varies with contractile state, has been suggested as a more sensitive index of LV contractility.7–11 Recently, we reported that the slope value of this relation was highly sensitive to changes in inotropic state in normal human subjects.12

We explored the clinical value of the LV $P_{ES}$-$D_{ES}$ relation to assess contractile state in patients with thalassemia major. These transfusion-dependent patients, who have abnormalities in LV preload and afterload, are at extremely high risk for iron-induced cardiomyopathy.13–15 Traditional tests of LV function usually cannot identify patients with thalassemia who have significant abnormalities of LV contractile state before the time of clinical decompensation.13–16 We hypothesize that the LV $P_{ES}$-$D_{ES}$ relation can identify abnormalities in ventricular performance not evident by standard tests of LV function. The ability to assess intrinsic contractile state will permit critical evaluation of chelation therapy in this iron-overloading condition and will provide an accurate means of assessing cardiac function in other cardiomyopathies.

Methods

Patients

The study population consisted of 20 patients with thalassemia major followed at the Children’s Hospital Medical Center. These patients, 12 males and eight females, were 7–25 years old and were treated by standard techniques until 3.0 ± 0.8 years (range 2–5 years) before this study, when they were begun on continuous deferoxamine therapy and a transfusion regimen that continually maintained their hemoglobin at levels greater than 12 g%. The transfusion load before the initiation of deferoxamine and hypertransfu-
sion therapy varied from 30 to 250 units; the cumulative transfusion load at the time of this study ranged from 55 to 380 units. All patients were on daily oral ascorbic acid supplementation (100 mg/day) since the initiation of deferoxamine therapy, and none were on cardiotonic or antiarrhythmic drugs. Fifteen patients had also undergone splenectomy before this study.

The control group consisted of 14 healthy subjects, ages 8–25 years, who had normal intracardiac anatomy by M-mode echocardiography and who were taking no cardioactive medications.

Cardiac Evaluation

Within 72 hours after blood transfusion, all patients had a cardiac assessment, including clinical examination, standard 12-lead scalar ECG resting M-mode and two-dimensional echocardiograms, systolic time interval determination, exercise duration on treadmill, and methoxamine afterload challenge testing (described below). Exercise capacity and electrocardiographic response to dynamic exercise were evaluated by treadmill exercise testing using the Bruce protocol. Fifteen of 20 patients had 24-hour ambulatory ECG (Holter monitor) recordings performed, with exclusions only in the case of scheduling problems. For both the exercise and Holter monitor studies, ventricular arrhythmias were graded using the classification proposed by Lown et al. Each patient’s overall cardiac status was estimated using the New York Heart Association (NYHA) functional classification.

Experimental Protocol

The detailed protocol has been reported. Briefly, M-mode and two-dimensional echocardiographic, phonocardiographic, electrocardiographic and carotid pulse recordings were made during the infusion of i.v. methoxamine. The noninvasive recordings were repeated every 1–2 minutes, permitting careful assessment of the LV response to a wide range of afterload conditions. End-systolic pressure was estimated from the dicrotic notch of a calibrated carotid pulse tracing. The LV D/ED were measured directly from M-mode echocardiograms. The LV %ΔD was then calculated as D/ED = D/ED/D/ED. All subjects were studied using protocols approved by the Human Studies Committee of the Children’s Hospital Medical Center and the Brigham and Women’s Hospital.

Data Analysis

Measurements of LV %ΔD, systolic time intervals and maximum endurance time on treadmill were compared with previously published normal values for age. Unless otherwise noted, the data are presented as the mean ± SD. The hemodynamic data were compared among the patient groups using an unpaired t test. A p value < 0.05 was considered statistically significant. Simple linear regression (least-squares method) was used to fit each subject’s data to a pressure-dimension (P = mD + b) equation. The slope value (m) used was the basis for comparison. Since the D for normal subjects between infancy and early adulthood varies linearly with the cube root of the body surface area (D(BSA)1/3), this function was chosen as a method of correction. Abnormality was defined as actual (m) or ‘corrected’ (m*) slope values more than 2 standard deviations below the mean value for the control group (i.e., m < 84 mm Hg/cm; m* < 101 mm Hg/cm).

