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The role of cardiac diagnostics in cryptogenic stroke: the current state of knowledge

Rola diagnostyki kardiologicznej u pacjentów z udarem kryptogennym — aktualny stan wiedzy

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Abstract

Cryptogenic stroke is a stroke of unknown aetiology. Over two thirds of cryptogenic strokes have an embolic, mainly cardiogenic, source. This is why cardiac imaging and looking for cardiac arrhythmia, especially atrial fibrillation, are so important.

In patients with implanted devices, the routine use of recording intracardiac electrocardiography in the device's memory is recommended in order to find so-called atrial high-rate episodes. The improvements in diagnostic tools and the progress in atrial fibrillation monitoring have lowered the number of strokes of unknown aetiology, and in many cases have allowed the application of appropriate secondary prophylaxis.

Key words: cryptogenic stroke, embolic strokes of undetermined source, cardiac diagnostics, patent foramen ovale, atrial fibrillation

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Introduction

Stroke is the third most common cause of death in developed countries and the leading cause of permanent disability in adults [1]. The annual incidence in the general population is estimated to be 0.2%, which gives a total of approximately 15 million patients annually. According to the World Health Organisation (WHO) definition, stroke is a clinical syndrome consisting of rapidly developing clinical signs of focal (or global in the case of coma) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin [2]. More than 85% of strokes are ischaemic strokes. The current classification of ischaemic stroke with the acronym TOAST (Trial of Org 10172 in Acute Stroke Treatment) distinguishes five subtypes of stroke:

- large-artery atherosclerosis;
- cardioembolism;
- small-vessel occlusion;
- stroke of other determined aetiology;
- stroke of undetermined aetiology.

In about 25%, or even as much as 30–40% of cases [3], despite extended diagnostics being performed, the direct cause of ischaemic stroke remains unknown, and such a stroke is referred to as cryptogenic stroke (CS) [4]. It is believed that a significant proportion of cryptogenic strokes (more than two thirds) are embolic, which is associated with a much worse prognosis, a higher risk of relapse, more severe disability in the future, and higher mortality compared to strokes with a different aetiology [5]. For this reason, in 2014 the expert group Cryptogenic Stroke/ESUS International Working Group introduced the

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Table 1. Causes of embolic stroke from an undetermined source (ESUS) (based on [4])

Atrium	Silent, paroxysmal atrial fibrillation
	Atrial high-rate episodes
	Atrial asystole and sick-sinus syndrome
	Chiari network
Paradoxical embolism	Atrial septal aneurysm
	Patent foramen ovale
Mitral valve	Myxomatous valvulopathy with prolapse
	Mitral annular calcification
Left ventricle	Systolic or diastolic dysfunction
	Ventricular non-compaction
	Endomyocardial fibrosis
Aortic valve, aorta	Calcific aortic valve
	Aortic valve stenosis
	Aortic arch atherosclerotic plaques
Cancer-associated	Covert non-bacterial thrombotic endocarditis
	Tumour emboli from occult cancer

concept of embolic stroke from an undetermined source (ESUS) into clinical practice (Table 1) [4].

After the end of treatment of the acute phase of an ischaemic stroke, diagnostic steps should be taken immediately to determine the most likely cause of it, including the exclusion of a cardiogenic embolism. This is done by appropriately collected medical history, physical examination, preliminary imaging of the brain and cerebral vessels [computed tomography (CT), magnetic resonance imaging (MRI), Doppler artery], laboratory tests, 12-lead electrocardiogram (ECG), or at least 24-hour Holter ECG during a patient's stay in the hospital and transthoracic echocardiography (TTE).

The methods of extended cardiac diagnostics, and their application in patients after an ischaemic stroke of unknown aetiology, ESUS, are presented below.

