Blood Pressure and Heart Rate in Young Thalassemia Major Patients
Franco Veglio, Remo Melchio, Franco Rabbia, Paola Molino, Gianluca Cat Genova, Gianpiero Martini, Domenica Schiavone, Antonio Piga, and Livio Chiandussi

The analysis of blood pressure (BP) and heart rate (HR) variability is currently used to investigate the mechanisms responsible for cardiovascular control; therefore, we assessed whether an impairment of 24-h BP and HR profiles and sympathovagal interaction modulating cardiovascular function was present in patients with thalassemia major (TM) in preclinical phase of heart disease. Nine β-thalassemic patients 18 years old without clinical signs of cardiac failure and 9 age- and sex-matched controls were studied. Twenty-four-hour-ambulatory BP and HR were measured using the SpaceLabs 90207 device. A truncated Fourier series with four harmonics was used to describe the diurnal blood pressure profile. Mean 24-h ambulatory systolic BP, diastolic BP, and mean arterial pressure were significantly lower in TM patients than in normal subjects ($P < .05$). A significantly higher nighttime HR value was found in TM patients ($P < .05$). More than 40% of the TM patients did not show a significant diurnal BP and HR rhythm. In TM patients, the overall amplitude of systolic BP, diastolic BP, and HR was significantly lower than in controls ($P < .01$). The night/day differences of systolic BP, diastolic BP, and HR were significantly lower in TM patients than in normals ($P < .01$). Furthermore, we performed power spectral analysis on short-term continuous finger BP and HR data in supine position and during passive head-up tilt. Total spectral power of systolic BP was significantly lower in patients than controls ($P < .05$). Low-frequency (LF) power of systolic BP and diastolic BP and LF/high-frequency (HF) ratio of HR were significantly lower during tilt in TM patients compared to controls ($P < .05$). High-frequency power of HR was significantly higher in patients than controls ($P < .05$). The baroreflex gain assessed by $\alpha$-index was the same in supine position but was higher in TM patients during passive tilt ($P < .05$). An inverse relationship between LF/HF ratio of HR and hemoglobin levels in TM patients was found. Finally, plasma norepinephrine levels were significantly lower in thalassemics ($P < .005$). In young TM patients in a preclinical stage of heart disease, these findings demonstrated abnormal 24-h BP and HR rhythms and a decreased short-term variability of BP and HR, in particular in the LF range, showing a diminished sympathetic activity. Am J Hypertens 1998;11:539–547 © 1998 American Journal of Hypertension, Ltd.

**KEY WORDS:** Blood pressure, heart rate, spectral analysis, thalassemia.
Although in the past years notable improvements in therapy of thalassemia major (TM) have been realized, constant and progressive cardiac impairment still leads to irreversible cardiac failure, which remains the major cause of death for these patients.1–3 Moreover, few studies have documented initial cardiovascular dysfunction even in thalassemics without clinical manifestation of heart failure.3–6 Recent findings7,8 showed that left ventricular diastolic filling is altered in a preclinical phase of cardiac involvement in β-thalassemic patients. Although the analysis of blood pressure (BP) and heart rate (HR) variability is currently used to investigate the mechanisms responsible for cardiovascular control in normal and pathophysiologic conditions,9–14 to our knowledge there have been no systematic studies on behavior of 24-h BP and HR profile and on short-term BP and HR variability in TM patients. Recently Thijs et al15 provided a comprehensive two-step method for the parametrization of the diurnal BP profile obtained by ambulatory BP monitoring; the model combines the runs test to the application of Fourier series with four harmonics. On the other hand, in frequency domain analysis of short-term variability, autoregressive algorithms as well as maximum entropy method (MEM), have remarkable resolution properties and superiority over other spectral estimators, in particular for short data length.12,16,17 The rhythm synchronous with respiration waves and present in arterial pressure variabilities, defined as low-frequency (LF) component, is a marker of sympathetic modulation; the LF component of HR variability may reflect sympathetic and parasympathetic modulation of HR and is strongly affected by the oscillatory rhythm of the baroreflex system. Actually, under strictly controlled circumstances (tilt-table studies), LF power may be used as an indicator of sympathetic activity.9 The respiratory component, definable as the high-frequency (HF) component, is attributed to vagal mechanisms.9,13 In addition, a reciprocal relationship exists between HF and LF and it is similar to that characterizing the sympathovagal balance.13,18

The purpose of the present study was to evaluate whether an impairment of BP and HR 24-h profile and sympathovagal interaction modulating cardiovascular function was present in patients with TM in a preclinical phase of heart disease.

