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Diagnostic value of electrocardiographic (resting and 24-h Holter) monitoring in comparison with NT-proBNP in the differential diagnosis of patients with cardiogenic and neurogenic syncope

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SOUHRN

Kontext: Synkopa je důvodem pro 1–6 % hospitalizací. Evropské i americké doporučené postupy pro léčbu synkopy uvádějí dvanáctisvodový EKG záznam jako součást vyšetření všech pacientů s nevysvětlenou ztrátou vědomí.
Cíle: Cílem této studie bylo posoudit význam EKG, 24hodinového holterovského monitorování EKG a koncentrací N-terminálního fragmentu natriuretického propeptidu typu B (NT-proBNP) při rozlišování pacientů s kardiální a reflexně zprostředkovanou synkopou.
Metody: Za poslední tři roky jsme vyšetřili 100 pacientů (56 mužů) ve věku 18–77 let s reflexně zprostředkovanou nebo kardiální synkopou. Byly sledovány následující faktory: věk, pohlaví, systolický a diastolický tlak a přítomnost kardiovaskulárního onemocnění. Mimoto jsme hodnotili základní parametry klidového EKG záznamu a 24hodinového holterovského EKG monitorování a koncentrace NT-proBNP v diferenciální diagnostice synkopy.
Výsledky: Pacienti s reflexní synkopou byli mladší než pacienti s kardiální synkopou (44,4 ± 16,5 vs. 60,8 ± 12,6 roku; $p < 0,001$). Patologický klidový 12svodový EKG záznam byl častěji nalezen ve skupině s kardiogenním typem synkopy – 12 (24 %) vs. 8 (16 %). Čtyřiadvacetihodinové holterovské EKG monitorování neprokázalo statisticky významný rozdíl mezi oběma skupinami v minimální, průměrné a maximální srdeční frekvenci. Statisticky významné rozdíly mezi hodnocenými skupinami byly nalezeny ve výskytu komorových a supraventrikulárních arytmií. Pacienti s kardiální synkopou měli významně vyšší koncentrace NT-proBNP než pacienti s reflexně zprostředkovanou synkopou (448,7 ± 212,2 vs. 68,2 ± 64,1; $p < 0,0001$).
Závěry: U pacientů s kardiogenním mechanismem synkopy je přítomna zvýšená koncentrace NT-proBNP, přestože klidový EKG záznam nemá v tomto smyslu jednoznačně výpovědní hodnotu.

ABSTRACT

Background: Syncope is a cause of 1–6% of hospitalizations. Both European and American syncope guidelines recommend a 12-lead ECG as part of the evaluation of all patients with unexplained loss of consciousness.

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Objectives: The aim of this study was the assessment of the significance of ECG, Holter ECG and the concentration of NT-proBNP that would be useful in the differentiation of patients with cardiac and reflex syncope.
Methods: We investigated 100 patients (56 men), aged 18–77 years with reflex or cardiac syncope over the last 3 years. The following factors were investigated: age, sex, systolic and diastolic blood pressure, the presence of cardiovascular disease. Moreover, we assessed basic resting ECG parameters and 24-hour Holter ECG parameters, and NT-proBNP concentration in the differential diagnosis of syncope.
Results: Patients with reflex syncope were younger compared to patients with cardiac syncope (44.4 ± 16.5 vs. 60.8 ± 12.6; $p < 0.001$). A pathologic resting 12-lead ECG was present more frequently in the group with a cardiogenic type of syncope – 12 (24%) vs. 8 (16%). 24-hour Holter ECG monitoring showed no statistically significant difference between minimal, mean and maximal heart rates in the analyzed groups. However, statistically significant differences were observed in the occurrence of ventricular and supraventricular arrhythmias between the investigated groups. Patients with cardiac syncope had significantly higher concentrations of NT-proBNP compared to patients with reflex syncope (448.7 ± 212.2 vs. 68.2 ± 64.1; $p < 0.0001$).
Conclusions: Elevated NT-proBNP concentration is present in patients with a cardiogenic mechanism of syncope, despite the fact that a resting ECG is inconclusive.

