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RISK STRATIFICATION OF SUDDEN CARDIAC DEATH IN YOUNG PATIENTS WITHOUT STRUCTURAL HEART DISEASE

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Aim. To stratify the risk of recurrent syncope and the risk of sudden cardiac death (SCD) / sudden cardiac arrest in young patients with cardiogenic syncope without structural heart disease using the Evaluation of Guidelines in Syncope Study (EGSYS score). To conduct the first retrospective analysis of the personalized risk of sudden cardiac death, as well as the sensitivity of the EGSYS scale for patients with different nosological entities.

Methods. The study included 63 patients with syncope aged 18 to 44 years, the average age of the patients was 25,98±6,69 years. The patients were divided into 5 groups: the first group (12 patients, average age: 21,84±4,37 years) consisted of patients with cardiac channelopathies, the second group (16 patients, average age 25,84±6,56 years) consisted of patients with sinus node dysfunction in the form of arrest of the Kiss-Fleck node, the third group consisted of patients with atrioventricular block (15 patients, the average age 26,71±7,13 years), the fourth group consisted of patients with paroxysmal monomorphic and polymorphic ventricular tachycardia (15 patients, the average age of the group was 25,74±7,79 years), the fifth group consisted of patients with syncope in the Wolff-Parkinson-White (WPW) syndrome (5 patients, average age - 25,64±3,05 years). The frequency of recurrence of syncope and SCD episodes was assessed over a 2-year period from the time of the first syncope. The EGSYS score was used to stratify the risk of recurrence of syncope and SCD.

Results: A total of 23 patients, or 36.5% of the study population, had an EGSYS score more than 5 points (very high), with a 2-year risk of SCD of 21% and a risk of recurrent syncope of 77%. In addition, the highest score on the EGSYS scale was associated with a higher frequency of cardiogenic syncope and SCD episodes. Patients with cardiac channelopathies had the highest EGSYS score (mean score 5.84), which was associated with the highest incidence of syncope and episodes of SCD with cardiopulmonary resuscitation over a 2-year period (r=0,58, p=0,01). The risk of developing SCD over a 2-year period in the group of patients with sinus node dysfunction (sinus node arrest) does not exceed the average population (less than 2%), which was associated with the absence of episodes of sudden cardiac death (sudden cardiac arrest) for a period of 2 years in the patients in this group. The highest validation of the EGSYS score and the frequency of syncope over a 2-year period were in patients with ventricular tachycardia ((r=0,73, p=0,002).

Conclusion: Thus, already at the debut syncopal state there is a possibility of determining the personalized risk of recurrent syncope and sudden cardiac death using the EGSYS scale. According to the study, the area of the highest sensitivity of the scale was patients with ventricular tachycardia (the main cause of SCD), which allows us to consider this scale as a basis for constructing a prognostic model for stratifying the risk of sudden cardiac death in young patients with cardiogenic syncope without structural heart disease.

Key words: sudden cardiac death, sinus node arrest, complete atrioventricular block, channelopathies, ventricular tachycardia, long QT syndrome, syncope, implantable cardiac monitor.

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The term sudden cardiac death (SCD) refers to non-violent death occurring instantaneously or within less than 1 hour from the onset of acute changes in a patient's clinical status [1-3]. This term is used in the following situations: the deceased had a congenital or acquired heart disease that was potentially life-threatening during life; autopsy revealed a cardiac or vascular disease that could have been the cause of sudden death; or autopsy failed to identify any extracardiac causes of death, and death is presumed to have been caused by an arrhythmia [1-4]. According to contemporary studies, ventricular arrhythmias account for 85% of all causes of SCD, including ventricular tachycardia (VT) and ventricular fibrillation (VF) [1, 5].

According to the World Health Organization, 30 individuals per 1 million population die each week worldwide from ventricular arrhythmias. Based on the 2015 European Society of Cardiology clinical guidelines on SCD (sudden cardiac arrest (SCA)), 4.25 million people die annually worldwide from SCD. In the Russian Federation, 200,000-250,000 individuals die each year from ventricular ar-

rhythmias, with this number increasing annually [1, 6, 7]. Of particular concern is mortality among young patients (aged 18-44 years) without structural abnormalities of the cardiovascular system, occurring against a background of complete clinical, laboratory, and instrumental well-being [6, 7]. According to various reports, this patient group accounts for up to 10% of all SCD cases [8].