**METHODS**

**Patients** Nine young patients with TM (5 men and 4 women, age median 18 years; range, 17 to 19 years) were studied. This was the entire population of TM patients in this age range followed by the Micocitemia Center at Pediatric Hospital in Turin. All thalassemic patients were affected by β-thalassemia major (homozygous forms) and had been splenectomized. Each of the patients was receiving blood transfusions every 3 to 4 weeks to maintain hemoglobin levels between 10.5 and 13.5 g/dL. They were also receiving dexferoxamine subcutaneously as chelation therapy (25 to 50 mg/kg body weight infused 4 to 6 days a week to maintain serum ferritin level <1500 ng/mL). The studies were performed at 6 ± 1.3 days after transfusion. At the time of the BP monitoring their hemodynamic parameters were normal. Also, all patients were without clinical or electrocardiographic evidence of cardiac failure and arrhythmia and the standard echocardiographic evaluation was normal.

All clinical data of the patients are summarized in Table 1.

**Control Group** Nine healthy subjects matched for age and sex (5 men and 4 women, median age 18 years, [range, 17 to 19 years]; weight (kg): 64 [range, 62 to 66]; height (m): 1.68 [range, 1.60 to 1.75]; body mass index (kg/m²): 19 [range, 18.2 to 20.1]) without clinical, electrocardiographic, and echocardiographic evidence of cardiovascular disease as well as hematologic, nephrologic, and urologic disease were studied. Moreover they were without parental history of hypertension and not undergoing pharmacologic treatment (ie, contraceptives). All subjects gave informed consent to the study.

**Twenty-Four Hour Blood Pressure and Heart Rate Monitoring and Analyses** Ambulatory BP and HR were measured for 24 h, every 20 min from 8:30 AM

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**TABLE 1. CLINICAL AND HEMATOLOGIC PROFILE OF PATIENTS WITH B-TALASSEMIA MAJOR**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>5.4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>18 (17–19)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19 (18.2–20.1)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12.5 (11.8–12.9)</td>
</tr>
<tr>
<td>Transfusion (years)</td>
<td>17 (16.2–18)</td>
</tr>
<tr>
<td>Transfusion (total no.)</td>
<td>461 (332–592)</td>
</tr>
<tr>
<td>Serum ferritin (mg/L)</td>
<td>1578 (1006–2231)</td>
</tr>
<tr>
<td>Chelation therapy (y)</td>
<td>17.4 (15.8–18)</td>
</tr>
<tr>
<td>Dose of subcutaneous dexferoxamine (mg/kg)</td>
<td>48 (41–55)</td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>48 (42–53)</td>
</tr>
<tr>
<td>LVDS (mm)</td>
<td>32 (29–37)</td>
</tr>
<tr>
<td>FS (%)</td>
<td>33 (31–38)</td>
</tr>
<tr>
<td>IVS thickness (mm)</td>
<td>9.5 (7.8–11.1)</td>
</tr>
<tr>
<td>LVPW thickness (mm)</td>
<td>8.5 (7.9–9.1)</td>
</tr>
<tr>
<td>EF (%)</td>
<td>63 (58–71)</td>
</tr>
</tbody>
</table>

Data are expressed as median (25th to 75th percentiles)

BMI = body mass index; LVDD, left ventricular diastolic diameter; LVDS, left ventricular systolic diameter; FS, left ventricular fractional shortening; IVS, interventricular septum; LVPW, left ventricular posterior wall; EF, ejection fraction.
using the SpaceLabs 90207 monitor. Systolic BP (SBP),
diastolic BP (DBP), mean arterial pressure (MAP), and
HR were downloaded from the monitor to a IBM PC
(Armonk, NY) and processed by custom software us-
ing the SAS (Cary, NC) system.

The 24-h BP readings were excluded from analysis
when missing or labeled as technically erroneous by
the software of the monitor. Standard statistical anal-
ysis was performed on each data field and the median
was assessed by the runs test with a one-side proba-
bility level of 5% against random variation in BP, as
previously described.15,19 Patients with significant
runs test results for a variable were defined as having
a circadian rhythm for that variable.

