Am J Cardiovasc Dis 2021;11(3):391-397
www.AJCD.us /ISSN:2160-200X/AJCD0134554

Original Article

Evolution of electrocardiographic abnormalities and arrhythmias in adult patients with beta-thalassemia major during a short-term follow-up

Marios Kolios[1], Tong Liu[2], Antonios P Vlahos[3], Eleni Kapsali[4], Panagiotis Korantzopoulos[1]

[1]First Department of Cardiology, Faculty of Medicine, University of Ioannina, Ioannina, Greece; [2]Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin, China; [3]Department of Pediatric Cardiology, Faculty of Medicine, University of Ioannina, Ioannina, Greece; [4]Department of Hematology, Faculty of Medicine, University of Ioannina, Ioannina, Greece

Received April 22, 2021; Accepted June 8, 2021; Epub June 15, 2021; Published June 30, 2021

Abstract: Objective: Adult beta-thalassemia major (TM) patients exhibit electrocardiographic abnormalities and cardiac autonomic dysfunction. We aimed to investigate the evolution of electrocardiographic abnormalities and arrhythmias in TM patients during a 12-month follow-up period. Methods: Forty-seven adult TM patients (median age: 36 years, 57% men) without overt heart failure were studied. We examined 12-lead electrocardiograms, 24-hour electrocardiographic Holter recordings, and treadmill exercise stress tests at baseline and after 12 months. Conventional electrocardiographic measurements, as well as contemporary indexes of depolarization and repolarization/dispersion of repolarization (QRS fragmentation; T peak-to-end; T peak-to-end/QT) were assessed. Moreover, we examined markers of autonomic dysfunction such as heart rate variability, and heart rate recovery after exercise testing. Results: The electrocardiographic markers of atrial/ventricular depolarization and repolarization, as well as indexes of autonomic imbalance, were not significantly changed. However, the recorded supraventricular ectopic beats increased significantly. Paroxysmal atrial fibrillation (PAF) detection was greater in 12 months (4/47 at baseline vs. 8/47 at 12 months; P=0.38). However, 5/8 patients who were diagnosed with PAF at the second examination did not have the arrhythmia at the initial evaluation. Thus, PAF was present in a total of 9/47 (19%) TM patients. Notably, 3/9 of the patients were asymptomatic. The mean duration of PAF was 5±2 minutes and the mean number of these episodes was 8±2. Conclusion: TM patients have repolarization and autonomic function abnormalities that do not significantly change during a 12-month follow-up period. However, supraventricular ectopy and AF burden further evolve.

Keywords: Beta thalassemia, arrhythmic indexes, electrocardiographic abnormalities, supraventricular ectopy, atrial fibrillation

Introduction

Beta-thalassemia is the commonest hereditary hemoglobinopathy and is associated with reduced or absent synthesis of beta globin chains. In beta thalassemia major (TM) the complete absence of beta globin moieties leads to significantly reduced hemopoiesis and poses the need for frequent blood transfusions enhancing the risk of iron-induced toxicity. Indeed, this condition is associated with marked cardiac morbidity and mortality in the long-term [1, 2]. Electrocardiographic (ECG) and arrhythmic abnormalities are not uncommon in TM patients, especially in the setting of inadequate chelation and in the presence of congestive heart failure [3-5]. Notably, several ECG abnormalities can occur in TM patients before the advent of TM-induced cardiomyopathy. These include T wave abnormalities, ST interval changes, QT interval prolongation, conduction disturbances, and others [4]. With regard to arrhythmias, atrial fibrillation (AF), atrial flutter, and atrial tachycardias are not uncommon even in TM patients without overt heart disease while ventricular arrhythmias are more frequent in

cases with advanced iron cardiotoxicity [4, 5]. In a previous study we demonstrated that TM patients with preserved left ventricular ejection fraction (LVEF) exhibit various ECG abnormalities, including abnormalities in ventricular depolarization and repolarization [6]. Also, abnormal autonomic parameters were evident in 24-hour ECG monitoring as well as in the recovery phase of the exercise testing [6]. In this report, we provide data on these parameters and on arrhythmia occurrence, after a 12-month follow-up period of our TM patients cohort. Of note, there are no data in the literature regarding the evolution of ECG abnormalities and arrhythmias in TM over time.