Electrocardiography, telemetry

A final diagnosis of atrial fibrillation (AF) can be made only on the basis of an ECG record. In people with AF, arrhythmia may be both symptomatic and asymptomatic (so-called 'silent atrial fibrillation') [6]. The search for AF in a stroke patient should begin as early as during hospitalisation. ECG is recommended on admission to hospital, but this procedure must not delay the use of appropriate treatment. During further observation, continuous heart rhythm monitoring should be used for at least 24 hours, which exceeds the detectability of AF compared to serially performed ECG or 24-hour Holter (4.1–7%) [7]. Studies show that diagnostic efficiency increases in proportion to the duration of heart rhythm monitoring. On average, about 25% of patients after a stroke or transient ischaemic attack (TIA) will be diagnosed with AF with long-term heart rate monitoring [8]. ECG recording, in addition to the ability to detect arrhythmias, can also be used to pre-assess anatomical changes of the left atrium. There is a proven relationship between prolongation of PR interval > 200 ms, features of left atrial enlargement (two-phase P wave in lead V1, duration of negative phase ≥ 40 ms and amplitude ≥ 0.1 mV), and the occurrence of ischaemic stroke, especially embolic types [9]. In 2015, Kamel et al. [10] proposed the hypothesis of thrombus formation in the left atrium regardless of the presence of AF. The arguments presented at the time were based on the results of both meta-analyses and randomised clinical trials [AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Strokes) and WARSS, (Warfarin-Aspirin Recurrent Stroke Study)], which showed a greater benefit from treatment of respectively apixaban and warfarin than aspirin, as well as the lack of an advantage of the rhythm-controlling strategy over the strategy of controlling heart rate in people with AF in the prevention of ischaemic stroke. This led to the concept of so-called atrial cardiopathy, in which not the arrhythmia itself is the reason for the formation of thrombi and thromboembolic complications, but the unfavourable remodelling of the left atrium, with its enlargement, fibrosis and abnormal function. ARCADIA (Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke) is an ongoing clinical trial that is comparing the efficacy of apixaban to that of aspirin in patients with signs of atrial cardiopathy and a recent stroke of unknown cause. Patients over 45 years of age without known AF will be observed for a minimum of 1.5 years and a maximum of 4 years for subsequent ischaemic strokes and complications of treatment such as intracranial bleeding or severe haemorrhage other than intracranial haemorrhage. ARCADIA has adopted the definition of atrial cardiopathy as the presence of PTFV1 (P-wave terminal force) — the product of the duration of the negative phase of the P wave and its depth in the lead V1 > 0.05 mV × ms, N-terminal pro-B-type natriuretic peptide (NT-proBNP) > 250 pg/mL, and left atrial dimension index ≥ 3 cm/m^2 in echocardiography.

Long-term ECG recording

There are currently many methods available for long-term ECG registration. The basic technique is a 24-hour Holter test recommended for all patients with a stroke of undetermined cause. Extending the Holter test from 24 hours to 30 days increases the detection of AF from 4.38% to 15.2%, and extended registration up to 180 days gives a possibility

Table 2. Risk factors for atrial fibrillation

Features associated with risk of atrial fibrillation	Diagnostic criteria
Electrocardiography (ECG)	
PR interval	> 200 ms
Features of LA anomalies	P wave duration in lead II > 120 ms (often two-hump, the time between two peaks ≥ 40 ms) or in lead V1, two-phase (positive-negative) P waves with negative phase duration ≥ 40 ms and amplitude ≥ 0.1 mV (1 mm)
Features of left ventricle hypertrophy	In patients without intraventricular conduction disturbances (anterior fascicular block beam, right and left bundle branch block) — at least one of the following is sufficient to diagnose left ventricular hypertrophy: R in aVL > 1.1 mV (11 mm); R in I + S in III > 2.5 mV (25 mm); R in V5 or V6 > 2.6 mV (26 mm); S in V1 + R in V5 or V6 > 3.5 mV (35 mm); S in V2 + R in V5 or V6 > 4.5 mV (45 mm); S in V3 + R in aVL > 2.8 mV (28 mm) (men); S in V3 + R in aVL > 2.0 mV (20 mm) (women)
Echocardiography	
Increased size of left atrium (LA)	LA dimension from the back of the aorta to the posterior wall of LA in the parasternal long axis at the end-systolic phase Norm: 3–4 cm in men, 2.7–3.8 cm in women
IVSd	Thickness of the ventricular septum in diastole > 1.2 cm
Heart failure with reduced ejection fraction (HFrEF)	EF < 40%
Clinical data	Age > 75 years Diabetes Heart palpitations in the past Positive family history Coronary heart disease