A truncated Fourier series with four harmonics was
used to describe the diurnal BP profile; each harmonic
is characterized by a period (ie, the time interval be-
tween successive maxima), an amplitude (ie, the half
of the difference between the minimum and the max-
imum of the i th harmonic), and a phase (ie, the time
lag between midnight and the first maximum of the
i th harmonic).

The nocturnal BP decrease was defined as the dif-
ference between the average daytime and nighttime
BP.

Short-term BP and HR Variability  Studies were
performed in a quiet room between 9 and 10 AM, 2 to
5 days after the last blood transfusion. In each patient
continuous finger BP and HR were measured by a
Finapres device (Ohmeda 2300, Ohmeda, Englewood,
CO) and by electrocardiogram monitoring (Cardio-
line, ETA 150, Remco, Milan, Italy). Both devices were
connected to a personal computer (IBM 386) and beat-
to-beat SBP and DBP and pulse interval (RR) were
recorded and stored in separate series. Each patient
was placed supine on an electrically driven tilt-table.
Finapres calibration (self adjustment) was performed
at the beginning for 20 min (data not calculated in
analysis), then it was switched off to obtain a contin-
uous undisturbed recording for another 20 min. Fi-
nally, passive head-up tilt was performed from 0 to 60
degrees. Finapres calibration was switched on for 5
min and then was switched off to obtain a 10-min
undisturbed record for analysis.

The same procedure was performed with the con-
trol group.

Data Analysis and Statistics  For each period (su-
pine and upright), a sequence of 400 stationary data (5
min) was analyzed. Stationarity of BP and RR interval
data was checked by visual inspection. Mean and
standard deviation (as a measure of overall variance)
was calculated for each time data series. In the fre-
quency domain, power spectral analysis by autore-
gressive method (MEM) was applied on finger BP and
pulse interval data before and during tilting. The or-
der of the autoregressive model was chosen according
to the minimization Akaike’s information criterion.20

With MEM, the total variance (total power) may be
divided in three spectral components (fractions of to-
tal variance) centered around different frequencies.
The study of component centered at 0.00 to 0.03 Hz
(very low frequency, VLF), was not evaluated in the
present study because it requires specific methodol-
ogy and long periods of uninterrupted data. The am-
plitude of spectral components defined as LF (0.03 to
0.14 Hz) and HF (0.14 to 0.35 Hz) was assessed as the
area of each component and was expressed also in
normalized units (NU) (by dividing the power of a
given component by the total variance, from which the
component VLF has been subtracted, and multiplying
by 100).

The LF/HF ratio was used as an index of sympa-
thovagal balance.

A quantitative assessment of the overall gain of the
baroreflex mechanism was computed as shown by the
formula:

\[ \alpha = \frac{\sqrt{LF_{RR}}}{LF_{SBP}} \]

ie, the square root of the ratio of the powers of RR LF
to the corresponding SBP spectral component (where
both RR and SBP powers were found to have a degree
of coherence >0.5).13,21

Hormonal Measurements  Hormonal measurements
consisted of plasma renin activity (PRA), aldosterone,
and plasma catecholamines.

In all the subjects blood samples were taken after
1 h supine and 30 min standing, and were placed
into ice cold tubes containing EDTA heparin. After
centrifugation at 4°C, plasma was stored at −70°C
until assay. PRA and plasma aldosterone concentra-
tions were determined by radioimmunoassay com-
mercial kits (Sorin, Saluggia, Italy). The coefficient
of variance (CV) (interassay and intraassay) of PRA
and aldosterone was <7.5%. Catecholamine plasma
levels (epinephrine, norepinephrine) were assayed
using reversed phase, ion pair high-performance
liquid chromatography (HPLC) coupled with elec-
trochemical detection (Waters Assoc., Milford, MA).
The CV (interassay and intraassay) for norepineph-
rine and epinephrine was <5%.

