Stroke as a result of cardioembolism – characteristic features in the context of diagnostic methods and secondary prevention

Udar jako wynik zatoru kardiogennego – charakterystyczne cechy w kontekście diagnostyki i wtórnej prewencji

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Abstract

Embolism of cardiac origin accounts for around 15–30% of ischaemic strokes. It is worth noting that stroke from a cardiac source carries a poorer outcome compared with other sources, having a 50% mortality at three years. Diagnosis of the cardioembolic source of stroke is frequently uncertain and relies on the identification of the potential cardiac source of embolism in the absence of significant autochthone cerebrovascular occlusive disease. Early diagnosis and appropriate treatment are mandatory to prevent the recurrent events that can lead to greater disability and the increased healthcare cost. Since cardioembolic stroke is not a single disease entity, its diagnosis requires initial clinical suspicion and a comprehensive evaluation, including electrocardiography, echocardiography, brain imaging, and cardiac monitoring. There are characteristic features suggestive of cardioembolic stroke, which help the clinicians to choose a right direction of diagnosis. The primary role of echocardiography is to establish the existence of the source of embolism, determine the likelihood that such a source is a plausible cause of stroke or systemic embolism, and guide the therapy in an individual patient. There is still a need for further studies assessing the optimal diagnostic methods of potential cardiac sources of embolism and establishment of the rules of the optimal medical prevention (antiplatelet therapy versus oral anticoagulation) and interventional procedures to reduce the incidence of ischaemic strokes.

Key words: ischaemic stroke, echocardiography, embolism, brain imaging

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Introduction

Stroke is a major public health issue. It is typically characterised as a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause, including cerebral infarction, intracerebral haemorrhage, and subarachnoid haemorrhage (SAH). Stroke is becoming a common disease worldwide, and has an increased rate of recurrence yearly after a transient ischaemic attack (TIA) or stroke [1]. Ischaemic stroke is a heterogeneous disease with different mechanisms and aetiologies and specific treatments. Identification of the right cause is essential in order to prepare an adequate preventive strategy [1]. A substantial proportion of stroke risk remains unexplained [2].

Using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, ischaemic strokes may be further subdivided into the following types:
- thrombosis or embolism associated with large vessel atherosclerosis;
- embolism of cardiac origin (cardioembolic stroke);
- small blood vessel occlusion (lacunar stroke);
- other determined cause;
- undetermined (cryptogenic) cause (no cause identified, more than one cause, or incomplete investigation) [3].

The aetiological diagnosis of stroke in adults has changed over time as a result of improvements in the diagnostic workup.

While cryptogenic stroke was the most frequent diagnosis in the past, today specific causes (non-atherosclerotic vasculopathy, large-artery atherosclerosis, cardioembolism and haematological disorder) are identified in the majority of patients [4].

Early diagnosis and treatment of stroke improves the patient outcomes, and knowledge of the cause of the initial event is crucial to identify the appropriate therapy to maximally reduce the risk of recurrence. Cardioembolic stroke carries a higher risk of death, recurrent stroke, and hospital readmission as well as higher risk of severe disability compared with other stroke subtypes. Its frequency is expected to rise because of the age-related incidence of atrial fibrillation and an aging population. Early diagnosis and appropriate treatment are therefore mandatory to prevent the recurrent events that lead to greater disability and increased healthcare cost.

Since cardioembolic stroke is not a single disease entity, its diagnosis requires initial clinical suspicion and a comprehensive evaluation, including electrocardiography (ECG), echocardiography, brain imaging, and cardiac monitoring [5, 6].