LA — left atrium; IVSd — interventricular septal defect; HFrEF — heart failure with reduced ejection fraction; EF — ejection fraction

of detecting arrhythmias in 29.15% of patients [11]. ECG registration can also be carried out using the direct data transmission method via wireless communication. This allows prompt reaction by the centre ordering the examination and the start of appropriate treatment. In patients with symptomatic arrhythmia, Event Holter — a mobile telemonitoring device, can be used, in which pressing the appropriate button automatically sends an alert to the monitoring centre. ECG prolongation should be considered especially in patients with risk factors for arrhythmia such as hypertension, age ≥ 75 years, valvular heart disease, coronary artery disease, peripheral atherosclerosis, obesity, and heart failure [12]. In order to better select patients, it is also possible to use electrocardiographic and echocardiographic parameters that are associated with the occurrence of AF [13, 14] (Table 2).

In the future, telemedicine will greatly facilitate the diagnosis of patients with silent AF. There are modern techniques combining standard event loggers with algorithms that automatically interpret the heart rhythm and have the ability to send data over the telephone network. An application for smartphones is available (AliveECG operating with a special overlay for ECG testing), which has been approved for use as a medical product by the US Food and Drug Administration (FDA). Thanks to this, you can easily carry out an ECG test and send the result to the doctor [15].

Implantable loop event recorder

An implantable loop event recorder is a device implanted under the skin in the subclavian region which automatically records the rhythm of the heart, up to a period of several years. The reading is made using an appropriate programmer, as well as by communicating with the phone using an appropriate application. In the CRYSTAL-AF (Study of Continuous Cardiac Monitoring to Assess Atrial Fibrillation After Cryptogenic Stroke) clinical trial, in which implantable rhythm recorders (ILRs) were used in patients with cryptogenic stroke, AF was detected in 8.9% of patients after six months and in 12.4% after 12 months, compared to 1.4% and 2.0% in a control group in which routine 24-hour Holter heart rate monitoring was performed [16].

Implantable devices

Stimulators of the heart such as implantable cardioverter-defibrillator and cardiac resynchronisation therapy have the ability to record the patient's own rhythm in a given time interval alongside their basic functions, thanks to the presence of intracardiac electrodes. There is a relationship between the occurrence of rapid atrial rhythms (AHRE) and the risk of ischaemic stroke, which is nearly 2.5 times higher in this group of patients [17]. AHRE is defined as atrial episodes with a frequency > 190/min lasting > 6 minutes detected by a two-chamber implantable device. Although an association between AHRE and stroke has been proven, the question of the total duration of AHRE found in the device control which would clearly indicate the need to include oral anticoagulation remains unanswered. This time should be 5.5–6 hours according to some authors [18], and even > 24 hours according to others [19]. Therefore, due to the lack of clear guidelines, decisions regarding anticoagulant therapy in this group of patients are still made individually.

Echocardiography

The 'gold standard' in the search for cardiogenic causes of embolic stroke is transthoracic echocardiography (TTE). According to the 2018 guidelines for the management of ischaemic stroke it is not recommended to perform TTE routinely, but it may be considered in special cases such as cryptogenic stroke [20]. This is a widely available, cheap and safe study, with the help of which we can recognise the majority of potential sources of thrombus formation for which there are specific treatment methods and secondary prophylaxis of stroke.