Statistical Analysis  Statistical evaluation was per-
duced by Statistical Analysis System (SAS Institute
Inc., Cary, NC). Nonparametric statistics was per-
formed using Mann-Whitney and Wilcoxon tests
where appropriate.
TABLE 2. TWENTY-FOUR-HOUR AMBULATORY BLOOD PRESSURE MONITORING DATA IN THALASSEMIC PATIENTS AND CONTROL SUBJECTS

<table>
<thead>
<tr>
<th>Blood Pressure</th>
<th>Patients With Thalassemia Major</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP 24-h mean (mm Hg)</td>
<td>106 (97–114)*</td>
<td>118 (109–125)</td>
</tr>
<tr>
<td>DBP 24-h mean (mm Hg)</td>
<td>74 (65–83)*</td>
<td>86 (78–92)</td>
</tr>
<tr>
<td>MAP 24-h mean (mm Hg)</td>
<td>58 (50–70)*</td>
<td>68 (60–77)</td>
</tr>
<tr>
<td>HR 24-h mean (beats/min)</td>
<td>75 (66–86)</td>
<td>73 (68–87)</td>
</tr>
<tr>
<td>SBP daytime (mm Hg)</td>
<td>109 (100–117)*</td>
<td>121 (117–128)</td>
</tr>
<tr>
<td>DBP daytime (mm Hg)</td>
<td>78 (69–73)*</td>
<td>86 (77–89)</td>
</tr>
<tr>
<td>MAP daytime (mm Hg)</td>
<td>62 (53–73)*</td>
<td>73 (62–80)</td>
</tr>
<tr>
<td>HR daytime (beats/min)</td>
<td>79 (70–89)</td>
<td>80 (71–90)</td>
</tr>
<tr>
<td>SBP nighttime (mm Hg)</td>
<td>99 (93–107)*</td>
<td>110 (102–116)</td>
</tr>
<tr>
<td>DBP nighttime (mm Hg)</td>
<td>68 (61–73)*</td>
<td>78 (70–81)</td>
</tr>
<tr>
<td>MAP nighttime (mm Hg)</td>
<td>52 (44–58)*</td>
<td>61 (54–68)</td>
</tr>
<tr>
<td>HR nighttime (beats/min)</td>
<td>70 (62–78)*</td>
<td>65 (58–72)</td>
</tr>
</tbody>
</table>

Values are expressed as median (25th to 75th percentile).
* P < .05 v controls.

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean blood pressure; HR, heart rate.

Spearman’s rank correlation test was performed to measure the strength of the relationship between two variables.

A value of P < .05 was taken as the level of statistical significance. Values are expressed as median (25th to 75th percentiles).

RESULTS

Twenty-four-Hour Blood Pressure and Heart Rate Monitoring Analysis Median 24-h, daytime, and nighttime ambulatory SBP, DBP, and MAP were significantly lower in TM patients than in healthy subjects (Table 2, Figure 1). A significantly higher nighttime HR value was found in TM (Table 2). According to the one-sample runs test, four TM patients did not show a significant diurnal rhythm for SBP and for HR, whereas all normal subjects showed a significant diurnal rhythm for BP and HR. The Fourier parameters of all subjects are summarized in Table 3. In TM patients, the overall amplitude (AMP) of SBP, DBP, and HR curves modeled with four harmonics, was significantly lower than in controls (P < .05). The overall acrophase (AP), ie, the time of the maximum of the SBP in TM patients, was significantly delayed compared to normals. The night/day differences of SBP, DBP, and HR were significantly lower in TM patients than in normals (P < .01). The percentages of the BP variance explained by the model were similar in both groups.

All patients were ranked according to the night/day ratio of their directly measured mean ambulatory BP and the ratios were performed by the Fourier analysis software based on data from population studies. Thus, among the patients ranked according to the night/day ratio for the nocturnal BP decrease, all controls were dippers, in contrast four TM patients were nondippers.

Short-term Variability Analysis Table 4 shows the mean SBP, DBP, and RR interval values before and
after passive tilt for each group. Median RR interval values decreased significantly after passive tilt in both groups studied (P < .01). In normal subjects SBP decreased after passive tilt (P < .01), whereas DBP did not show a significant change. No statistically significant difference was found in SBP and DBP median values after passive tilt compared to supine position in TM patients. Moreover, in this group, the SBP and DBP median values at rest were significantly lower compared to the control group (P < .05 and P < .02, respectively), and no differences in these parameters were found after tilt.

Finally, RR interval median values in upright position were significantly higher in thalassemics than in control subjects (P < .01).

**Spectral Analysis of SBP Variability**

Data are summarized in Table 5 and Figure 2.