Results

Routine Cardiac Studies

All patients were free of cardiac symptoms (NYHA functional class I), had normal systolic time intervals, and had normal exercise duration on treadmill. Baseline resting echocardiographic studies showed normal LV %ΔD (≥ 28) in 14 patients (group 1, 30.9 ± 1.7), while in six patients abnormal values were obtained (group 2, 22.5 ± 3.0; p < 0.001 vs group 1). There was no difference between the groups for mean age, heart rate, peak systolic and diastolic pressures, LV prejection period to ejection time ratio (PEP/LVET) or exercise duration on treadmill. The treadmill exercise study provoked a brief episode of ventricular tachycardia (Lown grade 4B) in patient 13 and occasional ventricular premature complexes (VPCs) (Lown grades 1 and 2) in patients 11, 14, 16, 17 and 19. Holter monitor studies were remarkable for ventricular tachycardia (grade 4B) in patients 13 and 17; multi- VPCs (grade 3) in patient 16; and occasional VPCs (grade 1) in patients 12, 15 and 20.

Response to Increased LV Afterload

Hemodynamic Response

Baseline mean heart rate after atropine premedication was 95 ± 11 beats/min for the thalassemia major patients and 98 ± 20 beats/min for the control subjects (NS). Aortic pulse pressures under resting conditions were similar in both groups. During methoxamine infusion, the ranges for peak, diastolic, and end-systolic pressures were similar for the thalassemia patients and control subjects. In no patient was there evidence of a gross LV wall motion abnormality on the two-dimensional echocardiogram.

End-Systolic Pressure-Dimension Relation

In all cases P and D had a direct linear relation (r = 0.90–0.99), while P and %ΔD were inversely related (r = −0.80 to −0.99). For the control subjects, the value for the slope of the P -D relation was 114 ± 15 mm Hg/cm and the corrected slope value (m*) was 133 ± 16 mm Hg/cm (fig. 1).

All six thalassemia patients with depressed resting %ΔD (group 2) had abnormal P -D slopes. Ten of the 14 patients with a normal resting %ΔD had normal slopes (group 1A) and the other four had abnormal slopes (group 1B). Representative echocardiographic, carotid pulse and phonocardiographic recordings from a patient with a normal resting %ΔD and an abnormal slope value are shown in figure 2. Table 1 shows each thalassemia patient’s response to the afterload challenge. Table 2 is a summary of the results of the cardiac tests of LV function performed on these patients.
Heart rate, resting PEP/LVET, and exercise duration on treadmill did not differ between groups. Although the baseline %ΔD for patients in groups 1A and 1B were similar (31.1 ± 2.2 vs 30.0 ± 1.3, NS), there was a marked difference in their $P_{ES}^D$-$D_{ES}$ slopes when calculated directly (121 ± 16 vs 62 ± 10; $p < 0.001$) or when corrected (124 ± 19 vs 68 ± 10; $p < 0.001$). When groups 1B and 2 were compared, the slopes showed no significant difference whether actual (63 ± 9 vs 56 ± 10, NS) or corrected (68 ± 10 vs 62 ± 12, NS). The patient’s age at the time of study correlated well with the results of the methoxamine test. All patients younger than 13 years of age had normal slopes and all seven patients 15 years of age or older had abnormal slopes. Three of seven patients ages 13–15 years had depressed slope and corrected slope values.

**Clinical Follow-up**

The follow-up period ranged from 6 to 16 months (mean 12 ± 3 months). Patient 17, who had a mild depression of his resting %ΔD and an abnormal $P_{ES}^D$-$D_{ES}$ slope value, died of severe LV dysfunction 8 months after study. Patient 13, with a normal resting %ΔD and a low $P_{ES}^D$-$D_{ES}$ slope value, developed congestive heart failure 9 months after study and has received digoxin and diuretic therapy. All other patients are asymptomatic.

**Discussion**

The physiologic basis for the clinical value of the $P_{ES}^D$-$D_{ES}$ as an index of LV muscle fiber performance lies in its independence of preload, incorporation of afterload and sensitivity to alterations in inotropic state. Our findings suggest that the value for the slope of this relation can be used to detect LV dysfunction in patients with thalassemia major who have normal ventricular function at rest and normal exercise duration on treadmill.