Transoesophageal echocardiography

Transoesophageal echocardiography (TEE) is a more sensitive test to detect potential embolus sources because it allows for a more accurate depiction of the left atrium, aortic arch, abnormal intracardiac structures, and leaks (Table 3) [21, 22]. The disadvantage of TEE is its invasive nature and potential complications such as hoarseness, dysphagia, odynophagia, and damage to mucous membranes, teeth, oesophagus, and vocal cords as well as bradycardia [23]. Despite the high sensitivity of TEE, the presence of thrombus, spontaneous echocardiographic contrast or cardiac tumours is found in less than 1% of patients with ESUS. The most frequently detected potential sources of an embolism in TEE are aortic laminae and intracardiac leaks, mainly through the patent foramen ovale and defects of the atrial septum.

The results of many studies have shown a much higher occurrence of patent foramen ovale (PFO) in patients with a cryptogenic stroke [24], especially in young patients where the prevalence is 70–80% [25]. We report the presence of a PFO if there is a permanent connection between the left and right atrium lumen in a place corresponding to the location of the foramen ovale. The results of randomised trials [RESPECT (Patent Foramen Ovale Closure or Medical Therapy After Stroke), CLOSE (Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence), REDUCE (GORE® Septal Occluder Device for Patent Foramen Ovale (PFO) Closure in Stroke Patients)] for secondary stroke prophylaxis in patients with PFO comparing pharmacological treatment and percutaneous surgical techniques to closing the oval opening indicate the benefits of invasive treatment in reducing the risk of recurrent ischaemic stroke. A PFO is difficult to identify in a transthoracic study due to its small size, thin primary septum at the level of the foramen ovale, and the position at the back of the heart which is associated with a greater distance from the chest wall. The gold standard for PFO diagnostics is TEE using a contrast agent and a correctly performed Valsalva manoeuvre. However, TEE is not required if there is good image quality in the TTE [26]. As a contrast agent, about 8 mL of heparinised saline and 1 mL of air are used [27]. The first application of the contrast should be made during steady breathing, because a small left-right leak may persist in a chronic elevation in the right atrium pressure. Subsequent administration takes place during the patient's Valsalva manoeuvre, which temporarily increases the pressure in the right atrium. The risk of stroke in patients with PFO is thought to increase with an increasing size of leak [28], something which can be assessed in two ways: either by counting the number of air bubbles in the left atrium during the first three heart contractions after the right atrium is completely filled with contrast agent, or by making a morphological description in the TEE which determines the degree of separation of the primary and secondary plaque and the size of the foramen ovale. However, there is a lack of a standardised projection in which this assessment should be made. To make a therapeutic decision, it

Table 3. Two-dimensional (2D) accuracy of transthoracic and transoesophageal echocardiography in selected clinical situations (based on [22])

Clinical situation	2D TTE	2D TEE
Infective endocarditis	++	+++
Tumours inside heart	++	+++
Thrombus in left ventricle	+++	+
Thrombosis on artificial valve	+	+++
Atherosclerotic plaque in aorta	+	+++
Patent foramen ovale	+	+++

Precision: + low, ++ average, +++ high

is also necessary to assess the presence of anatomical risk factors such as resting right-left leak, large PFO > > 4 mm, large leak (> 20 bubbles in TEE), large Eustachian valve > 10 mm, Chiari network, long PFO channel, and the presence of an atrial septal aneurysm.

An isolated atrial septal aneurysm (ASA) occurs in 2–3% of the population, and in 20% of cases it coexists with a PFO. It is believed that in people < 55 years, the risk of stroke increases in the presence of isolated ASA [odds ratio (OR) 6.1], PFO (OR 3.1) and is highest with the coexistence of PFO and ASA (OR 15.5) [29]. Diagnosis is made on the basis of the assessment of the atrial septum in a TTE or TEE study. The exact criteria are not precisely determined, but it is assumed that the width of the base of the aneurysm should be 10–15 mm, with an inclination towards the left or right atrium of at least 10 mm. A special RoPE (Risk of Paradoxical Embolism) scoring scale has been created to assess the likelihood of a cryptogenic stroke in patients with PFO (Table 4) [30, 31]. A total score > 6 points indicates a high risk of stroke in the mechanism of a paradoxical embolism.

