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Prospective risk stratification of sudden cardiac death in Marfan's syndrome

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ABSTRACT

Background: Marfan syndrome (MFS) is a variable, autosomal-dominant disorder of the connective tissue. In MFS serious ventricular arrhythmias and sudden cardiac death (SCD) can occur. The aim of this prospective study was to reveal underlying risk factors and to prospectively investigate the association between MFS and SCD in a long-term follow-up.
Methods: 77 patients with MFS were included. At baseline serum N-terminal pro-brain natriuretic peptide (NT-proBNP), transthoracic echocardiogram, 12-lead resting ECG, signal-averaged ECG (SAECG) and a 24-h Holter ECG with time- and frequency domain analyses were performed. The primary composite endpoint was defined as SCD, ventricular tachycardia (VT), ventricular fibrillation (VF) or arrhythmogenic syncope.
Results: The median follow-up (FU) time was 868 days. Among all risk stratification parameters, NT-proBNP remained the exclusive predictor (hazard ratio [HR]: 2.34, 95% confidence interval [CI]: 1.1 to 4.62, $p = 0.01$) for the composite endpoint. With an optimal cut-off point at 214.3 pg/ml NT-proBNP predicted the composite primary endpoint accurately (AUC 0.936, $p = 0.00046$, sensitivity 100%, specificity 79.0%). During FU, seven patients of Group 2 (NT-proBNP ≥ 214.3 pg/ml) reached the composite endpoint and 2 of these patients died due to SCD. In five patients, sustained VT was documented. All patients with a NT-proBNP < 214.3 pg/ml (Group 1) experienced no events. Group 2 patients had a significantly higher risk of experiencing the composite endpoint (logrank-test, $p < 0.001$).
Conclusions: In contrast to non-invasive electrocardiographic parameter, NT-proBNP independently predicts adverse arrhythmogenic events in patients with MFS.

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1. Introduction

The Marfan syndrome (MFS) is an autosomal-dominant inherited monogenic disorder of the connective tissue leading to an increased risk of cardiovascular manifestations like aortic root dilatation, aortic valve regurgitation, mitral valve prolapse (MVP) and mitral regurgitation [1]. The main cause of sudden death in MFS is aortic dissection [2], but recent data has shown that sudden cardiac death (SCD) might be an evident problem, too [3]. A recently published study identified ventricular ectopy as an independent risk factor for SCD in MFS [3]. However, actual and prospective data regarding further risk factors in MFS are not currently available. Thus, we performed a prospective cohort study to test the predictive value of various tools for SCD risk stratification in MFS.

2. Material and methods

2.1. Population

All consecutive patients with diagnosed MFS, seen at our Marfan Outpatient Clinic between January 2007 and December 2009, were enrolled. The study population comprises i.) patients who presented for annual follow-ups and ii.) new patients with clinical presentation of MFS. All patients were diagnosed in accordance with the revised Ghent criteria [4,5]. Survived SCD or known coronary artery disease were exclusion criteria for this study. The Hamburg research ethics committee approved the protocol. The study was conducted in accordance with the provisions of the Declaration of Helsinki and amendments. All subjects were informed individually and provided their informed consent in writing.

2.2. Baseline examination

At the baseline visit, clinical examination and patient interrogation were performed. For analysis of NT-proBNP, venous serum blood was collected after at least 30 min of supine rest from all patients. NT-proBNP was assayed on the Elecsys 2010 analyser (Roche Diagnostics, Mannheim, Germany) according to the manufacturer specifications.

2.3. FBN1 mutation analysis

All 65 coding exons and flanking intronic regions, including splice sites of the fibrillin-1 (FBN1) gene, were amplified by polymerase chain reaction (PCR) from

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genomic deoxyribonucleic acid (DNA). Primers were used, as published previously [6]. The PCR products were subsequently purified and sequenced with a Genetic Analyser (ABI 3130XL, Applied Biosystems Inc., Foster City, CA, USA). Deletions/duplications of one or more sequences in the FBN1 gene were detected with multiplex ligation-dependent probe amplification (MLPA) (SALSA® MLPA® kit, probemix P065, MRC Holland, Amsterdam, The Netherlands). Patients with transforming growth factor beta-receptors I and II (TGFBR1 and TGFBR2) gene mutation were excluded.