Patients and methods

Study population and examinations

The population and the methodology of this study were clearly described in our previous study [6]. Specifically, consecutive adult patients with TM were screened (from January 2013 to January 2015). All TM patients were studied in the Department of Hematology (Thalassemia Unit) of our tertiary Academic center, and they were following a regular blood transfusion and iron chelation program. Our patients were studied at baseline and 12 months after the initial evaluation. Exclusion criteria were left ventricular systolic dysfunction, persistent or permanent AF, electrolyte abnormalities, end-stage renal disease, acute or recent infectious disease, liver failure, cancer of hematologic dyscrasia, thyroid abnormalities, chronic inflammatory diseases, antiarrhythmic drug use, use of QT-prolonging drugs, and neurological or musculoskeletal diseases making the accomplishment of a treadmill exercise test unfeasible. A written informed consent was obtained from all patients whereas the Hospital Ethics Committee gave approval to the study protocol (University Hospital of Ioannina Scientific and Ethics Committee-Approval number 10782/15-04-2013).

Demographic (age, sex, height, weight), clinical (medical history parameters), echocardiographic, and ECG parameters were recorded at baseline and after a 12-month follow-up period. All examinations were performed while the patients were in stable condition, 4-8 days after the last red blood cell transfusion (patients were being transfused every 10-15 days). A transthoracic echocardiographic examination was performed in each patient using a GE Vivid 7 ultrasound machine (San Jose, CA, USA). The LVEF was calculated by the Simpson's method. Left atrial (LA) diameter was determined from the parasternal long-axis view at end-systole while LA volume was calculated using the biplane Simpson's method. A 12-lead electrocardiogram (ECG) was also performed at a paper speed of 25 mm/sec. Baseline electrocardiographic parameters were blindly measured by an experienced arrhythmia specialist (P.K.). In specific, all ECGs were scanned and measured using a specific computer program (Cardio Calipers, Iconico.com, NY, USA). QT interval was assessed as the time between the first deflection of QRS and the point of return of the T wave to the isoelectric line. Modern indexes of dispersion of the ventricular repolarization were also assessed. Specifically, the Tpe interval was calculated as QT-QTpeak. The QT interval was measured in as many of the 12 leads as possible, while the T peak-to-end (Tpe) interval was assessed in leads II, V2, V5 and the maximal value as well as the mean value were measured. The Tpe/QT ratio was calculated using the corresponding values from each lead. The measurements were obtained in three consecutive complexes of each lead and the resulting average value was finally accepted. In order to avoid diurnal variations, all procedures were performed during the same time interval (from 9.00 a.m. to 11.00 a.m.). The Tpe and QTc reported values were the maximum obtained ones. Given that Bazzett's formula is not reliable for rates <60/min or >100/min, the Hodges formula was used to calculate the QTc interval. The QRS was characterized as fragmented according to the standard electrocardiographic criteria.

All participants underwent 24-hour ECG Holter monitoring (Model: Braemar DXP1000 Series, Eagan, MN, USA). A detailed analysis of the 24-hour recordings was performed while the type of beats (normal, ectopic), noise, and artifacts were characterized. Besides classic electrocardiographic indexes, heart rate variability (HRV) parameters and arrhythmia episodes were carefully analyzed. Abnormal beats and artifacts were deleted before HRV analysis. HRV was assessed in the time domains. Time domain analysis indexes included standard deviation of the R-R intervals during the entire

Table 1. Variation of the clinical and echocardiographic characteristics in the studied population

Thalassemia Patients (N=47)	Baseline	12 Months	*P*-value
BMI (kg/m^2)	22.8±3	21.1±4	0.81
Hypertension, n (%)	1 (2%)	1 (2%)	1
Diabetes, n (%)	5 (11%)	5 (11%)	1
Dyslipidemia, n (%)	0 (0%)	0 (0%)	1
History of paroxysmal AF	3 (6%)	3 (6%)	1
Current Smokers, n (%)	9 (19%)	9 (19%)	1
Systolic blood pressure (mmHg)	116±16	110±14	0.85
Hemoglobin (gr/dl)	9.7 [9-10.1]	10 [9.1-10.8]	0.77
Ferritin	1,280 [710-1705]	1,150 [770-1800]	0.81
Creatinine (mg/dl)	0.9 [0.8-1]	0.85 [0.6-1.1]	0.37
Creatinine clearance (ml/min)	89 [69-105]	100 [85-115]	0.01
LVEF (%)	56 [54-62]	57 [54-64]	0.78
LA diameter (mm)	36 [31-39]	36 [31-40]	0.86
LA volume (ml)	59 [43-72]	57 [37-67]	0.66
PASP (mmHg)	30 [15-37]	32 [15-36]	0.90

AF: atrial fibrillation; BMI: body mass index; LA: left atrial; LVEF: left ventricular ejection fraction; PASP: pulmonary artery systolic pressure.