Keywords:
24-h Holter
Electrocardiography
NT-proBNP
Syncope

Introduction

Syncope is a transient loss of consciousness caused by transient global cerebral hypoperfusion and is characterized by rapid onset, short duration, and spontaneous complete recovery [1].

Syncope is common in the general population and constitutes a significant clinical problem. It is the cause of 1–6% of hospital admissions, numerous outpatient consultations and 1–1.5% of emergency medical interventions [2]. In syncope patients who are referred to the emergency room minor injuries are found in 29.1% and severe injuries in 4.7% of cases [1].

In general, syncope is divided into reflex (neurally mediated) syncope, syncope due to orthostatic hypotension and cardiac (cardiovascular) syncope [1]. The most common cause of syncope is a reflex syncope, which is benign in nature. Vasovagal syncope is the most predominant type of reflex syncope and it constitutes up to 40% of all syncopes of unclear origin [1]. It is defined as a sudden loss of consciousness caused by a reflex overreaction of the autonomic nervous system [1].

Cardiac syncope is the second most prevalent type of syncope, mainly caused by arrhythmias: (supraventricular and ventricular) tachycardias, and bradyarrhythmias, as a consequence of sinus node dysfunction, atrioventricular (AV) node disease or a dysfunction of implanted cardiac devices. All these conditions lead to hemodynamic instability, which can cause a fatal decrease in the cardiac output and cerebral blood flow [1].

The etiological diagnosis and the assessment of syncope are challenging for the physician due to the unpredictability of the symptoms, an unknown recurrence rate and the short- and long-term risks associated with variable causes of syncope. The prognosis varies markedly with both underlying comorbidities and the etiological causality of the syncopal event. The initial investigations (history, physical examination, ECG and orthostatic blood pressure measurements) can provide the diagnosis in up to 50% of cases [3].

Syncope is a risk factor for sudden cardiac death (SCD) in many conditions associated with structural heart disease as well as inherited heart disease. Both European and American syncope guidelines recommend a 12-lead ECG as part of the evaluation of all patients with unexplained loss of consciousness. However, clinical research suggests that an ECG is performed as part of the evaluation in only 60–95% of patients with syncope [4].

Contemporary diagnostics of syncope based on the European Society of Cardiology (ESC) guidelines [1] does not include the routine biochemical determinations. In recent years there have been a few reports that have shown the usefulness of B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) in the diagnosis of syncope [5–7]. Still, there are no conclusive data to determine the value of NT-proBNP that could guide differentiation of patients with cardiac and reflex syncope.

The aim of this study was the assessment of the significance of ECG, Holter ECG and the concentration of NT-proBNP that would be useful in the differentiation of patients with cardiac and reflex syncope.

Methods

It was a prospective cohort study. One hundred consecutive patients were enrolled, 50 with reflex and 50 with cardiac syncope, including 56 women and 44 men, aged 18–77 years (mean age 52.6 ± 16.7 years) admitted to the Emergency Room, Medical School of Jagiellonian University, John Paul II Hospital, Cracow from January 2009 to December 2011 due to syncope.

According to the ESC guidelines [1], in order to determine the cause of the loss of consciousness all the patients were interviewed and clinical examination, including blood pressure as well as anthropometric measurements was performed. Additional diagnostic steps were taken, comprising a 12-lead resting ECG, 24-hour ECG monitoring, echocardiography, and laboratory tests. The concentration of NT-proBNP was assessed in 100 patients enrolled in the study.

At admission to the Cardiology Department blood samples were collected into tubes containing an anticoagulant (edetate). Then the material was centrifuged in a centrifuge at the speed of 3000/min for 10 min. The obtained plasma samples were frozen at –30 °C for no longer than 7 days.

