Disorders of Hematopoiesis

Heart rate variability and ventricular late potentials in β-thalassemia major

Cardiac failure and sudden death, the latter probably due to arrhythmias, remain the major causes of death in β-thalassemia major (TM).[1] Many studies have shown that reduced heart rate variability (HRV), as well as the presence of ventricular late potentials (VLP) are associated with a higher risk of ventricular arrhythmias and sudden cardiac death in heterogeneous populations of patients, independently of other risk factors.[2-3]

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The purpose of the present study was to evaluate HRV and the incidence of VLP in a group of patients with TM in a preclinical phase of cardiac involvement. Nineteen patients (12 males9 with a mean age of 18.4±8.3 years and a body mass index (BMI) of 20.1±1.7 Kg/m^2 with hematologic evidence of TM (homozygous form) were studied. They were free of cardiovascular disease as assessed by clinical history, basal and stress electrocardiography (ECG), and echocardiography. They all showed normal left ventricular end-diastolic cavity dimensions (≤ 53 mm) and systolic fractional shortening (≥ 30%). Moreover, none of them was taking antiarrhythmic agents or cardiovascular drugs. Patients with complete or incomplete bundle branch block on superficial ECG or with a history of myopericarditis during their life were excluded. Additionally, 19 matched healthy volunteers (12 males) with a mean age of 19.1±7.5 years and BMI of 20.2±2.5 Kg/m^2) were recruited to form the control group. The study protocol was approved by the Ethics Committee of the University of Pisa, and all subjects or their relatives gave written consent to the study. Patients and controls underwent 24-hour Holter monitoring and signal-averaged ECG. Holter tapes were analyzed to measure HRV in the time and frequency domains, as an index of sympatho-vagal balance, and to assess the incidence of ventricular arrhythmias (Lown scoring system). Three signal-averaged ECG parameters were examined and compared between groups. VLP were considered to be present if the following parameters were present: (a) filtered QRS complex: >114 ms, (b) the duration of the terminal QRS of low amplitude signal <40 μV (LAS) >38 ms, and (c) the root-mean-square of the terminal 40 ms (RMS40): <20 μV. Differences in characteristics between groups were compared by ANOVA analysis. Differences in characteristics within the TM group were compared by the unpaired t-test. Results were considered statistically significant when p <0.05.

Time and frequency domain HRV parameters were significantly lower in the TM group than in the control group (p <0.001 for all) (Table 1). Using the aforementioned criteria, VLP were absent in all the control subjects, while they were present in 6/19 (31.5%) of the TM patients (Table 1). Comparing the subgroup of TM patients with VLP with the subgroup without VLP, patients who had VLP showed a higher incidence of ventricular ectopic beats with some episodes of non-sustained ventricular tachycardia (p <0.0001) on their Holter recordings. Four patients exhibited episodes of non-sustained ventricular tachycardia (from 3 to 12 beats) (Table 2), whereas none of the control subjects showed significant arrhythmias.

Table 1. HRV and signal-averaged ECG results in the β-thalassemia major (TM) group and the control group (mean±SD).

Characteristic	*TM*	*Control*
Mean RR (ms)	785±97†	914±104
SDNN (ms)	98.9±13.3‡	171.7±44.1
SDANN (ms)	86.7±23.2‡	149.3±41.5
rMSSD (ms)	23.9±10.7‡	48.3±8.9
pNN50 (%)	4.8±3.1‡	20.5±6.8
LF (ms^2)	549±173‡	1573±424
HF (ms^2)	129±18‡	402±37
LF/HF ratio	4.2±1.2	3.91±0.5
Filtered QRS duration (ms)	108.8±16.5†	92.5±6.3
LAS (ms)	36.4±11.3‡	21.5±4.2
RMS40 (μV)	25.4±12.5‡	54.2±15
VLP+	6/19‡	0/19

SDNN: standard deviation of all RR intervals; SDANN: standard deviation of 5 minute mean values of RR; rMSSD: root mean square of successive difference of RR; pNN50: percent of successive RR differences >50 ms for each 5-minute interval. LF: low frequency power; HF: high frequency power. †p<0.01; ‡p<0.001 vs control group.

Table 2. Characteristics of patients with and without ventricular late potentials (VLP) (mean±SD).