The development of SCD in young patients without structural cardiovascular abnormalities is most commonly associated with primary electrical diseases of the heart, as well as several other relatively rare conditions. Among the most prevalent primary electrical heart diseases are channelopathies, inherited forms of sinus node dysfunction, complete atrioventricular block, genetically determined progressive disorders of the cardiac conduction system, idiopathic ventricular arrhythmias, and several others [9-13].

In many cases, the only (and sometimes the first and last) predictor of SCD in young patients is a syncopal episode (syncope). Syncope is defined as a transient loss of consciousness resulting from cerebral hypoperfusion, characterised by rapid onset, inability to respond to external stimuli, short duration, and spontaneous recovery. Syncope accounts for approximately 5% of all emergency medical visits across healthcare facilities of various profiles [14, 15].

Syncope has a broad spectrum of causes, ranging from potentially benign and non-life-threatening to life-threatening conditions. Depending on the underlying mechanism, all syncopal episodes can be classified as cardiogenic and non-cardiogenic (reflex-mediated, orthostatic). Several studies have demonstrated significantly higher mortality in patients with cardiogenic syncope (CS), regardless of age. At the same time, patients with syncope may differ substantially in their risk of recurrence and in their risk of developing SCD [16, 17]. Thus, patients without a prodrome or typical triggering events; those with syncope occurring in the supine position or at peak physical exertion; those with a family history of SCD at a young age; those with a prior history of disease, including previously diagnosed rhythm or conduction disorders; or those with pathological ECG findings at the time of syncope are at high risk of cardiogenic syncope. Notably, only 4% of patients who experience a first syncopal episode seek medical attention. For the majority of these patients, risk stratification for syncope recurrence and SCD is not performed, and as many as 75% of patients after a first syncopal episode do not undergo comprehensive evaluation [3].

Several tools have been developed to date for stratifying the risk of syncope recurrence and SCD in patients with cardiogenic syncope, including the San Francisco Syncope Rule, the OESIL Risk Score, the Evaluation of Guidelines in Syncope Study (EGSYS) score, and the Canadian Syncope Risk Score. Each of these tools has its own advantages and limitations. A cohort study conducted by the developer of the EGSYS score, Italian cardiologist Attilio Del Rosso from the San Giuseppe Clinic in Empoli, demonstrated high specificity and sensitivity of the score, which was also confirmed by external validation studies. However, its prognostic value does not significantly exceed that of clinical assessment alone. Despite evidence of high specificity and sensitivity of the EGSYS score in diagnosing cardiogenic syncope, data on its prognostic value in determining personalised risk of SCD and syncope recurrence for specific nosological entities are currently lacking in the international literature. Moreover, the clinical context in which the score demonstrates the highest sensitivity has not been clearly defined. Using the present study as an example, we aim to demonstrate experience in determining personalised risk of syncope recurrence and SCD in patients with specific nosological entities, as well as to identify the setting in which the EGSYS score shows the highest validity, which may serve as a practical reference point for clinicians in stratifying SCD risk in patients with syncope [2, 18-21].

Study objective: to stratify the risk of syncope recurrence and the risk of SCD (SCA) in young patients with cardiogenic syncope without structural heart disease using the EGSYS score; to perform a retrospective analysis of personalised SCD risk; and to evaluate the sensitivity of the EGSYS score in patients with different nosological entities.

MATERIALS AND METHODS

The study included 63 patients presenting with complaints of syncope who were followed at a medical institution between 2018 and 2025.

Inclusion criterias

1. Young age (18-44 years).
2. History of at least one syncopal episode.
3. Presence of diagnosed cardiac rhythm disorders in accordance with the 2015 European Society of Cardiology guidelines as causes of cardiogenic syncope: bradyarrhythmias (sinus node dysfunction, atrioventricular block), tachyarrhythmias (supraventricular and ventricular), as well as a diagnosed channelopathy [1, 2].
4. Presence of at least one high-risk feature for syncope according to the European Society of Cardiology criteria [1, 2]: syncope without prodrome; syncope without an identifiable provoking factor (except for triggers suggestive of channelopathy, such as fever, loud sounds, etc.); positive family history (sudden cardiac death in first-degree relatives or a history of frequent syncope in relatives); syncope occurring at peak physical exertion; syncope in the supine or sitting position, or syncope unrelated to body position (in cases of recurrent syncope); presence of pathological ECG changes documented during syncope or on resting ECG.
5. Written informed consent provided by the patient.