After determining the etiology of syncope and patient enrollment, NT-proBNP concentration was assessed using electrochemiluminescence immunoassay in previously prepared plasma. The analysis was performed using Cobas 6000 analyzer and two polyclonal antibodies that rec-

Table 1 – Baseline characteristics of the study groups depending on the cause of syncope

	Total n = 100 n (%) or X ± SD	Reflex syncope n = 50 n (%)	Cardiac syncope n = 50 n (%)	*p*-Value
Female gender	56 (56)	31 (62)	25 (50)	NS
Age [years]	52.6 ± 16.7	44.4 ± 16.5	60.8 ± 12.6	0.001
Height [cm]	167.6 ± 8.6	168.1 ± 9.3	167.0 ± 8.0	NS
Weight [kg]	73.7 ± 14.0	70.4 ± 13.9	77.0 ± 13.5	0.01
Waist circumference [cm]	91.2 ± 12.8	86.8 ± 13.1	94.1 ± 11.4	0.01
BMI [kg/m^2]	26.3 ± 4.8	24.86 ± 4.13	27.70 ± 5.02	0.01
SBP [mmHg]	126.8 ± 14.9	117.5 ± 11.9	135.9 ± 11.7	0.001
DBP [mmHg]	72.9 ± 9.4	69.3 ± 9.5	76.5 ± 7.8	0.001
Mean heart rate [beats per minute]	66.1 ± 10.2	63.7 ± 7.0	68.5 ± 12.5	0.02
CVDs				
Hypertension	52 (52)	14 (28)	38 (76)	0.001
Coronary artery disease	36 (36)	9 (18)	27 (54)	0.001
Hypertrophic cardiomyopathy	3 (3)	0	3 (6)	NS

Data given as mean ± SD, median (interquartile range) or number and (%). BMI – body mass index; CVD – cardiovascular disease; DBP – diastolic blood pressure; ECG – electrocardiogram; HR – heart rhythm; NS – not statistically significant; NT-proBNP – N-terminal pro-B-type natriuretic peptide; SBP – systolic blood pressure.

Table 2 – Etiology of cardiac syncope

Cause of cardiac syncope	Cardiac n = 50 n (%)
I. Arrhythmia	47 (94)
A) Tachycardia	37 (74)
- Supraventricular	23 (46)
- Ventricular	14 (28)
B) Bradycardia	10 (20)
- Sinus node dysfunction	6 (12)
- Atrio-ventricular conduction system disease	4 (8)
II. Structural disease	3 (6)
- Hypertrophic cardiomyopathy	3 (6)

ognize epitopes within the chain of NT-proBNP. The total assay duration was 18 minutes. Roche reagent was used in the study. The immediate precision of the assay applied in the study was based on the producer's information and its value ranged from 1.7% to 3.1%.

All patients underwent a tilt test (maximum of 24 h after the last syncope) according to the Westminster protocol published by Fitzpatrick et al. [9]. Forty-one patients had carotid sinus massage, 19 subjects carotid ultrasound, while coronary angiography was performed in 15 patients. Before admission to the Coronary Disease Department the structural neurological causes of the loss of consciousness and orthostatic hypotension were excluded in all patients.

Table 3 – Basic resting ECG parameters in the investigated groups

ECG parameters	Group I n = 50 n (%) or X ± SD	Group II n = 50 n (%) or X ± SD	*p*-Value
Pathological resting ECG	8 (16)	12 (24)	NS
HR [1/min]	63.7 ± 7.0	68.5 ± 12.5	< 0.02
PQ [ms]	154 ± 20	161 ± 21	NS
QRS [ms]	81 ± 20	84 ± 16	NS
QTc [ms]	377 ± 20	382 ± 24	NS
AV I grade	1 (2)	0	NS
AV II grade	2 (4)	1 (2)	NS
AV III grade	0	4 (8)	NS
LAH	2 (4)	1 (2)	NS
LBBB	0	2 (4)	NS
RBBB	3 (6)	1 (2)	NS
Pathological Q wave	0	2 (4)	NS
SVT	0	1 (2)	NS

AV I grade – first degree atrio-ventricular block; AV II grade – second degree atrio-ventricular block; AV III grade – third degree atrio-ventricular block; HR – heart rate; LAH – left anterior hemiblock; LBBB – left bundle branch block; RBBB – right bundle branch block; SVT – supraventricular tachycardia.