All of our thalassemia patients older than 15 years of age at the time of study had abnormalities of myocardial contractile function (i.e., depressed $P_{ES}^D$-$D_{ES}$ slopes) regardless of their %ΔD and PEP/LVET at rest or exercise capacity on treadmill. The inability of these traditional measurements of LV performance to assess accurately LV contractility is, in part, a result of two
TABLE 1.  Response to the Afterload Challenge

<table>
<thead>
<tr>
<th>Group 1A</th>
<th>Group 1B</th>
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Mean ± SD: 11 ± 2 31.1 ± 2.2 121 ± 16 124 ± 19

Mean ± SD: 18 ± 5 30.0 ± 1.3 63 ± 9 68 ± 10

Table 1: Response to the Afterload Challenge

<table>
<thead>
<tr>
<th>Age at study (years)</th>
<th>Resting %ΔD</th>
<th>PES-D_Es slope value (mm Hg/cm)</th>
<th>P_Es-D_Es* slope value (mm Hg/cm)</th>
<th>BSA</th>
<th>Group 1A</th>
<th>Group 1B</th>
<th>Group 2</th>
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Table 2: Cardiac Findings

<table>
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<th>Group 1A</th>
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<th>Group 2</th>
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<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>96 ± 11</td>
<td>97 ± 11</td>
<td>91 ± 12</td>
</tr>
<tr>
<td>Resting PEP/LVET</td>
<td>0.32 ± 0.02</td>
<td>0.34 ± 0.02</td>
<td>0.36 ± 0.03</td>
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<tr>
<td>Exercise duration (minutes)</td>
<td>14'52&quot; ± 2'23&quot;</td>
<td>13'55&quot; ± 1'27&quot;</td>
<td>13'34&quot; ± 2'33&quot;</td>
</tr>
<tr>
<td>Resting %ΔD</td>
<td>31.1 ± 2.2</td>
<td>30.0 ± 1.3</td>
<td>22.5 ± 3.0</td>
</tr>
<tr>
<td>PES-D_Es slope</td>
<td>121 ± 16</td>
<td>63 ± 9</td>
<td>56 ± 10</td>
</tr>
<tr>
<td>P_Es-D_Es* slope</td>
<td>124 ± 19</td>
<td>68 ± 10</td>
<td>62 ± 12</td>
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</tbody>
</table>

Table 2: Cardiac Findings

Abbreviations: PEP = preejection period; LVET = left ventricular ejection time; %ΔD = percent fractional shortening; PES = end-systolic pressure; D_Es = end-systolic dimension; D_Es* = end-systolic dimension corrected for (body surface area)³⁰. compensatory mechanisms can help maintain normal LVEF and %ΔD despite progressive deterioration of contractile reserve. Eventually, the contractile abnormality becomes so severe that even these optimally functioning compensatory mechanisms cannot maintain normal LV shortening characteristics. Covert LV dysfunction becomes overt LV decompensation and results in death.²⁸

Although 50% of our thalassemia patients had abnormal slopes for the line relating end-systolic pressure to dimension, none had diminished exercise capacity on treadmill. The ability to perform dynamic exercise is dependent on a competent cardiopulmonary system with intact reflex responses. During exercise, sympathetic tone, heart rate, and LV inotropic state increase and systemic vascular resistance falls.²⁹ These changes can augment LV shortening and increase cardiac output, resulting in preservation of normal exercise capacity even in patients with moderately depressed LV contractility. Recently, radionuclide ventriculographic measurement of LVEF during dynamic exercise has been proposed as a more reliable index of LV contractile state. Initial studies reported an invariable rise in EF above resting values.¹,² Leon et al.³ used this finding to study LV performance in patients with transfusion-dependent congenital anemias. Thirteen of their 24 patients failed to increase their EF with exercise and were therefore classified as having LV dysfunction. The predictive value of this response to exercise has been questioned, however, because normal subjects do not always increase their EF with dynamic exercise.³⁰,³¹ Our experimental design, which uses pharmacologic manipulation of afterload to assess LV systolic reserve capacity, may have two major advantages over radionuclide ventriculographic EF measurement during exercise. First, it evaluates intrinsic contractile state independent of fluctuations in inotropic, chronotrophic and loading conditions that occur with dynamic exercise. Second, it requires minimal patient cooperation and thus is a feasible approach even in children.