2.4. Transthoracic echocardiography

Two-dimensional, pulsed, colour-Doppler and colour tissue-Doppler images (TDI) were recorded through optimum parasternal, apical and sub-xiphoid views using an echocardiography system (iE33, Philips Medical Systems, Eindhoven, The Netherlands) equipped with a 4S probe. Four consecutive cardiac cycles were recorded for each parameter with breath held in expiration. An ECG was recorded simultaneously at a sweep speed of 100 mm/s. The measurements were performed off-line by using an ultrasound workstation (syngo 3.5, Siemens Medical Solutions, Erlangen, Germany). The aortic root diameter was obtained from 2D images using a leading edge to leading edge measurement of the maximum distance between the anterior root wall and the posterior aortic root wall at end diastole in a parasternal long-axis view [7]. In case of aortic root surgery the preoperative diameter were used. The left ventricular ejection fraction (LVEF) was calculated from apical two and four chamber 2D views using Simpson's rule [8]. Peak mitral flow velocity during rapid early filling (E) and early diastolic longitudinal motion of the mitral valve annulus (e′) were used to calculate the E/e′ ratio. Left ventricular diastolic function was classified as normal (E/e′ < 8; Grade I), mild (E/e′ = 8–15; Grade II) or moderate/severe (E/e′ > 15; Grade III) dysfunction [9].

2.5. Resting ECG and signal-averaged electrocardiography (SAECG)

The 12-lead resting ECG and the SAECG were recorded using a commercially available system (CS-200, Schiller Inc., Baar, Switzerland). Two hundred cardiac cycles recorded from the standard Frank orthogonal X, Y, and Z leads were averaged. Analogue to digital conversion was performed with a sampling rate of 2000 Hz and 16-bit accuracy. The signal was filtered with a 40 Hz bidirectional high-pass filter. The following SAECG parameters were calculated: (a) total duration of the filtered QRS complex (SAECG-QRS), (b) the root-mean-square voltage of the last 40 ms of the filtered QRS complex (RMS40) and (c) the duration of the low amplitude signals at the terminal portion of the QRS complex with values less than 40 μV (low amplitude signal (LAS)). The SAECG was considered to be abnormal if at least two of the following three criteria were met: (1) the filtered QRS complex is ≥114 ms, (2) ≤20 μV of signal in the RMS40, or (3) LAS ≥ 38 ms. Otherwise, the SAECG was classified as normal [10].

2.6. 24-h Holter ECG

All participants underwent a 24-h Holter ECG recording to assess basic rhythm, minimum, maximum and mean heart rate, premature atrial (PAC) and ventricular complexes (PVC), ventricular arrhythmia and heart rate variability (HRV). Holter ECG was performed on a high-resolution, 5-channel digitised recorder (Medilog AR12, Schiller Medilog Inc., Baar, Switzerland) with a sampling rate of 4096 Hz and a 16-bit accuracy.

Analysis of the Holter ECG recordings was performed by two experienced electrophysiologists (B.A.H., S.W.), who were blinded to the study population. The data was manually pre-processed before analysis with a semi-automatic software package (Medilog Darwin Holter Analysis, Schiller Medilog Inc., Baar, Switzerland) was performed. Recordings of sufficient signal quality and a minimum duration of at least 18 h were included in the analysis.

The time domain HRV indices were computed by using statistical methods according to the Task Force of The European Society of Cardiology [11] with the previously described semi-automatic Holter analysis software. The parameters SDNN (standard deviation of all NN intervals), SDNN index (mean of the standard deviations of all NN intervals for all 5 min segments of the entire recording), pNN50 (proportion of adjacent NN intervals differing by more than 50 ms during the 24-h recording) and RMSSD (square root of the mean of the sum squares of differences between adjacent NN intervals) were calculated using complex statistical time domain measurements. The circadian index (CI) was calculated as the ratio of the average heart rate during daytime and the average heart rate at night.

The frequency domain analysis of HRV included the total power [ms²], the power of the high frequency (HF) component (0.15–0.40 Hz) [ms²], the low frequency (LF) component (0.04–0.15 Hz) [ms²], and the very low frequency (VLF) component (0.003–0.04 Hz) [ms²]. The normalised HF power (HF norm = (HF power [ms²]/total power [ms²]) × 100), the normalised LF power (LF norm = (HF power [ms²]/total power [ms²]) × 100), and the LF/HF ratio = LF power [ms²]/HF power [ms²] were calculated subsequently.