Exclusion criterias

1. Syncope clearly associated with food intake, change in body position, fear, hunger, or another identifiable trigger (except for factors suggestive of channelopathy, such as fever, loud sounds, etc.).
2. Presence of structural heart or vascular disease (coronary artery disease, valvular heart disease, cardiomyopathies, atherosclerosis, diffuse connective tissue diseases, myocarditis, etc.).
3. Presence of concomitant internal organ pathology (anaemia, thyrotoxicosis, autoimmune vasculitides, diabetes mellitus with micro- and/or macroangiopathy, electrolyte disturbances, etc.).
4. Diagnosed and instrumentally confirmed epilepsy with a positive response to antiepileptic therapy.

5. Presence of an established or diagnosed non-cardiogenic cause of syncope (intoxication, orthostatic hypotension, reflex-mediated syncope, etc.).
6. Informed refusal to participate in the study.

The study was conducted in several stages. At the first stage, a thorough collection of patient complaints and medical history was performed, along with assessment of clinical status. Particular attention was paid to a history of syncopal and presyncopal episodes, episodes of tachycardia and bradycardia, and associated symptoms such as general weakness and non-systemic dizziness. In the presence of a history of syncope, detailed characterisation of syncopal episodes was undertaken. Cardiogenic syncope is characterised by the following features: sudden onset and sudden termination; variable duration of episodes; a relatively small number of syncopal episodes over a lifetime (one or two); a short prodrome preceding syncope (tachycardia or a sensation of cardiac pause in the chest); possible sudden loss of consciousness without prodrome; absence of a clear trigger for syncope (or presence of a trigger in certain specific nosological entities, such as fever in patients with Brugada syndrome); pathological findings on cardiac evaluation (signs of sinus node dysfunction or prolonged QT interval in long QT syndrome); a family history of inherited cardiac disease; or SCD in first-degree relatives before the age of 50 years [2-5]. At this stage, a detailed analysis of the patient's ECG archive was also performed; when rhythm disturbances were documented, their temporal association with syncope was clarified.

At the second stage, more comprehensive laboratory and instrumental examinations were performed. All patients included in the study underwent complete clinical and biochemical blood testing, coagulation profile assessment, and immunological blood analysis. If abnormalities were identified at this stage, further diagnostic evaluation was carried out, and specialist consultation and treatment were provided when necessary. Transthoracic echocardiography and 24-hour ECG monitoring were performed, during which an active orthostatic test was conducted according to a standard protocol. Ultrasound examination to detect developmental anomalies of the brachiocephalic arteries with significant impairment of intracerebral haemodynamics was performed when indicated. Video electroencephalography was carried out for the diagnosis of epileptic activity, and brain magnetic resonance imaging was performed to detect structural pathology, when clinically indicated. Based on the results of the latter two examinations, patients were evaluated by a neurologist and, if necessary, an epileptologist.

At the third stage, transoesophageal electrophysiological study was performed according to indications, with pharmacological testing (using atropine) applied when required. Implantation of implantable cardiac monitors - Confirm Rx (Abbott, USA) and Reveal LINQ (Medtronic, USA) - was performed, followed by prolonged remote ECG monitoring for up to 2 years. Exercise stress testing was conducted according to indications. A subset of patients underwent invasive intracardiac electrophysiological study. When necessary, pharmacological tests with atropine and procainamide were used. Molecular genetic testing was performed only in accordance with clinical guidelines specific to the corresponding nosological entity.

A retrospective assessment of the frequency of syncope and episodes of SCD over a 2-year period from the first syncopal episode was performed using the EGSYS score. Based on the obtained results, risk stratification for syncope recurrence and SCD was carried out for each patient. The total EGSYS score, as well as the calculated probabilities of SCD and syncope recurrence expressed as percentages, were then compared with the actual observed frequency of syncope and SCD episodes. Subsequently, correlation analysis was performed to assess the relationship between the final EGSYS score and the frequency of syncope and SCD episodes within each patient group over the 2-year period, using Pearson's linear correlation coefficient according to standard methodology in the Statistical Package for the Social Sciences software (IBM, USA).