Moreover, recent clinical trials have indicated that embolic stroke of undetermined source may often stem from subclinical atrial fibrillation, which can be diagnosed with prolonged heart rhythm monitoring. What is more, emerging evidence indicates that thrombogenic atrial substrate can lead to atrial thromboembolism even in the absence of atrial fibrillation. Such an atrial cardio-myopathy may explain many cases of embolic stroke of undetermined source, and oral anticoagulant drugs may prove to reduce the stroke risk from atrial cardiomyopathy given its parallels to atrial fibrillation. Non-vitamin K antagonist oral anticoagulant drugs have recently expanded therapeutic options for preventing cardioembolic stroke and are currently being tested for stroke prevention in patients with embolic stroke of undetermined source. Also increasing appreciation of thrombogenic atrial substrate and the common coexistence of cardiac and extracardiac stroke risk factors suggest benefits from global vascular risk factor management in addition to anticoagulation. Finally, improved imaging of ventricular thrombus plus the availability of non-vitamin K antagonist oral anticoagulant drugs may lead to better prevention of stroke from acute myocardial infarction and heart failure [7].

Clinical and imaging features suggestive of cardioembolic stroke

The evaluation of suspected cardiac source of embolism requires rapid diagnostic efforts, which should include detailed history, comprehensive physical examination, blood workup, and imaging of the heart and the organs damaged by the embolus. In many patients medical history, risk factor profile, physical exploration, and basic explorations (ECG and thorax X-ray) may already indicate or suggest some specific causes, such as the presence of carotid bruits originated by a carotid stenosis, rheumatic or prosthetic valve disease and atrial fibrillation. If no aetiology is found, the next step is usually directed towards identifying the arterial causes of embolism using ultrasound techniques, transcranial Doppler (TCD) and cervical arteries Doppler (CD), colour coded transcranial or cervical arteries duplex (transcranial colour coded Doppler (TCCD), arteries colour Doppler CCD) or angiography, usually magnetic resonance imaging (MRI) or computed tomography (CT) based, of the intracranial and cervical vessels.

Echocardiography should be the primary form of cardiac imaging, supplemented by the chest X-ray, computed tomography, magnetic resonance imaging, and nuclear imaging when necessary. Computed tomography or MRI, as well as angiography, may be indispensable in the evaluation of organs and tissues affected by cardiac sources of embolism. Cardiac emboli often occlude middle — large size arteries and multiple vascular territories [8].

Diagnosis of the cardioembolic source of stroke is frequently uncertain and relies on the identification of the potential cardiac source of embolism in the absence of significant autochthon cerebrovascular occlusive disease [9]. Cardiac emboli can travel along to the intracranial vessels and due to their variable size cause either
massive infarcts by occlusion of proximal arteries, small superficial infarcts in distal arterial territories, single large deep infarcts or multiple infarcts in different arterial territories [9]. Clinical presentation is characterised by sudden neurological deficits maximal at onset due to abrupt interruption of blood flow. While a stuttering course has usually been attributed to atherothrombotic stroke, cardioembolic strokes can have a progressive course in at least one-fifth of cases, given that emboli can recanalise, move and fragment after the initial impaction. Non-cardioembolic strokes can appear with sudden deficits in two-fifths of cases [9]. Rapid regression of symptoms (the spectacular shrinking syndrome) reflecting early recanalisation has also been related to cardioembolic stroke [9]. Neurological deficits and syndromes may indicate embolic mechanisms, but all have suboptimal discriminatory capacity [9]. Some neurological syndromes such as Wernicke’s aphasia, global aphasia without hemiparesis, Wallenberg’s syndrome, cerebellar infarcts, top-of-the-basilar artery syndrome have been commonly associated with cardiac embolism [9]. Also visual-field abnormalities and neglect are clinical deficits more frequent in cardioembolic stroke [9]. Ultrasonic exposure could non-invasively enhance the clot lysis of tissue plasminogen activator (t-PA) with the presence of microbubbles (MBs). A variety of sonography systems are available in the market, and whether sonothrombolysis is only successful using specific devices is unknown [10].