24-hour recording (SDNN), average of the standard deviation of all 5-min R-R intervals (ASDNN5), standard deviation of all 5-min mean R-R intervals (SDANN5), and square root of mean squared differences of successive R-R intervals (RMSSD). Paroxysmal AF was defined as an episode of irregular R-R intervals without visible P waves lasting at least 30 seconds with spontaneous restoration of sinus rhythm. Finally, a treadmill exercise stress test according to the Bruce protocol was successfully performed by each participant in the morning hours. Heart rate recovery was defined as maximum heart rate at peak exercise minus heart rate at a specified time point after exercise.

Statistical analysis

The continuous variables are presented as mean ± SD, or as median [25th-75th percentile] if did not follow a normal distribution. The Kolmogorov-Smirnov test was used for the examination of normality. The continuous variables were compared by the paired Student's t-test or the non-parametric Wilcoxon signed-rank test, as appropriate. The categorical variables are expressed as frequencies and compared with the use of McNemar's test. A two-tailed *P* value <0.05 was considered significant. The SPSS software (version 21.0; SPSS Inc., Chicago, Illinois) was used for the aforementioned analyses.

Results

The studied cohort consisted of 47 TM patients; median age 37 [33-44] years; 28 (59%) males. All patients successfully underwent the 12-month follow-up and they successfully repeated the baseline diagnostic examinations and tests. The clinical and echocardiographic parameters of the TM patients were comparable between baseline and follow-up, apart from a significant improvement in the estimated creatinine clearance (**Table 1**). The ECG markers of atrial and ventricular depolarization and the markers of ventricular repolarization/repolarization heterogeneity were not significantly altered during the 12-month follow-up period (**Table 2**).

Of note, the number supraventricular ectopic beats in the 24-hour Holter recordings were significantly increased (**Table 3**). No significant variation was evident in the detection of PAF (4/47 at baseline vs. 8/47 at 12 months; P= 0.38) (**Table 3**). However, 5/8 patients that had PAF at the second evaluation did not have the arrhythmia at the initial screening. Thus, in total 9/47 (19%) of TM patients had evidence of PAF whereas one third of the patients had clinically silent PAF. The mean duration of PAF was 5±2 minutes while the mean number of AF episodes was 8±2. It should be noticed that no patient was taking a b-blocker or any antiar-

Table 2. Variation of electrocardiographic characteristics

Thalassemia Patients (N=47)	Baseline	12 Months	*P*-value
Heart rate (bpm)	80 [72-85]	76 [71-81]	0.223
P duration (ms)	80 [70-100]	78 [60-100]	0.667
PR interval (ms)	160 [140-170]	150 [135-170]	0.377
QRS duration (ms)	100 [90-102]	90 [88-92]	0.380
Sokolov index (mm)	24 [21-31]	23 [19-28]	0.420
QRS fragmentation	11/47	11/47	1
QTc (msec)	410 [381-413]	424 [395-432]	0.249
QT dispersion	18 [10-20]	17 [11-19]	0.670
Tpe (msec)	60 [58-70]	60 [50-70]	0.491
Tpe/QT mean	0.15 [0.13-0.16]	0.16 [0.14-0.19]	0.552
Tpe/QT max	0.18 [0.16-0.19]	0.18 [0.15-0.19]	0.770

Tpe: T peak-to-end interval.

rhythmic drug during the study period. Given that none of the 9 patients had CHA_2DS_2VASc score >1, no anticoagulation treatment was advocated. Finally, the indexes of autonomic imbalance both in the 24-hour Holter recordings and in the recovery phase of the exercise test were not significantly changed (**Tables 2**, **4**).

Discussion

We demonstrated that the ECG and autonomic function abnormalities in TM patients with preserved LVEF do not progress significantly over a 12-month follow-up period. However, the supraventricular ectopy burden was significantly increased while more patients proved to have PAF during the follow-up. Thus, in total one fifth of patients had PAF in the 24-hour Holter recordings while one third of these episodes were asymptomatic. It is therefore tempting to speculate that longer and/or more frequent ECG monitoring may offer a greater diagnostic yield in terms of arrhythmia detection.