RESULTS

Based on the inclusion and exclusion criteria, 63 patients aged 18 to 44 years were enrolled in the study; the mean age of the study population was 25.98 ± 6.69 years. The frequency of syncope and episodes of SCD was assessed over a 2-year period from the first syncopal episode. To determine personalised SCD risk and to evaluate the sensitivity of the EGSYS score for this specific nosological spectrum, all patients were divided into several groups.

The first group (12 patients) consisted of individuals with channelopathies (mean age 21.84 ± 4.37 years): long QT syndrome type 1 with a mutation in the KCNQ1 gene (3 patients), long QT syndrome type 2 with a mutation in the KCNH2 gene (5 patients), one patient with Jervell-Lange-Nielsen syndrome (KCNQ1 genotype), two patients with Brugada syndrome, and one patient with a diagnosed early repolarisation syndrome. The second group (16 patients; mean age 25.84 ± 6.56 years) included patients with symptomatic sinus node dysfunction. The third group comprised patients with atrioventricular block (15 patients; mean age 26.71 ± 7.13 years): 9 patients with complete AV block and 6 patients with second-degree AV block, Mobitz type II.The fourth group included patients with paroxysmal ventricular tachycardia (15 patients; mean age 25.74 ± 7.79 years), including 11 patients with monomorphic VT and 4 patients with polymorphic VT and/or documented ventricular fibrillation. The fifth group (5 patients; mean age 25.64 ± 3.05 years) consisted of patients with syncope in the setting of Wolff-Parkinson-White syndrome.

In patients with channelopathies, the mean EGSYS score was 5.84, corresponding to a probability of cardiogenic syncope of 77% and a probability of SCD of 21%. In reality, the mean frequency of syncope over the 2-year period in this group was 7.84, and the frequency of SCD was 0.38. The correlation coefficient between the EGSYS score and syncope frequency was $r = 0.58$ ($p = 0.01$), and between the EGSYS score and SCD frequency $r = 0.55$ ($p = 0.02$).

In the group of patients with sinus node dysfunction, the mean EGSYS score was 1.54, with a probability of cardiogenic syncope of 2% and a probability of SCD of 2%. Over the 2-year period, the frequency of syncope was 4.43,

while the frequency of SCD (SCA) was 0. Thus, in this patient group, the SCD risk according to the EGSYS score did not exceed the average population risk. No clear association was observed between the EGSYS score and syncope frequency (correlation coefficient r = 0.12, p = 0.3).

In patients with atrioventricular block, the mean EGSYS score was 3.13, corresponding to a probability of cardiogenic syncope of 13% and a probability of SCD of 21%. The mean syncope frequency during the observation period was 3.1, and the frequency of SCD was 0.21. The correlation between the EGSYS score and syncope frequency was weak (r = 0.21, p = 0.2), whereas a moderate correlation with SCD frequency was observed (r = 0.54, p = 0.02).

In the VT group, the mean EGSYS score was 4.4, with a probability of cardiogenic syncope of 33% and a probability of SCD of 21%. The mean syncope frequency over the 2-year period was 4.2, and the frequency of SCD was 0.33. A significant correlation was observed between the EGSYS score and syncope frequency (r = 0.73, p = 0.002), as well as between the EGSYS score and SCD episode frequency (r = 0.52, p = 0.02).

In patients with Wolff-Parkinson-White syndrome, the mean EGSYS score was 3.4, corresponding to a probability of cardiogenic syncope of 13% and a probability of SCD of 21%. During follow-up, the mean syncope frequency over the 2-year period was 3.4, and the frequency of SCD was 0.2. The correlation coefficient between the EGSYS score and syncope frequency was r = 0.32 (p = 0.29), and between the EGSYS score and SCD episode frequency r = 0.32 (p = 0.12).

DISCUSSION

A retrospective risk stratification of syncope recurrence and SCD (SCA) was performed in young patients with arrhythmogenic syncope using the EGSYS score, along with an assessment of the actual frequency of syncope and SCD episodes over a 2-year period from the first syncopal event. It was found that in 23 patients included in the study (36.5%), the EGSYS score exceeded 5 (very high), corresponding to a 2-year SCD risk of 21% and a syncope recurrence risk of 77%. These findings are comparable with data from the Framingham Study, which demonstrated that one-year mortality in patients with cardiogenic syncope was higher (up to 33%) than in patients with non-cardiogenic causes of syncope (up to 12%) or syncope of unknown origin (up to 6%) [37].