Commercially available products containing microbubbles to enhance ultrasound images, termed “ultrasound contrast agents” (UCA) are indicated for use with trans-thoracic echocardiography to improve cardiac structure and function assessment, but can also be used with transoesophageal echocardiography (TEE). The primary mechanism for UCA relies on the difference in density and compressibility between the microbubbles and the surrounding fluid and solid interfaces thus creating an efficient reflector of ultrasound and enhancing blood echogenicity [11]. The acoustic power (mechanical index) of the transmitted ultrasound beam plays a major role affecting the UCA oscillation [11]. These improvements in contrast specific imaging presets enable excellent visualisation of UCA within cardiac chambers and myocardial microvasculature, as well as Doppler enhancement [11]. Neuroimaging of cardioembolic stroke is typically performed acutely via non-contrast head CT for patients presenting to the emergency room. However, in case of patients who present with subacute to chronic stroke symptoms or TIA, or when CT is non-diagnostic, MRI is often used.

Magnetic resonance imaging has demonstrated to be clearly superior to CT in identifying ischaemic lesions not visible on CT and has the capacity to detect cerebral ischaemia within minutes of onset by diffusion-weighted sequences (DWI). Magnetic resonance imaging is superior to CT in detecting cortical involvement and multiple ischaemic lesions correlating with cardioembolic stroke. The presence of the hyperdense cerebral artery sign on non-contrast CT scanning, or the corresponding hyperintense artery sign on MRI, originated by an occluding thrombus, suggests the diagnosis of an embolic arterial occlusion that may be of cardiac origin if no arterial pathology is detected [8].

In the absence of local arterial disease, more distant sources of potential embolism are sought. In cardioembolism, the pattern of infarct is territorial in type and distribution. Multiplicity of lesions involving both the anterior and posterior circulation and/or both hemispheres particularly if separated by time (infaerts of different age), more than one infarct within a territorial distribution, or if there are concomitant signs of systemic thrombo-embolism (such as splenic or renal infarcts, or peripheral limb ischaemia), is highly suggestive of cardiogenic embolism [12].

In comparison, small deep penetrator infarcts of the lenticulostrate or brainstem (< 1 cm in size) are typically not cardioembolic in origin and most likely relate to small vessel (≤ 100 microns in diameter) disease processes, such as hypertension or diabetes. But there is also a specific type of subcortical infarct, the ‘large lenticulostrate infarct’, which typically indicates an embolic stroke mechanism [13]. The identification of cortical involvement is characteristic of the embolic mechanism. The reports of migratory cardioembolic events that occlude penetrating vessel ostia are reported, but their involvement is typically greater than 1 cm in parenchymal size. Cardioembolic stroke affecting the posterior circulation accounts for ≤ 25% of posterior circulation ischaemic events in some registries [9, 14, 15]. In Figure 1 we present the schematic drawings of patterns of brain infarctions signaling different stroke mechanisms [13].

Bilateral thalamic strokes are rare manifestations of posterior circulation infarcts. Usually the aetiology is cardioembolic or small vessel disease combined with individual anatomical predisposition. The symptoms include a variety of neurological deficits depending on thalamic structure involvement, such as paresthesias or numbness, hemiparesis with increased reflexes and Babinski sign, third cranial nerve palsy, speech and cognition disturbance, memory impairment and stupor. Neuroimaging usually reveals ischaemic loci in adequate thalamic nuclei. Bilateral thalamic stroke due to artery of Percheron occlusion is a rare presentation of stroke, which can be overlooked in the routine CT scan. If diagnosed, it requires further evaluation for stroke risk factors, especially cardiovascular disorders associated with the increased embolic risk [16].

Cerebral ischaemia with haemorrhagic transformation has been associated to cardioembolic stroke. Haemorrhagic transformation occurs in up to 71% of cardioembolic strokes and 91% of haemorrhagic infarcts are caused by a cardiac embolism. Haemorrhagic transformation has
been traditionally explained by recanalisation of an occluded vessel to a damaged ischaemic tissue and vessel walls. Recanalisation after six hours of ischaemia and the detection of microbleeds on gradient-echo T2-weighted MRI are predictors of haemorrhagic transformation [8].

The features suggestive of cardioembolic stroke are presented in Table 1 [13].