Table 4. Risk calculator of paradoxical embolism among patients with embolic stroke from an undetermined source and patent foramen ovale [RoPE (Risk of Paradoxical Embolism)] (based on [30])

Risk factors	Points
Lack of history of hypertension	1
Lack of history of diabetes	1
Lack of history of stroke/transient ischaemic attack	1
Lack of history of smoking	1
Cortical infarct on imaging	1
Age [years]:	
• 18–29	5
• 30–39	4
• 40–49	3
• 50–59	2
• 60–69	1
• ≥ 70	0

Magnetic resonance

An alternative non-invasive diagnostic method for TEE may be cardiac magnetic resonance imaging (CMRI). CMRI is ideal for the evaluation of left ventricular mass and left atrial volume and for the differentiation of thrombus with abnormal structures in the heart cavities, such as myxomas. When performing a contrast study, areas of scarring or fibrosis in the myocardium may be identified, and the addition of phase contrast may identify a leak in the heart, such as an atrial septal defect [32]. CMRI is a good method for imaging tumours and cardiomyopathy, as well as the aortic arch. Information on the use of CMRI in the diagnosis of cryptogenic stroke is negligible. Although there is data regarding a larger percentage of the diagnosis of the cause of ESUS, there has been insufficient research into the possibility of using it as an alternative to TEE [33].

Conclusions

Cardiac assessment is an indispensable element of patient management following a stroke. Each patient in a Stroke Unit should have an electrocardiographic examination performed in addition to a detailed interview, physical examination, and brain imaging study to confirm the diagnosis. In selected cases, especially among patients with structural heart disease or in patients < 45 years of age, easily available and non-invasive transthoracic echocardiography should be considered.

However, for the majority of patients, a transoesophageal examination is necessary to detect the embolic source because TEE is characterised by a higher sensitivity and higher specificity than TTE [34]. The concept of atrial cardiopathy seems to be attractive, but it requires validation from ongoing randomised clinical trials. The diagnosis and documentation of silent AF remain a major diagnostic challenge. In the case of stroke of unknown aetiology, it is reasonable to prolong the monitoring of cardiac function up to 30 days or even longer by means of Holter recording or an implantable event recorder. The choice of appropriate method depends on the patient's preferences as well as on the availability of diagnostic methods in a given centre. There are many ways, both pharmacological and surgical, to prevent incidences of recurrent stroke, which is why it is so important to determine its aetiology as early as possible and to apply appropriate secondary prophylaxis.

Conflict(s) of interest

The authors report no conflict of interest.

Streszczenie

Udar kryptogenny to udar mózgu o nieznanej etiologii. Ponad 2/3 udarów kryptogennych ma podłoże zatorowe, głównie kardiogenne. Dlatego tak ważne są obrazowa diagnostyka kardiologiczna oraz diagnostyka zaburzeń rytmu serca, zwłaszcza migotania przedsionków.

U osób z implantowanymi urządzeniami wszczepialnymi należy rutynowo wykorzystywać zapisy wewnątrzsercowego elektrokardiogramu w pamięci urządzenia, w poszukiwaniu tak zwanych szybkich rytmów przedsionkowych. Udoskonalenie narzędzi diagnostycznych oraz postępy w wykrywaniu migotania przedsionków sprawiają, że coraz mniej udarów mózgu pozostaje bez ustalonej przyczyny, co w wielu przypadkach pozwala na odpowiednio wczesne wdrożenie profilaktyki wtórnej.

Słowa kluczowe: udar kryptogenny, udar zatorowy z nieokreślonego źródła, diagnostyka kardiologiczna, przetrwały otwór owalny, migotanie przedsionków

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