In this study we investigated plenty of electrocardiographic indexes as well as arrhythmic events detected by Holter monitoring in a well-defined cohort of TM patients without systolic heart failure. Furthermore, for the first time we examined the results of exercise stress testing in all participants focusing on heart rate recovery, a novel marker of autonomic dysfunction. In fact, recent reports examined ECG abnormalities and arrhythmic risk indexes in the setting of TM [4, 5]. We have previously shown that TM patients have important differences in arrhythmic indexes compared to age- and sex-matched healthy control subjects [6]. In specific, these patients have prolonged QTc intervals whereas they have increased markers of heterogeneity of the ventricular repolarization including QT dispersion, and T peak-to-end/QT ratios [6]. Moreover, our patients exhibited decreased markers of heart rate variability whereas the heart rate recovery values were significantly attenuated compared to control subjects [6]. In addition, increased P wave duration and QRS duration were observed while QRS fragmentation was more frequent. Most of these abnormalities have been related to increased arrhythmic risk and mortality in the setting of underlying cardiac diseases, and in the general population as well [7-11]. However, the aforementioned ECG abnormalities did not show significant variation during the 12-month period of follow-up. Possibly, the duration of follow-up was relative short in order to detect a significant change.

In fact, TM is related to significant cardiovascular morbidity and mortality while arrhythmic burden has been recently implicated in these unfavorable outcomes. Specifically, the regular blood transfusions as well as the increased hemolysis and iron absorption lead to iron-mediated cardiac toxicity [5, 12, 13]. Indeed, iron accumulation exerts deleterious effects caused by non-bound labile iron (Fenton reactions producing hydroxyl radicals) [13, 14]. The resulting iron-induced oxidative stress causes cellular and cardiac injury as well as inflammation, ion channel dysregulation, and abnormal calcium handling [5, 12-14]. Regardless of the presence or not of cardiomyopathy, iron-mediated injury facilitates the development of arrhythmias [12, 13]. However, the arrhythmic burden increases as the myocardial function worsens over time [12, 13].

Remarkably, AF is highly prevalent in adult TM patients ranging between 10% and 34%, depending on the studied population and the monitoring method used [14, 15]. The increased prevalence of AF in TM could be attributed

Table 3. Variation of 24-hour Holter recording parameters in the studied population

Thalassemia Patients (N=47)	Baseline	12 Months	*P*-value
Minimum heart rate (bpm)	53 [45-59]	52 [47-61]	0.91
Maximum heart rate (bpm)	142 [129-152]	138 [122-150]	0.87
QTc (msec)	430 [407-445]	424 [390-440]	0.70
QT dispersion	204 [162-230]	206 [168-240]	0.92
SDNN	123 [97-144]	129 [95-161]	0.30
ASDNN5	54 [42-64]	56 [42-70]	0.57
SDANN5	109 [82-125]	105 [80-122]	0.80
RMSSD	37 [32-55]	35 [31-54]	0.76
Supraventricular extra beats/24 h	17 [3-96]	33 [22-144]	0.01
Ventricular extra beats/24 h	2 [1-10]	4 [2-13]	0.75
Non sustained ventricular tachycardia, no. of patients (%)	2 (4%)	3 (6%)	1
Paroxysmal atrial fibrillation, no. of patients (%)	4 (8.5%)	8 (17%)	0.38

Table 4. Treadmill exercise stress test parameters variation in the studied population

Thalassemia Patients (N=47)	Baseline	12 Months	*P* value
Duration (min)	8.56 [6.47-10.01]	9.10 [7-10.40]	0.34
METs	9.8 [8.2-11.6]	10 [8.5-12.2]	0.49
HRR1	30 [21-36]	29 [15-34]	0.77
HRR2	59 [52-69]	60 [55-70]	0.61
HRR3	67 [66-67]	65 [64-67]	0.88
HRR6	75 [66-83]	75 [65-79]	0.79

HRR: heart rate recovery [HR at peak exercise-HR at a specific time point at the recovery phase (minute after exercise cessation)]; MET: metabolic equivalent.

to atrial structural and electrical remodeling along with autonomic disturbances [14, 15]. Indeed, atrial electrical and structural alterations reflected by increased P wave duration, P wave dispersion, and atrial electromechanical delay, have been related to paroxysmal AF in TM patients [16-18]. It has also been indicated that P wave dispersion is related to cardiac iron overload as assessed by cardiac magnetic resonance (CMR) [16]. Consequently, iron accumulation seems to play a significant role in atrial structural and electrophysiological remodeling, promoting AF.