2.7. Follow-up and endpoint

The composite primary endpoint was SCD, sustained ventricular tachycardia (VT), ventricular fibrillation (VF) or arrhythmogenic syncope. SCD was defined as either a witnessed cardiac arrest or death within one hour after the onset of acute symptoms, or an unexpected death in a patient known to have been well within the previous 24 h [12]. Sustained VT was defined as a regular broad-complex arrhythmia with a QRS width ≥ 120 ms and a duration ≥ 30 s. VF was defined as a grossly disorganised, rapid ventricular rhythm that varies in interval and waveform in the absences of QRS complexes. Arrhythmogenic syncope was defined as a Calgary Syncope Symptom Score-(CSSS)-Score < −2, as described previously [13]. All included patients were seen every six months during the follow-up (FU) in our MFS outpatient clinic. No patients were lost during follow-up.

Table 1
Univariate analysis for comparison between MFS patients.

	Composite endpoint not reached (n = 70)	Composite endpoint reached (n = 7)	p value
Age, years	36.1 (26.5–44.5)	50.1 (41.8–57.5)	0.075
NT-proBNP, pg/ml	94.5 (57.8–174.7)	1420.0 (229.3–3345.0)	0.007
Left ventricular ejection fraction, %	51.0 (41.0–56.0)	41.0 (35.0–42.0)	0.015
RMSSD, ms	39.6 (23.7–63.0)	69.2 (42.2–109.43)	0.026
Premature ventricular complexes	8.0 (2.5–61.0)	1196.0 (117.8–4843.0)	0.007
Ventricular tachycardia	0.0 (0.0–0.0)	2.0 (0.0–49.8)	<0.001
QTc interval, ms	414.5 (394.0–429.5)	417.5 (402.5–431.0)	0.64
QT dispersion, standard deviation, ms	13.6 (10.1–18.9)	13.9 (12.3–19.0)	0.57
E/e′ ratio	8.7 (6.7–11.0)	17.3 (9.3–22.0)	0.01
Left ventricular diastolic dysfunction Grade III	0.0 (0.0–0.0)	1.0 (0.0–1.0)	0.006
ß-blocking agents	1.0 (0.0–1.0)	1.0 (1.0–1.0)	0.86

NT-proBNP: N-terminal pro-brain natriuretic peptide; RMSSD: square root of the mean of the sum squares of differences between adjacent normal-to-normal (NN) intervals; E/e′ *ratio*: *ratio of* peak mitral flow velocity during rapid early filling (E) and early diastolic longitudinal motion of the mitral valve annulus (e′).

2.8. Statistical analysis

Numerical data is given as mean ± standard deviation (SD), or as median and 95% confidence interval (CI), where appropriate. In the univariate analysis, all variables were tested using the χ^2-test or Fisher exact t-test for categorical data and Student's t-test for continuous variables. Multivariate analysis by means of a Cox regression model was performed to identify significant and independent predictors of SCD and was presented as the hazard ratio (HR) and 95% CI. Independent variables were chosen for multivariate analysis when a p value < 0.05 emerged on univariate analysis. Variables in the initial model for SCD included Age, NT-proBNP, LVEF, RMSSD, PVC, VT, QTc interval, QT dispersion (standard deviation), E/e′ ratio, LV diastolic dysfunction Grade III and ß-blocking agent medication.

Receiver operator characteristic (ROC) analysis was performed to determine sensitivity and specificity of NT-proBNP in predicting SCD. Kaplan–Meier analysis was used for survival comparison between independent risk predictors identified by Cox regression analysis. A two-tailed p value of <0.05 was considered statistically significant. Statistical analysis was performed with a commercially available software package (PASW Statistics, Version 18, IBM SPSS Inc., Chicago, Illinois). ROC analysis and figures were generated using SigmaPlot (Version 12, Systat Software Inc., Chicago, Illinois).

3. Results

A total of 77 eligible patients (48.1% male, median age 37.9 years (27.0–45.4)) were enrolled. During a median follow-up (FU) time of 872.0 days (752.5–990.5), seven (9.1%) patients exhibited the composite endpoint. Two of these patients (2.1%) died due to sudden cardiac death. In both patients, post-mortem examination was performed and showed

Table 2
Multivariate Cox regression analysis of predictors of composite endpoint.

	Hazard ratio (HR)	95% confidence interval (CI)		p value
		Lower	Upper	
NT-proBNP	2.34	1.1	4.62	0.01
Left ventricular ejection fraction	1.76	0.24	12.99	0.54
RMSSD	1.07	0.88	1.25	0.44
Premature ventricular complexes	1.00	0.95	1.03	0.78
Ventricular tachycardia	1.39	0.76	2.53	0.32
Difference of Δ_{max}	1.22	0.75	1.9	0.51
E/e′ ratio	1.34	0.98	1.8	0.62
Left ventricular diastolic dysfunction Grade III	1.53	0.05	30.8	0.75

Abbreviations are the same as in Table 1.

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