**Methods of diagnosis of cardiac embolism sources**

Echocardiography is being increasingly used as a screening test to identify the sources of cardiogenic embolism in patients with ischaemic stroke or TIA. The echocardiographic diagnosis of cardiac thrombi, vegetations and tumours, as well as the identification of predisposing conditions such as patent foramen ovale, aortic atherosclerosis and other minor causes (e.g., mitral valve prolapse, mitral and aortic valve calcification) have crucial clinical relevance, affecting the choice of surgery and/or of pharmaceutical therapy in the setting of patients presenting embolism. The echocardiographic assessment helps not only for the retrospective diagnosis of the sources of embolism, but also for the prevention of events in the asymptomatic patients [17].

Figure 1A–D. Schematic drawings of patterns of brain infarctions signaling different stroke mechanisms (based on [13]): A. In cortical infarcts with territorial distribution, cardioembolic stroke is probable; B. The same holds true for large striatocapsular infarcts; C. This is not the case in lacunar infarctions by definition located subcortically; D. Low flow infarct can be located subcortical (upper panel) or cortical (lower panel), but their distribution is not territorial but interterritorial.

The hierarchy of echocardiography investigations begins with a standard transthoracic echocardiography study (TTE). If the heart is deemed structurally normal, a bubble contrast transthoracic study (cTTE) is performed to evaluate the presence of intra-cardiac shunting. For example, Kolo et al. [18] recruited prospectively 126 consecutive stroke patients in their study. The potential cardiac source

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<td>Rapid regression of symptoms</td>
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<td>Visual field defect, neglect or aphasia</td>
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<td>Concomitant palpitations or oppressive chest pain</td>
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<td>MRI or CT</td>
<td>Simultaneous or sequential infarcts in different arterial territories</td>
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<td>Haemorrhagic transformation</td>
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<td>Hyperdense artery sign in absence of arterial pathology</td>
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<td>Ultrasound</td>
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<td>Early recanalisation of an arterial occlusion</td>
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<td>Microembolism (HITS) in both middle cerebral arteries</td>
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<td>Laboratory</td>
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Table 1. Features suggestive of cardioembolic stroke (source [13])

MRI — magnetic resonance imaging; CT — computed tomography; HITS — high-intensity transient signals
of emboli (CSE) was identified in 23.0% of the stroke patients. Five (4.0%) patients had rheumatic valvular heart disease with demonstrable clots in the left atrium. On the other hand, four (3.2%) patients had rheumatic heart disease without thrombi. Two patients had biventricular thrombi. One of these patients had giant clots within the ventricles and multiple freely mobile thrombi in right ventricle without obvious cardiac structural defect [18].

Transoesophageal echocardiography is indicated where transthoracic imaging is poor and so non-diagnostic; when a cardiac lesion is identified and requires further detailed assessment (e.g. mitral stenosis and suitability for percutaneous balloon mitral valvuloplasty or a positive cTTE requiring further detailed anatomical assessment of the atrial septum for risk stratification and suitability for device closure) or where no cardiac source for stroke has been identified and specific pathologies need to be excluded. Transoesophageal echocardiography provides high resolution images from an almost non-invasive approach and has revolutionised the search for cardiac sources of embolism. Its good sensitivity and high specificity results not only from its excellent resolution, but also from its ability to image structures that are not seen well or not seen at all from the transthoracic approach, including the left atrial appendage, the atrial septum, and the thoracic aorta. Transoesophageal echocardiography has therefore particular strengths in elucidating potential aetiology in cardiac sources of embolism [19].