Total variance (ie, total spectral power) was significantly lower in TM patients compared to normal controls, at rest as well as after tilting (P < .005). Moreover, the difference between total variance values in supine position and in upright position was significantly higher in TM patients than in normals (Δ = 5.27 mm Hg² v ∆ = −33.8 mm Hg²; P < .05). LF power in TM patients after tilting was significantly

### Table 4. Average SBP, DBP, and RR Interval Values Before and After Passive Tilt Test

<table>
<thead>
<tr>
<th></th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>RR (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Upright</td>
<td>Supine</td>
</tr>
<tr>
<td>Thalassemic patients</td>
<td>104.7 (100–112)</td>
<td>101 (92–106)</td>
<td>58.8 (56–61)†</td>
</tr>
<tr>
<td>Normal controls</td>
<td>112.6 (108–126)</td>
<td>99 (95–110)</td>
<td>63.7 (63–68)</td>
</tr>
</tbody>
</table>

Data are expressed as median (25th to 75th percentiles).

* P < .05 v supine.
† P < .05 v controls.

SBP, systolic blood pressure; DBP, diastolic blood pressure.

### Table 5. Power Spectral Analysis of Systolic and Diastolic Blood Pressures and Interbeat Interval Variability

<table>
<thead>
<tr>
<th></th>
<th>Thalassemics</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Upright</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total variance (mm Hg²)</td>
<td>32.9 (24.5–35)</td>
<td>27.7 (21.6–44.7)†</td>
</tr>
<tr>
<td>LF (mm Hg²)</td>
<td>9.4 (7–15)</td>
<td>9.9 (7.3–13)†</td>
</tr>
<tr>
<td>HF (mm Hg²)</td>
<td>2.1 (2–2.7)</td>
<td>2.8 (1.9–3.1)</td>
</tr>
<tr>
<td>LF/HF</td>
<td>3.7 (3.4–8.1)</td>
<td>4.5 (2.4–5.2)†</td>
</tr>
<tr>
<td>LF NU</td>
<td>75 (70–87)</td>
<td>77 (68–81)†</td>
</tr>
<tr>
<td>HF NU</td>
<td>19 (10–21)</td>
<td>17 (15–27)†</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total variance (mm Hg²)</td>
<td>13.2 (11.6–15.8)</td>
<td>16.1 (9.2–17.8)†</td>
</tr>
<tr>
<td>LF (mm Hg²)</td>
<td>6.4 (4.5–8)</td>
<td>5.8 (4.2–8.2)†</td>
</tr>
<tr>
<td>HF (mm Hg²)</td>
<td>1.1 (0.5–1.3)</td>
<td>0.6 (0.3–1)</td>
</tr>
<tr>
<td>LF/HF</td>
<td>6.5 (2.8–9.6)</td>
<td>8.2 (6–10.7)</td>
</tr>
<tr>
<td>LF NU</td>
<td>84 (72–88)</td>
<td>84 (82–85)†</td>
</tr>
<tr>
<td>HF NU</td>
<td>13 (9–24)</td>
<td>10 (7–13)</td>
</tr>
<tr>
<td>Interbeat interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total variance (msec²)</td>
<td>4789 (3820–10,204)</td>
<td>3361 (2069–4940)*</td>
</tr>
<tr>
<td>LF (msec²)</td>
<td>1648 (1166–2155)</td>
<td>1018 (527–1598)*</td>
</tr>
<tr>
<td>HF (msec²)</td>
<td>1591 (1210–4766)</td>
<td>239 (136–333)*</td>
</tr>
<tr>
<td>LF/HF</td>
<td>0.73 (0.37–1)†</td>
<td>4.2 (3.2–4.4)†</td>
</tr>
<tr>
<td>LF NU</td>
<td>45 (37–51)</td>
<td>75 (70–77)†</td>
</tr>
<tr>
<td>HF NU</td>
<td>52 (46–73)†</td>
<td>18 (17–21)††</td>
</tr>
</tbody>
</table>

Data are expressed as median (25th to 75th percentiles).

* P < .05 v supine; †P < .05 v controls.

LF, low frequency; HF, high frequency; NU, normalized units.
lower than in normal controls ($P < .005$), whereas HF power was higher in thalassemics compared to normals ($P < .005$).