The ECG was analyzed for the presence of disturbances of chronotropic competence in the sinus node, conduction in the AV node (first, second and third degree AV block), left bundle branch block, right bundle branch block, pathological Q waves and the presence of complex arrhythmias (ventricular and/or supraventricular tachycardia) was assessed.

The following parameters of 24-h ECG monitoring were analyzed: the minimal (min), maximal (max) and average (avg) heart rate (HR), the sinus heart rate and the presence of arrhythmias and conduction disorders, according to the current recommendations [8].

Detailed echocardiographic studies were performed in all subjects. Systolic and diastolic function and structure, left ventricular ejection fraction and valvular heart diseases were assessed in particular. The measurements were performed in compliance with the guidelines of the American Society of Echocardiography (ASE) [9].

Statistical analysis was performed using Statistica 8.1, Statsoft. The analysis of normality was performed using the Kolmogorov-Smirnov test and the Shapiro-Wilk test. The comparison of the groups for variables with normal distribution was performed using the Student t-test. The comparison of continuous variables with non-normal distribution between groups was performed by nonparametric rank tests (Mann–Whitney U test and Kruskal–Wallis test) and the comparison of qualitative variables was performed by Pearson chi-square test. The diagnostic value of NT-proBNP was assessed by the ROC curve analysis. *p* values below 0.05 were considered statistically significant.

Results

General characteristics of the studied groups are presented in Table 1. Patients with cardiac syncope were characterized by a significantly older age and a higher incidence of comorbidities (Table 1).

Based on the diagnostics performed with the compliance to the ESC guidelines [1], it was found that in patients with reflex syncope, the most common cause of syncope was vasovagal syndrome, diagnosed in 49 patients (98%) – 29 patients presented with orthostatic stress and 20 with emotional distress (fear, pain, blood phobia). In one person (2%) carotid sinus hypersensitivity was found.

In group II, the most common causes of the loss of consciousness were arrhythmias and conduction disturbances, which were found in a total of 47 (94%) patients. Three patients (6%) were diagnosed with structural heart disease. Detailed causes of syncope in patients with cardiac syncope are shown in Table 2.

Basic ECG parameters in the investigated groups

A pathologic resting 12-lead ECG was present more frequently in the group with a cardiogenic type of syncope – 12 (24%) vs. 8 (16%). However, the difference was not statistically significant. Patients with a neurogenic type of syncope showed a significantly lower resting heart rate (65.6 vs. 68.5; $p < 0.02$). In a resting ECG no differences between the PQ or QTc times were observed. In four patients with a cardiogenic etiology of syncope paroxysmal atrio-ventricular block of third grade was diagnosed. Basic data concerning ECG are presented in Table 3.

24-hour Holter ECG monitoring

24-hour Holter ECG monitoring showed no statistically significant difference between minimal, mean and maximal heart rates in the analyzed groups. However, statistically significant differences were observed in the occurrence of ventricular and supraventricular arrhythmias between the investigated groups. Data are presented in Table 4.

In three patients with hypertrophic cardiomyopathy in 24-h Holter ECG monitoring we observed a high number of ventricular extrasystoles and episodes of nonsustained ventricular tachycardia with concomitant episodes of syncope. In all these patients implantable cardioverter-defibrillator (ICD) was placed in primary prevention of sudden cardiac death.

NT-proBNP concentration in relation to the type of syncope and concomitant diseases

Patients with cardiac syncope had significantly higher concentrations of NT-proBNP compared to patients with reflex syncope (448.7 ± 212.2 vs. 68.2 ± 64.1; $p < 0.0001$).