Figure 2 shows TEE utility in detection of patent foramen ovale (PFO). Also modern echocardiographic methods could be useful in detection and prediction of potential reasons of ischaemic stroke. Olsen et al. [20] aimed to evaluate whether speckle tracking echocardiography improves the risk stratification for atrial fibrillation in these patients. The study comprised of 373 patients with ST-segment elevation myocardial infarction (STEMI), treated with primary percutaneous coronary intervention. The endpoint was a composite of new-onset atrial fibrillation and ischaemic stroke. After a median follow-up time of 5.5 years, patients who reached the endpoint had significantly reduced systolic function by the left ventricular ejection fraction (LVEF) (43% vs 46%, p = 0.042) and global longitudinal strain (10.9% vs 12.6%, p = 0.004), both being univariable predictors. However, only global longitudinal strain remained a significantly independent predictor (hazard ratio [HR] 1.12, 95% confidence interval [CI] 1.00; 1.25, p = 0.042, per 1% decrease) after multivariable adjustment for baseline predictors (age, sex, diabetes, hypertension, diastolic dysfunction, and LVEF) [20].

A thrombus located in the left atrium (LA) or, more likely, the LA appendage (LAA) is the most prevalent source of cardioembolic events and is typically associated with atrial fibrillation (AF). Thromboembolic risk is similar between paroxysmal and persistent AF, but is strongly determined by associated cardiovascular risk factors. The severity and duration of these risk factors influence the extent of LA enlargement and consequently the likelihood of AF-associated thrombus formation. The development of real-time three-dimensional echocardiography (RT3DE) has enhanced our ability to interrogate the LAA, providing the perspective relative to LAA anatomy as well as to discriminate between the real and artificial mass within the cavity. Furthermore, its recent study demonstrated that RT3DE is accurate in determining LA volume, compared with two-dimensional TTE [21]. Cardiac magnetic resonance (CMR) imaging, the current gold standard, may have advantages over TEE [17].

Zahuranec et al. [22] performed a prospective pilot study comparing CMR to TEE after stroke to assist in planning future definitive studies. Individuals with non-lacunar stroke within 90 days of undergoing clinical TEE were prospectively identified and underwent a 1.5 Tesla research CMR scan. The exclusion criteria included > 50% relevant cervical vessel stenosis and inability to undergo non-sedated CMR. A descriptive comparison of cardioembolic source (intracardiac thrombus/mass, aortic atheroma > 4 mm, or PFO) by study type was performed. No patient had intracardiac thrombus or mass detected on either study. Aortic atheroma ≥ 4 mm thick was identified by TEE in one patient. CMR identified aortic atheroma as < 4 mm in this patient (3 mm on CMR compared with 5 mm on TEE). Patent foramen ovale was identified in six of 20 patients on TEE; CMR found only one of these. In this pilot study, TEE identified more potential cardioembolic sources than CMR imaging. Future studies comparing TEE and CMR after stroke should determine whether TEE, CMR, or both can best elucidate potential cardioembolic sources [22].
From a therapeutic viewpoint, it is important to differentiate the underlying causes of embolism in patients with cryptogenic stroke, such as aortic arch atheroma (AAA), PFO, and paroxysmal atrial fibrillation (PAF). Ryoo et al. [23] investigated the clinical and radiological characteristics of these three common causes of cryptogenic embolism to develop models for decision making in aetiologic workups. All the patients underwent ECG and brain magnetic resonance imaging and magnetic resonance angiography in the emergency room. Patients who had a determined cause of stroke before the admission were excluded from the study, based on the Stop Stroke Study Trial of Org 10172 in Acute Stroke Treatment (SSS–TOAST).

Aortic arch atheroma was considered as a cause of stroke if vulnerable AAA was observed on the TEE or MDCT. Vulnerable AAA was defined as aortic plaques in the ascending aorta or proximal arch that met ≥ 1 of the following criteria: 1) ≥ 4 mm of intima-media thickness on TEE or ≥ 6 mm of thickness adjacent to the aortic wall on MDCT or 2) ulcerated plaque or 3) mobile plaque on TEE or soft plaque on MDCT [23]. Patent foramen ovale was deemed present when one of the following criteria was observed: 1) the passage of > 3 microbubbles to the left atrium within three cardiac cycles after a complete pacification of the right atrium on the TEE, 2) microembolic signals within 40 seconds after the injection of agitated saline with microbubbles on the TCD, or 3) a distinct flap in the left atrium at the expected location of the septum primum or a continuous column of contrast material connecting both atria or jet of contrast material into the right atrium on the MDCT. Patients in the PAF group were those who had no history or ECG findings of atrial fibrillation at admission, but PAF was diagnosed using repetitive ECGs or 72-hour cardiac telemetry. If patients had PAF plus PFO or AAA, they were classified as belonging to the PAF group, because the current evidence–based classification system classifies PAF as a high–risk embolic source and PFO and AAA as low or uncertain sources of embolism [24].