Thus, LF/HF ratio after passive tilt was significantly lower in TM patients than in the other group ($P < .005$). Finally, the difference of LF/HF ratio values in an upright position and those measured in a supine position was significantly lower in TM patients compared to normal controls ($D \text{LF/HF} = 0.8 \text{ v} 2.4; P < .05$).

**Spectral Analysis of DBP Variability** In TM patients DBP total spectral power and LF power (Table 5; Figure 2) did not increase after passive tilt, whereas the increase was significant in normals ($\Delta \text{total power} = +22 \text{ mm Hg}^2, P < .01; \Delta \text{LF} = +8.4 \text{ mm Hg}^2, P < .05$, respectively). No significant change in LF, HF, or LF/HF ratio after passive tilt was found in TM patients. LF power in upright position was lower in this group than in controls ($\text{LF} = 5.8 \text{ mm Hg}^2 \text{ v} 12.6 \text{ mm Hg}^2; P < .05; \text{LF} = 84 \text{ NU v} 89; P < .03$).

**Spectral Analysis of RR Variability** Data are summarized in Table 5.

In TM patients LF power expressed in NU significantly increased ($\Delta \text{LF} = +30 \text{ NU}; P < .0005$) and HF power decreased ($\Delta \text{HF} = -34 \text{ NU}; P < .005$). Thus, LF/HF ratio increased significantly ($P < .001$), but it was lower than that of normal subjects (increase = $3.47 \text{ v} 15.13; P < .02$). LF/HF ratio at rest as well as after tilt was significantly lower in thalassemics than in controls ($P < .05$) (Figure 3A). HF power at rest in TM patients was higher compared to normals ($P < .05$). After passive tilt, TM patients showed LF power significantly lower ($P < .005$) and HF power significantly higher than normal controls ($P < .01$).

Hemoglobin level showed an inverse relationship with LF/HF ratio of RR interval ($r = -0.77, P = .01$). No relationships were found among serum ferritin levels, dose of dexferoxamine, or years of treatment and number of blood transfusions or years of blood transfusion and spectral analysis parameters.

**Baroreflex Gain** The index $\alpha$ (a measure of baroreflex gain) showed a decrease after passive tilt in nor-

![Figure 2](image_url)

**Figure 2.** Bar graphs show low frequency power spectral densities of systolic blood pressure (**top**) and diastolic blood pressure (**bottom**) in thalassemics and controls before (black bar) and during (hatched bar) passive tilt. Data are median. *$P < .05$ v resting value, $#P < .05$ v controls.

![Figure 3](image_url)

**Figure 3.** (A) Changes in the LF/HF ratio in thalassemics and controls in response to tilt. (B) Bar graphs show baroreflex gain (index $\alpha$) before and during passive tilt in thalassemics and controls. Black column represents the value during rest. Hatched column represents the value during tilt. Data are median. *$P < .05$ v resting value, $#P < .05$ v controls.
mal subjects as well as in TM patients, but only in the latter group the decrease was statistically significant ($P < .05$). Furthermore, after passive tilt the index $a$ was significantly higher in thalassemics than in normals ($P < .005$) (Figure 3B).

**Hormonal Parameters** In TM patients, plasma norepinephrine was significantly lower than controls both in supine and upright positions ($P < .005$); PRA and aldosterone plasma levels were significantly higher in thalassemics than in controls ($P < .005$).

Furthermore PRA increased significantly after passive tilt, whereas plasma aldosterone, epinephrine, and norepinephrine levels did not show a significant increase (Table 6).

### DISCUSSION

Few studies reported blood pressure values in TM patients. Spirito et al.\(^6\) reported that blood pressure measured by traditional cuff sphygmomanometry at the time of the Doppler examination was within the normal range but slightly and significantly lower in the TM patients compared with control subjects, whereas there were no differences in HR. Furthermore, some researchers have reported that the $\beta$-thalassemia Hb E patients had higher basal PRA levels than normal subjects, despite differences in PRA levels, the BP values were similar.\(^{22}\)

To our knowledge, no previous studies have assessed 24-h BP and HR rhythm and their short-term variability in TM patients.