According to the developer of the EGSYS score, a score ≥3 identifies recurrent cardiogenic syncope with a sensitivity of 92-95%. During long-term follow-up (614 days), mortality among patients with a score ≥3 was significantly higher than among those with a score <3 (17% vs 3%, p < 0.001). These data were also confirmed by external studies. Thus, a study conducted by Hamid Kariman and colleagues from Iran demonstrated high sensitivity of the EGSYS score in predicting syncope recurrence in patients with scores ≥3, with reported sensitivity reaching 91% [38]. A study by a Portuguese research group demonstrated a statistically significantly higher EGSYS score in patients with cardiogenic syncope compared with syncope of other aetiologies (1.85 ± 2.3 vs 0.64 ± 2.0, p = 0.005) [39]. Another study reported that death occurred in 9.2% of patients with recurrent syncope over a 2-year period, and deceased patients had significantly higher EGSYS scores (p < 0.001) [40].

Given that young patients with cardiogenic syncope represent a heterogeneous population, determination of personalised risk of syncope recurrence and SCD is of substantial clinical importance. According to our data, the highest EGSYS scores were observed in patients with channelopathies (mean score 5.84), which was associated with the highest frequency of syncope and SCD episodes requiring cardiopulmonary resuscitation over a 2-year period, demonstrating a correlation of moderate strength.

According to various authors, the annual incidence of SCD in untreated patients with long QT syndrome ranges from 0.33% to 0.9%, whereas the annual risk of syncope is estimated at approximately 5% [23, 26]. In patients with Brugada syndrome, cardiogenic events were observed in 7.7% of cases over one year, and 86% of patients with implanted cardioverter defibrillators experienced shocks. Convincing data on other channelopathies are lacking in the international literature due to their rarity and diagnostic challenges. Moreover, underdiagnosis among patients with channelopathies remains a significant issue, making it extremely difficult to establish accurate mortality rates in this patient group at present [1, 23, 25-27].

The 2-year risk of SCD in the group of patients with sinus node dysfunction did not exceed the average population risk (less than 2%), which was consistent with the absence of SCD episodes. Mortality from asystole has been reported at 15-20%; however, definitive data regarding the isolated contribution of sinus node dysfunction are currently lacking. Adverse outcomes have been described in patients with progressive involvement of the cardiac conduction system, as well as in those with combined binodal disease (sinus node dysfunction and atrioventricular block) [1, 2, 5, 7, 9, 11].

Considering the heterogeneity of high-risk patients with cardiogenic syncope and the variability in personalised risk of syncope recurrence and SCD, the question arises regarding the clinical setting in which the EGSYS score demonstrates the greatest sensitivity. Such studies are currently scarcely represented in the international literature. The strongest correlation between the EGSYS score and syncope frequency over the 2-year period was observed in patients with ventricular tachycardia (r = 0.73, p = 0.002). According to contemporary studies, ventricular arrhythmias account for 85% of all causes of SCD. Although numerous studies have demonstrated a high risk of SCD in patients with ventricular arrhythmias in the presence of structural heart disease, risk stratification for idiopathic ventricular tachycardia has not yet been established [8]. The frequency of syncope in patients with atrioventricular block was lower compared with other groups, likely due to more timely diagnosis.

Study limitations

This study has a single-centre design and a retrospective nature, which may limit the strength of the obtained results. The study included a cohort of young patients aged 18 to 44 years; children, adolescents, and older individuals

were not included, despite the fact that high-risk syncope and episodes of SCD may also occur in these age groups in the absence of structural heart disease. This may represent a potential source of selection bias. On the other hand, young patients without structural heart disease may more accurately reflect the true clinical profile of patients with arrhythmogenic syncope associated with primary electrical heart diseases. The sample size (63 patients) was determined by the single-centre nature of the study, as well as by the extremely low prevalence of certain nosological entities.

CONCLUSION

Already at the first syncopal episode, it is possible to determine a personalised risk of syncope recurrence and SCD using the EGSYS score. According to the study findings, the highest sensitivity of the score was observed in patients with VT, which allows the EGSYS score to be considered a basis for the development of a prognostic model for stratifying the risk of SCD in young patients without structural heart disease presenting with cardiogenic syncope.

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