Supraventricular ectopy represents a triggering factor for AF and, apart from new-onset AF [19], it is related to unfavorable outcomes such as stroke and all-cause mortality [20]. Moreover, autonomic dysfunction seems to play an important role in the genesis and perpetuation of arrhythmias. Indeed, attenuated HRV has been demonstrated in TM patients [6, 21, 22]. Notably, it has been shown that these autonomic dysregulations are not associated with biochemical and CMR indexes of iron accumulation [21, 22]. Furthermore, we have demonstrated that heart rate recovery after treadmill exercise testing is significantly attenuated in TM patients [6]. We have also shown that premature atrial extra beats and PAF episodes were more prevalent in TM subjects compared to controls [6]. In the present study we report that, in this cohort of stable TM patients who were reevaluated 12 months after the baseline evaluation, the supraventricular ectopy burden and the AF burden were further evolved. Notably, no study to date has examined serial electrocardiographic and arrhythmic parameters changes in a particular TM population. Very recently, Patsourakos et al. reported a case-control study indicating an increased prevalence of PAF (10.6%), prolonged PR interval (17%), and positive late potentials (38.3%) in TM patients compared to controls [23]. During a clinical follow-up period of one year, the authors reported only one patient with known PAF who became symptomatic and developed severe conduction abnormalities leading to implantation of a permanent pacemaker [23]. No data on repeat measurements of ECG parameters in the 47 TM patients during this follow-up period were provided [23]. Considering the longer survival of TM patients in the contemporary era, the increased burden of AF may have significant clini-

cal implications. It is tempting to speculate that early identification of arrhythmic risk markers might facilitate the early implementation of specific diagnostic and therapeutic procedures.

Some limitations should be acknowledged. Firstly, the study population was small. However, the design of the study and the strict inclusion and exclusion criteria offer a good level of reliability. Moreover, most of the published studies in this area have included a small number of participants. Secondly, specific data on cardiac iron status are not provided. It should be noted that at the time of patients' baseline evaluation and during follow-up there was no center providing CMR imaging in our isolated region of Northwestern Greece. Regardless of the status of cardiac iron accumulation, the merit of ECG abnormalities and arrhythmic burden in TM patients without overt heart failure cannot be disputed. Finally, we must admit that the duration of ECG monitoring was quite short. Indeed, longer and/or more frequent monitoring with external loop recorders or implantable loop recorders may have revealed a greater arrhythmia burden.

Conclusion

TM patients without overt heart failure exhibit ECG repolarization and autonomic function disturbances that do not significantly change during a short-term follow-up period. However, supraventricular ectopy and the AF burden in this population seems to be considerable and evolves over a short period of time (12 months) while a significant number of these episodes are asymptomatic. Therefore, a close follow-up regarding arrhythmia detection appears to be imperative. Undoubtedly, studies with a longer follow-up and more intensive ECG monitoring may further elucidate the exact burden and the prognostic impact of specific ECG and arrhythmic indexes in this setting.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Panagiotis Korantzopoulos, First Department of Cardiology, Faculty of Medicine, University of Ioannina, Ioannina, Greece. E-mail: p.korantzopoulos@yahoo.gr