Ventricular arrhythmias were present on treadmill exercise testing or 24-hour ambulatory monitoring studies in nine of 20 patients with thalassemia major.
Five of the nine patients had abnormal %ΔD at rest and all nine had decreased P_{ES-D_E} slopes. Ninety percent of the patients with an abnormal response to the afterload challenge had detectable ventricular ectopic activity. Thus, a much stronger correlation existed between the P_{ES-D_E} slope and ventricular arrhythmias than between resting %ΔD and ventricular arrhythmias.

**Methodologic Considerations**

Potential limitations to the method should be noted. First, we assumed a uniform contractile state under various afterload conditions. Although methoxamine is a selective α-receptor agonist without direct cardiac inotropic effect, centrally mediated alterations in LV contractility cannot be excluded. Heart rate was maintained relatively constant throughout the study, suggesting that gross changes in sympathetic tone did not occur. Minor fluctuations of sympathetic discharge, especially at higher arterial pressures in thalassemia patients with depressed LV contractility, would result in an upward and leftward shift of their P_{ES-D_E} points and an increased slope. While occasional false-negative results may occur in some patients with mild LV dysfunction, the sensitivity and predictive value of the slope of the P_{ES-D_E} relation as an index of depressed LV contractility should not be significantly affected by this theoretical consideration. Although no myocardial tissue correlations for the slope values were obtained in our study, two of the 10 patients with depressed slope values have gone into congestive heart failure during our brief follow-up period; none of the patients with normal slope values have become symptomatic. In several long-term clinical studies of patients with thalassemia major, overt LV failure was reported to appear usually during adolescence or young adulthood. Our findings of normal LV systolic reserve in patients younger than 13 years of age and abnormal reserve capacity in patients older than 15 years of age are consistent with these clinical observations.

Second, we assumed that the echocardiographic D_{ES} values used in this study were representative of actual end-systolic fiber length. Although the patients varied in body surface area and age, our conclusions did not change regardless of whether the measured or corrected D_{ES} were used to calculate the slope. Since none of the two-dimensional echocardiographic studies showed gross evidence of LV wall motion abnormalities, geometric factors probably did not affect our results.

Finally, we used the pressure at end ejection to approximate true end-systolic pressure. While the aortic dicrotic notch pressure may slightly underestimate the LV pressure at the instant of maximal ventricular active contraction, the difference between these two points in patients without aortic stenosis, aortic regurgitation or mitral regurgitation is probably quite small. Although some investigators have used peak systolic pressure to approximate true P_{ES}, we have shown recently that the P_{ES-D_E} relation using dicrotic notch rather than peak systolic pressure is more sensitive to alterations in LV contractility. 12

**Clinical Implications**

The most severe pathologic sequelae of chronic iron overload involve the heart. 13-16 Static or dynamic cardiac evaluations are not predictive, and therefore are not useful, as guidelines for modulating therapy. We have identified a group of older patients with no clinical symptoms who presently demonstrate myocardial abnormalities by methoxamine challenge despite "adequate" daily 12-hour subcutaneous deferoxamine therapy for 2–5 years. We do not know if they had a similar level of cardiac abnormalities at the time of the initiation of the therapy. However, these patients did have a significant degree of iron overload before they were placed on therapy, and the mere attainment of a state of daily net negative iron balance has not normalized cardiac function. As a result, we are intensifying our chelation efforts in patients with abnormal methoxamine challenge tests in an attempt to improve their clinical well-being. 35-37 We hope that the P_{ES-D_E} relation determined serially in patients with thalassemia major will prove predictive, and thus aid in the development of improved therapeutic alternatives for this disease, chronic LV volume overload from valvular regurgitation, and others in which progressive cardiomyopathy is a hallmark. Our preliminary results in patients receiving adriamycin indicate that this might be the case. 38, 39

**Acknowledgment**

We thank Lesia Stanchak, Mary Beth Giffune, Alexander Neumann, Debbie MacPherson, and Susan Marini for their technical assistance, Adele Slatko, Joanne Miccile, and Emily Flynn for assistance in preparation of this manuscript and Drs. David G. Nathan, Alexander S. Nadas, and Eugene Braunwald for review of the manuscript.

**References**

NONINVASIVE ASSESSMENT OF LV CONTRACTILE STATE/Borow et al.


K M Borow, R Propper, F Z Bierman, S Grady and A Inati

Circulation. 1982;66:980-985
doi: 10.1161/01.CIR.66.5.980

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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