In the group of patients with supraventricular tachycardia, concentration of NT-proBNP was higher than in

Table 4 – 24-hour Holter ECG parameters in the investigated groups

24-h Holter ECG parameters	Group I n = 50 n (%)	Group II n = 50 n (%)	*p*-Value
HR max [l/min]	122.22	118.56	NS
HR min [l/min]	43.44	47.68	NS
HR mean [l/min]	65.66	68.93	NS
VES	4 (8)	27 (54)	0.0001
SVT	1 (2)	19 (38)	0.0001
VT	0	13 (26)	0.0001

HR max – maximal heart rate; HR mean – mean heart rate; HR min – minimal heart rate; SVT – supraventricular tachycardia; VES – ventricular extrasystole; VT – ventricular tachycardia.

Table 5 – NT-proBNP concentration depending on the type of cardiac syncope

Cause of cardiac syncope	Ventricular tachycardia n (%) 14 (28)	Remaining causes of syncope n (%) 36 (72)	*p*-Value
NT-proBNP [pg/ml]	526 ± 217	225 ± 230	0.0001
Cause of cardiac syncope	**Supraventricular tachycardia n (%) 23 (46)**	**Remaining causes of syncope n (%) 27 (54)**	***p*-Value**
NT-proBNP [pg/ml]	472 ± 259	232 ± 233	0.0001

the remaining investigated population with cardiac syncope (472 ± 259 vs. 232 ± 233; $p < 0.0001$).

Similarly, in patients with ventricular tachycardia NT-proBNP concentration was statistically higher in comparison with the remaining patients with cardiac syncope (526 ± 217 vs. 225 ± 230 pg/ml; $p < 0.0001$) (Table 5).

Discussion

According to the definition, syncope is characterized by rapid onset, short duration and spontaneous complete recovery. Syncope is caused by transient, general cerebral hypoperfusion resulting from a range of causes.

In some forms of syncope in which prodromal signs could be present, the syncopal episode could be connected with particular circumstances. However, syncope occurrence is frequently unpredictable.

The most frequent form of syncope is reflex syncope. Cardiac syncope is the second most frequent cause of syncope. Despite the fact that syncope can adversely affect the quality of life, prognosis of patients with syncope is strictly connected with the presence of primary disease [1].

Patients after syncopal episode frequently ask for medical consultation. Therefore in this group of patients there exists a need for detecting a quick and reliable parameter enabling risk stratification.

A concomitant occurrence of syncopal episode with rhythm/conduction disturbances in an ECG examination is necessary in order to establish arrhythmogenic cause of syncope. This situation is very rare during a resting ECG examination. The probability of syncope during continuous Holter ECG monitoring is also very low.

According to Gibson and Heitzman, a diagnostic value of 24-h Holter ECG monitoring in order to confirm an arrhythmogenic cause of syncope was only 19% [10]. A 48h ECG increased a diagnostic value by 11% and 72h monitoring increased the value by 16% [11].

We observed that in the group of patients with a cardiovascular cause of syncope a relatively higher percentage of patients with ECG alterations (24% vs. 16%) was not related to statistical significance for prediction of cardiac syncope.

The cause of this phenomenon could be the fact that we enrolled only patients without previously diagnosed heart failure or organic heart changes (history of previous myocardial infarction or apparent heart failure), which predispose to changes in a resting ECG and different forms of rhythm and conduction disturbances.

The presented group of patients with cardiogenic syncope could be compared with patients admitted to an emergency department due to syncope, in which organic heart disease was initially excluded on the basis of preliminary diagnostic and clinical history.

In this group of patients with an inconclusive resting ECG searching for a new marker facilitating the guidance of further diagnostic evaluation seems to be particularly reasonable.

Our investigation showed a significantly higher NT-pro-BNP concentration in patients with cardiogenic syncope with rhythm and conduction disturbances when compared to the group of patients with reflex syncope.