The authors of the study based on observed distinct clinical and radiological characteristics for AAA, PFO, and PAF patients developed an equation to predict the most probable aetiology underlying cryptogenic embolisms. Their data indicate that patients with embolic stroke of undetermined source showed distinct clinical and radiological features depending on the underlying stroke cause. Specific diagnostic tests for aortocardiac sources could be guided by such features. Continuous efforts are needed to refine the approach to working up cases of suspected embolic stroke of undetermined source, incorporating other biomarkers, such as B-type natriuretic peptide or genetic risk factors [23].

Iwasaki et al. [25] analysed the potential utility of multidetector computed tomography (MDCT) to identify both cardiac embolic sources and coronary artery disease (CAD) in embolic-stroke patients. They performed MDCT for 184 patients with embolic stroke and investigated the prevalence of the potential source of the embolism. Overall, 64 potential embolic sources were detected in 59 patients (32.1%). Left atrial appendage thrombus, left ventricular thrombus and aortic atheroma were detected in 3.3, 0.5 and 15.8% of patients, respectively. Circulatory stasis and patent foramen ovale were detected in 8.7 and 6.5%, respectively. Their results suggest that MDCT has a potential to identify cardiac embolic sources in patients with embolic stroke, but without known CAD [25].

Lee et al. [26] performed a study, which purpose was to investigate cardiac computed tomographic (CT) findings predictive of recurrent stroke in patients with ischaemic stroke and determine the incremental risk stratification benefit of cardiac CT findings compared with TEE findings in patients with ischaemic stroke. Transthoracic echocardiography and cardiac CT images were assessed in 374 patients with ischaemic stroke for cardioembolic sources, including thrombus, tumour, spontaneous echo contrast, valvular vegetation, atrial septal aneurysm, patent foramen ovale, and aortic plaque. The primary end point was stroke recurrence. During a median follow-up period of 433 days, there were a total of 28 recurrent stroke events. The TEE parameter of plaque complexity (HR, 13.512; 95% CI: 3.668, 49.778; p < 0.001) and CT parameter of plaque complexity (HR, 32.538; 95% CI: 7.544, 140.347; p < 0.001) were predictors of the recurrent stroke. The time-dependent receiver operating characteristic curve analysis demonstrated no significant differences in prediction of recurrent stroke between TEE and CT parameters (integrated area under the receiver operating characteristic curve, 0.812 vs 0.840, respectively) [26].

**Summary**

Strokes due to cardiac embolism are generally associated with poor prognosis. Cardioembolic stroke has been associated with short and long-term recurrence, higher in-hospital mortality and a higher index of fatal recurrence versus other causes of stroke. Identification of the specific cause is crucial in order to choose the most optimal preventive strategy and these vary for the different subtypes of ischaemic stroke [27]. There are characteristic features suggestive of cardioembolic stroke which help clinicians to choose a right direction of diagnosis. About 80% of ischaemic strokes occur in persons without AF, and it is therefore important to develop a path to examine the optimal prevention of stroke when there is no obvious AF [28, 29]. The cryptogenic strokes are being recognised as sharing many characteristics with cardioembolic strokes [30]. Currently available data do not provide definitive evidence on the comparative benefits of OAC vs. APT in patients with cryptogenic stroke [31]. There are ongoing
studies assessing advantages and disadvantages of these two kinds of therapies. There is also a lack of antithrombotic treatment scheme in the time between stroke and diagnosis of potential sources of thromboembolism in cryptogenic stroke.

Conflicts of interest(s)

The authors of the paper do not declare any conflicts of interests.

References