In the present study the analysis of the ambulatory 24-h BP showed significant lower BP values in young TM patients than in normals. This finding may be explained at least in part by lower body mass index of TM children. Furthermore, the mathematical model based on Fourier transformation specifically designed for the parametrization of the diurnal BP profile, has shown a lack of circadian BP and HR rhythm in 45% of TM patients. Moreover, in TM patients a lesser nocturnal BP and HR decrease and amplitude than normals were present. This alteration of 24-h BP and HR profile can be attributed to disturbances in breathing and in cardiopulmonary functions,\(^{23}\) or in autonomic nervous activity and in hypothalamo-pituitary-adrenal periodicity. However, Pasqualetti et al.\(^{24}\) showed that circadian pattern of cortisol and aldosterone, that is closely related to BP circadian rhythm, was normal in TM patients without clinical evidence of endocrine abnormalities, whereas the secretion rhythmicity of corticotropin was modified.

Hence, to better understand the role of the autonomic nervous system modulating cardiovascular function in TM patients, we analyzed the noncasual oscillations in RR interval and BP short-term variability both in baseline conditions and during passive tilting, at LF (index of sympathetic activity) and HF (index of vagal tone to the heart). The major findings in the present study are: 1) a lower total power of SBP and DBP both at baseline and after passive tilt in thalassemics compared to normal controls; 2) a lower LF power of SBP and DBP particularly after tilt in the same patients; and 3) a lower LF/HF ratio of baseline RR interval with a significantly lesser increase after tilt in TM patients. LF component of BP variability, assessed by spectral analysis, has been proposed as a marker of sympathetic modulation of peripheral circulation in normal and pathologic conditions.\(^{9–11,13}\) Moreover the short-term BP variance (total power) during tilt seems to be closely related to sympathetic drive.\(^{25}\) Therefore, our data suggest that sympathetic modulation of BP is reduced in young TM patients. Furthermore, the LF/HF ratio of HR variability is reduced in TM patients compared to normals, as well as its physiologic increase after passive tilt, suggesting an impairment of sympathovagal balance.

These findings could be explained by the expansion of blood volume that follows the transfusion: in fact our patients underwent RR and BP recording 2 to 5 days after transfusion (mean hemoglobin levels 12.5 g/dL) and an inverse relationship was found between the LF/HF ratio of RR variability and hemoglobin levels. Thus, these data could suggest that increased blood volume stimulates thorax mechanoreceptors leading to a reduced sympathetic activity.
However, according to previous studies\textsuperscript{22,24,26} PRA and aldosterone plasma levels, while normal, were higher than in normal controls in the supine position. These findings not only argue against a transfusion-related blood volume expansion, but even suggest volume depletion, further emphasizing the inappropriate nature of the lower norepinephrine plasma levels found in the TM patients. Altogether, these hormonal measurements powerfully support the relevance of our spectral analysis results in these TM patients.

Elevated blood pressure values after blood transfusions, associated to convulsions and cerebral hemorrhages (HCC syndrome) have been reported in \( \beta \)-thalassemic patients as well as in sickle cell anemia patients and were related to expansion of blood volume.\textsuperscript{27–29} Moreover, Spirito et al\textsuperscript{30} demonstrated that in a preclinical phase of cardiac involvement, when symptoms of heart failure are absent and systolic function is normal, left ventricular diastolic filling is altered in patients with TM, reflecting an increase in left ventricular chamber stiffness. Our results could suggest that the suppression of sympathetic activity (likely by volume receptors stimulation) is a normal mechanism to control BP increase after blood transfusion in \( \beta \)-thalassemic patients; an impairment of this mechanism in a subgroup of patients with particularly increased ventricular chamber stiffness could lead to the elevated blood pressure levels of the HCC syndrome.

Moreover we found a normal baroreflex activity (assessed by \( \alpha \) index) in these patients. However, this result is not completely unexpected, considering the interactions between the cardiovascular reflexes. In fact, studies in anesthetized dogs have shown that the inhibitory influence of the cardiopulmonary receptors on the vasomotor center varies inversely with that of the arterial baroreceptors, therefore in this study population one should expect a reduced activity of the arterial baroreceptors.\textsuperscript{30,31}

In conclusion, in this group of young TM patients in a preclinical stage of heart disease, our data show abnormal 24-h BP and HR rhythms and a decreased short-term variability of BP and HR, in particular in the LF range, suggesting a diminished sympathetic activity. Further studies are needed to assess the prognostic significance of these findings and the role of cardiac volume mechanoreceptors in the development of BP and HR abnormalities.

REFERENCES