	With VLP	*Without VLP*
N. of subjects	6	13
Age (years)	19.4±5.2	18.7±8.2
Sex (M/F)	6/0	6/7
End-diastolic diameter (cm)	4.65±0.21	4.71±0.11
Ejection fraction (%)	67.9±5.1	67.2±4.3
Fractional shortening (%)	38.5±2.9	38.8±4.1
Hemoglobin	12.5±0.5	12.3±0.5
Serum ferritin	2098.4±881.2	2115±1008.5
Non-sustained ventricular tachycardia	4‡	0
SDNN (ms)	85.9±17.2	87.5±15.3
rMSSD (ms)	22.5±8.6	25±9.4
LF/HF ratio	4.4±0.6	4.1±0.8
Filtered QRS duration (ms)	124.4±5.2‡	95.6±10.4
LAS (ms)	47.5±4.3‡	29.6±8.1
RMS40 (μV)	12±5.2‡	32.7±7.3

‡p<0.z001 vs without VLP. Abbreviations as for Table 1.

The main findings of the present study were that patients with TM, even without clinical signs of cardiac functional involvement, have reduced HRV and an increased incidence of VLP, associated with some non-sustained ventricular tachycardia.

The reduced HRV, expression of impaired sympatho-vagal

activity, may be explained, as in other forms of anemia,[4,5] by the chronic anemia that characterizes TM, which may lead to a persistent, appropriate sinus tachycardia and a sustained decrease in autonomic fluctuations. Additionally, the expansion of blood volume during transfusion could represent an uncontrolled stimulation of cardiac receptors with sympathetic afferents, leading to a further decrease in vagal modulation of heart rate.[6] Of interest, we recorded VLP in 31.5% of TM patients, which is well above the prevalence reported in normal subjects (0-7%).[7] This result may be explained by intracellular iron deposition and myocardial fibrosis, which may create heterogeneous ventricular depolarization,[8] and could lead to abnormal excitability of iron-loaded heart cells.[9,10] The higher incidence of ventricular arrhythmias that we observed in patients with VLP demonstrates the usefulness of signal-averaged ECG in identifying those patients who have an increased risk of potentially malignant arrhythmias.[11,12]

No relationship was found between signal-averaged ECG parameters and hematologic data. This could be explained by a small amount of storage proteins in the heart cells, or greater sensitivity to iron-induced oxygen free radicals. Thus, the presence of VLP appears to be a critical component of the arrhythmogenesis rather than a reflection of the severity of the disease. The comparison of TM patients with healthy control individuals may represent a limitation of this study. Further investigations in a large cohort of TM patients might confirm the prognostic value of these parameters.

In conclusion, analysis of HRV and VLP may be helpful in TM patients by detecting an underlying electrophysiologic substrate predisposing to arrhythmias. Naturally, this needs confirmation from both larger prospective and electrophysiologic studies.

Ferdinando Franzoni, Fabio Galetta,* Carmine Di Muro,* Giuliana Buti,° Ferdinando Pentimone* Gino Santoro**

**Department of Internal Medicine; °Department of Pediatry, University of Pisa, Italy*

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Correspondence: Fabio Galetta, MD, Department of Internal Medicine, University of Pisa School of Medicine, via Roma 67, 56126 Pisa, Italy. Phone: international +39.050.993373. Fax: international +39.050.553414. E-mail: fgaletta@med.unipi.it

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Cytokines

Circulating levels and promoter polymorphisms of interleukins-6 and 8 in pediatric cancer patients with fever and neutropenia

We evaluated interleukin (IL)-6 and IL-8 as early markers of serious infection in febrile neutropenic children and found that both molecules had limited diagnostic value. Although the promoter polymorphisms IL-6 G-174C and IL-8 A-251T influence serum concentrations of the respective cytokines, genotyping for these polymorphisms does not improve the diagnostic value of IL-6 and IL-8 measurements.

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Several small studies[1-5] suggest that the assessment of interleukin (IL)-6 and IL-8 concentrations at the time of admission is a valuable tool for predicting serious infection in febrile neutropenic cancer patients. Since serum levels of both cytokines are influenced by known promoter polymorphisms,[6,7] we evaluated whether genotyping of IL-6 and IL-8 promoter polymorphisms improves the diagnostic value of these cytokines.

IL-6 and IL-8 concentrations were measured in duplicate by ELISA (R&D) in children with febrile neutropenia (>38.5°C, absolute neurophil count (ANC) ≤500/μL) at the time of admission and 24 hours later. Children with fever for longer than 24 hours prior to admission were excluded. Febrile episodes were classified as bacteremia with Gram-negative or Gram-positive organisms, microbiologically or clinically documented localized infection, pneumonia or fever without an identifiable source (FUO).

Genomic DNA isolated from peripheral blood was used for genotyping the promoter polymorphisms IL-6 G-174C