References

[1] Walker JM. Thalassaemia major and the heart: a toxic cardiomyopathy tamed? Heart 2013; 99: 827-834.
[2] Auger D and Pennell DJ. Cardiac complications in thalassemia major. Ann N Y Acad Sci 2016; 1368: 56-64.
[3] Mancuso L, Mancuso A, Bevacqua E and Rigano P. Electrocardiographic abnormalities in thalassemia patients with heart failure. Cardiovasc Hematol Disord Drug Targets 2009; 9: 29-35.
[4] Russo V, Rago A, Papa AA and Nigro G. Electrocardiographic presentation, cardiac arrhythmias, and their management in β-thalassemia major patients. Ann Noninvasive Electrocardiol 2016; 21: 335-342.
[5] Russo V, Melillo E, Papa AA, Rago A, Chamberland C and Nigro G. Arrhythmias and sudden cardiac death in beta-thalassemia major patients: noninvasive diagnostic tools and early markers. Cardiol Res Pract 2019; 2019: 9319832.
[6] Kolios M, Korantzopoulos P, Vlahos AP, Kapsali E, Briasoulis E and Goudevenos JA. Electrocardiographic abnormalities and arrhythmic risk markers in adult patients with beta thalassemia major. Int J Cardiol 2016; 221: 932-936.
[7] Mozos I and Caraba A. Electrocardiographic predictors of cardiovascular mortality. Dis Markers 2015; 2015: 727401.
[8] Desai AD, Yaw TS, Yamazaki T, Kaykha A, Chun S and Froelicher VF. Prognostic significance of quantitative QRS duration. Am J Med 2006; 119: 600-606.
[9] Jain R, Singh R, Yamini S and Das MK. Fragmented ECG as a risk marker in cardiovascular diseases. Curr Cardiol Rev 2014; 10: 277-286.
[10] Zhang Y, Post WS, Blasco-Colmenares E, Dalal D, Tomaselli GF and Guallar E. Electrocardiographic QT interval and mortality: a meta-analysis. Epidemiology 2011; 22: 660-670.
[11] Qiu S, Cai X, Sun Z, Li L, Zuegel M, Steinacker JM and Schumann U. Heart rate recovery and risk of cardiovascular events and all-cause mortality: a meta-analysis of prospective cohort studies. J Am Heart Assoc 2017; 6: e005505.
[12] Lekawanvijit S and Chattipakorn N. Iron overload thalassemic cardiomyopathy: iron status assessment and mechanisms of mechanical and electrical disturbance due to iron toxicity. Can J Cardiol 2009; 25: 213-218.
[13] Berdoukas V, Coates TD and Cabantchik ZI. Iron and oxidative stress in cardiomyopathy in thalassemia. Free Radic Biol Med 2015; 88: 3-9.

[14] Barbero U, Fornari F, Guarguagli S, Gaglioti CM, Longo F, Doronzo B, Anselmino M and Piga A. Atrial fibrillation in β-thalassemia major patients: diagnosis, management and therapeutic options. Hemoglobin 2018; 42: 189-193.
[15] Nomani H, Bayat G, Sahebkar A, Fazelifar AF, Vakilian F, Jomezade V, Johnston TP and Mohammadpour AH. Atrial fibrillation in β-thalassemia patients with a focus on the role of iron-overload and oxidative stress: a review. J Cell Physiol 2019; 234: 12249-12266.
[16] Russo V, Rago A, Pannone B, Di Meo F, Papa AA, Mayer MC, Spasiano A, Russo MG, Golino P, Calabrò R and Nigro G. Early electrocardiographic evaluation of atrial fibrillation risk in beta-thalassemia major patients. Int J Hematol 2011; 93: 446-451.
[17] Russo V, Rago A, Pannone B, Papa AA, Mayer MC, Spasiano A, Calabro R, Russo MG and Gerardo N. Atrial fibrillation and beta thalassemia major: the predictive role of the 12-lead electrocardiogram analysis. Indian Pacing Electrophysiol J 2014; 14: 121-132.
[18] Rago A, Russo V, Papa AA, Ciardiello C, Pannone B, Mayer MC, Cimmino G and Nigro G. The role of the atrial electromechanical delay in predicting atrial fibrillation in beta-thalassemia major patients. J Interv Card Electrophysiol 2017; 48: 147-157.
[19] Prasitlumkum N, Rattanawong P, Limpruttidham N, Kanitsoraphan C, Sirinvaravong N, Suppakitjanusant P, Chongsathidkiet P and Chung EH. Frequent premature atrial complexes as a predictor of atrial fibrillation: systematic review and meta-analysis. J Electrocardiol 2018; 51: 760-767.
[20] Huang BT, Huang FY, Peng Y, Liao YB, Chen F, Xia TL, Pu XB and Chen M. Relation of premature atrial complexes with stroke and death: systematic review and meta-analysis. Clin Cardiol 2017; 40: 962-969.
[21] Rutjanaprom W, Kanlop N, Charoenkwan P, Sittiwangkul R, Srichairatanakool S, Tantiworawit A, Phrommintikul A, Chattipakorn S, Fucharoen S and Chattipakorn N. Heart rate variability in beta-thalassemia patients. Eur J Haematol 2009; 83: 483-489.
[22] Alp A, Ozdogan O, Guloglu CC, Turker M and Atabay B. Heart rate variability in β-thalassaemia major with or without cardiac siderosis. Cardiol Young 2014; 24: 263-267.
[23] Patsourakos D, Gatzoulis KA, Aggeli C, Delicou S, Dimitroglou Y, Xydaki K, Toutouzas K, Androulakis A and Tousoulis D. Twelve-lead and signal-averaged electrocardiographic parameters among beta-thalassemia major patients. J Arrhythm 2020; 36: 920-928.