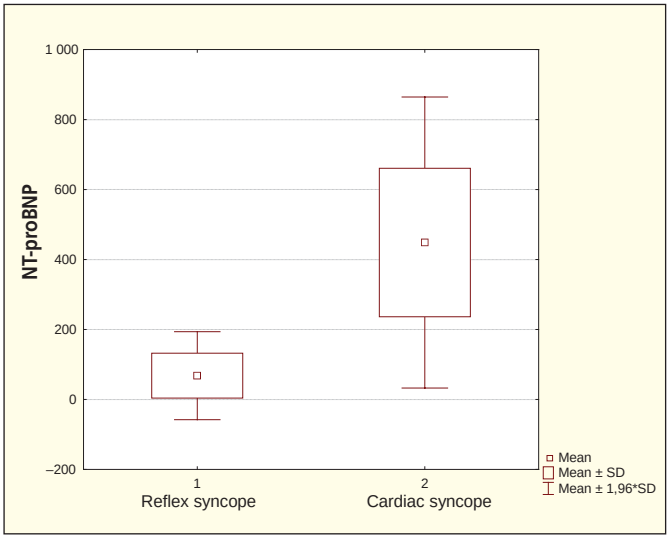

Fig. 1 – NT-proBNP concentration in the investigated groups. NT-proBNP – N-terminal pro-B-type natriuretic peptide.

A direct cause of syncope in such cases is hemodynamic instability leading to a significant decrease in brain perfusion.

The severity of symptoms (syncope, presyncopal episode, temporary discomfort during arrhythmia) depends on many factors, such as heart rate, type and duration of arrhythmia or left ventricular ejection fraction.

Bradycardia-related syncope is caused by a dysfunction of a natural pacemaker i.e. sinus node or conduction disturbances in electrical conduction system of the heart.

In the case of advanced atrio-ventricular conduction disturbances syncope occurs mostly as a consequence of delayed reaction of the escape rhythm [12].

Syncope may occur directly after cessation of atrial tachyarrhythmia as a consequence of concomitant sinus node dysfunction [12].

In the investigated group of patients with supraventricular tachycardia a higher NT-proBNP concentration was observed in comparison to the whole group (Fig. 1).

The cause of elevated NT-proBNP concentration in supraventricular arrhythmia could be an increased secretion not only from a ventricular muscle, but also from atria. There is a small number of studies in which the influence of supraventricular arrhythmia on NT-proBNP concentration was investigated.

Inoue et al. noted the highest NT-proBNP concentration in blood samples from the coronary sinus in patients with atrial fibrillation [13].

In the case of ventricular tachycardia syncope occurs as a consequence of fast, hemodynamically ineffective ventricular rhythm [14].

The role of ventricular tachycardia as a cause of syncope and subsequent sudden cardiac death was confirmed in large clinical trials [15,16].

Klein et al. defined the significance of NT-proBNP as a factor predicting the occurrence of ventricular tachycardia. In a group of 250 patients with ICDs they observed that a higher NT-proBNP concentration, exceeding 405 pg/ml was a factor indicating higher occurrence of ventricular tachycardia and ventricular fibrillation [17].

The cause of an increased NT-proBNP concentration in patients with ventricular tachycardia in comparison to all other patients with cardiogenic syncopal episodes in the presented group of patients could be explained by concomitant diseases such as coronary artery disease, arterial hypertension, which implicates the elevation of this marker [18].

Our observations are consistent with Manios et al. who showed a significant role of an elevated NT-proBNP concentration for prediction of the occurrence of ventricular tachycardia. In the population investigated by Manios et al. NT-proBNP value for prediction of ventricular tachycardia was 880 pg/ml [19]. Such a high cut-off value may result from the fact that in the above mentioned study the investigated patients presented with severely reduced left ventricular ejection fraction (LVEF < 35%), previous myocardial infarction or with ICD in primary prevention of sudden cardiac death, and the elevation of NT-proBNP was mainly a consequence of left ventricular dysfunction.

Conclusion

Patients with a preserved left ventricular ejection fraction, as shown in the present study, elevated NT-proBNP concentration is present in patients with a cardiogenic mechanism of syncope, despite the fact that a resting ECG is inconclusive. Furthermore, highly elevated NT-proBNP in the group of patients with cardiac syncope and normal left ventricular function indicates tachyarrhythmic cause of syncope.

Conflict of interest
No conflict of interest.

Funding body
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Ethical statement
Authors state that the research was conducted according to Declaration of Helsinki.

Informed consent
Informed consent was obtained from all patients participating in this study.

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