European Review for Medical and Pharmacological Sciences 2023; 27: 4046-4052

Is cardioembolic stroke more frequent than expected in acute ischemic stroke due to large vessel occlusion?

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Abstract. – INTRODUCTION: Cardioembolic and atherosclerotic occlusions are two leading causes of acute ischemic stroke with large artery occlusion. Cardioembolic cause is more frequent in strokes due to large vessel occlusion among strokes of all types. In this study, we aimed to analyze and determine the rate of cardioembolic cause in patients with LVO treated with mechanical thrombectomy.

PATIENTS AND METHODS: This study is a retrospective analysis of 1,169 patients with LVO that were treated with mechanical thrombectomy in 2019. Both anterior and posterior circulation occlusions eligible for thrombectomy were included.

RESULTS: Among the 1,169 patients who performed mechanical thrombectomy, there were 52.6 % males with a mean age of 63.2 ± 12.9 years and 47.4% females with a mean age of 67.4 ± 13.3 years. The average NIHSS score was 15.3 ± 4.8. The successful revascularization (mTICI 2b-3) rate was 85.2%, the 90-day good functional outcome rate (mRS 0-2) was 39.8% and mortality (mRS 6) rate was 22.9%. Most common causes of ischemic stroke were cardioembolism in 532/1,169 (45.5%), followed by 461/1,169 (39.5%) undetermined etiologies and others, 175/1,169 (15%) large vessel disease. Atrial fibrillation is found to be the most common cause of cardioembolic stroke with 76.3% incidence. We identified 11 (0.9%) acute stroke patients treated with MT who had recurrent LVO and received repeated MT. A cardioembolic cause was found to cause the recurrent LVO in 7 (63.6%) patients.

CONCLUSIONS: In this retrospective study, cardioembolic source seems to constitute majority of causes in acute ischemic strokes due to large vessel occlusions. Further exploration is needed especially in cryptogenic strokes to reveal possible cardioembolic source of emboli.

Key Words:
Acute stroke, Etiology, Cardioembolism, Mechanical thrombectomy, Large vessel occlusion.

Introduction

Stroke is the most common cause of morbidity and the second most common cause of mortality. Approximately 85% of strokes are ischemic[1]. Management of risk factors could help to prevent stroke[2]. According to the most widespread ischemic stroke subtype classification system – Trial of ORG 10172 in Acute Stroke Treatment (TOAST) – nearly 20-30% of strokes are of the cardioembolic origin[3,4]. Patients with cardioembolic etiology presents with a more severe neurological deficit and progresses with serious disability and mortality[5]. The most common cause (approximately 80%) of cardioembolic stroke is atrial fibrillation (AF) and its incidence increases with age. Ischemic stroke incidence also increases with age. Diagnosing cardioembolic stroke has its challenges. Therefore, long-term heart rhythm monitoring or transesophageal echocardiography may be required[6], which may not be possible to conduct in some patients. Large artery atherosclerosis is another ischemic stroke subtype which comprises approximately 10-20% of strokes. Generally, large vessel occlusion (LVO) is divided into three sub-categories according to etiology in clinical studies: large artery atherosclerosis, cardioembolic stroke, other etiologies, and undetermined causes[7-9]. In the current study, we evaluated the frequency of cardioembolic etiology among LVO cases reg-

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istered in the Turkish Interventional Neurology Database (TIND) in 2019.

Patients and Method

Study Design, Data Collection, and Study Population

This study is a retrospective analysis of patients with LVO that were treated with mechanical thrombectomy in 2019 and recorded in the TIND. Treated LVOs included both anterior and posterior circulation occlusions (internal carotid artery, middle cerebral artery M1-2, anterior cerebral artery A1, basilar, posterior cerebral artery P1, and tandem occlusions). The study is approved by the institutional ethics committee. Written informed consent was obtained from all patients. All clinical investigations were conducted according to the Declaration of Helsinki principles.

All patients underwent non-contrast computerized tomography (CT) and contrast-enhanced brain-neck CT angiography. Once a major vascular occlusion was detected, the patient was transferred to the angiography suite and mechanical thrombectomy was performed. Thrombolytic therapy was administered to eligible patients who presented within the first 4.5 hours. The choice of conscious sedation *vs.* general anesthesia during thrombectomy was left to the operators' discretion.

Patients younger than 18 years old and patients with Alberta Stroke Program Early CT Score (ASPECT) <6 were excluded from analysis.

For each patient, data collection included baseline demographics (age, sex), clinical findings, stroke etiology, vascular risk factors (hypertension, atrial fibrillation, diabetes mellitus, hypercholesterolemia, alcohol consumption, smoking, coronary heart disease, history of stroke or myocardial infarction, congestive heart failure), and procedural features (from symptom onset to groin puncture and groin puncture to final recanalization time, successful recanalization, complication) were recorded. National Institute of Health Stroke Scale (NIHSS) was used to assess stroke severity on admission. ASPECT score was calculated for all patients on axial CT. A control non-contrast CT was performed within 36 hours of symptom onset for all patients. Immediate non-contrast CT was performed in patients who experienced neurological deterioration (NIHSS change from baseline > 4) during the post-operative period. Successful reperfusion was defined as a modified Thrombolysis in Cerebral Infarction (mTICI) score of 2b-2c-3[10]. Good functional outcome was defined as a modified Rankin Scale (mRS) of 0-2 at 3 months. Hemorrhagic complications were defined according to European Cooperative Acute Stroke Study (ECASS) criteria: parenchymal hematoma (PH-1, PH-2) and hemorrhagic infarction (HI-1, HI-2)[11].

Continuous ECG monitorization was performed during the endovascular procedure and throughout the post-procedural recovery period in the stroke unit. Transthoracic echocardiography was performed within the first 7 days in each eligible patient. In cases where stroke subtype could not be determined, a 24-hour Holter recording was performed in the first 7 days. Transesophageal echocardiography was performed in patients below the age of 55 if there was a suspicion of cardioembolic source. If transesophageal echocardiography could not be performed for any reason, saline contrast transthoracic echocardiography (including Valsalva maneuver) was performed. AF was detected from serial 12-lead electrocardiograms and 24-hour Holter continuous monitoring according to definitions of the American Heart Association (AHA) and the European Society of Cardiology (ESC) guidelines[12].

Classification of Ischemic Stroke

Subtypes of ischemic stroke were defined according to the international Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.

Patients were classified into the "large artery atherosclerosis" sub-category if angiographic findings of significant ipsilateral artery stenosis (>50%) were observed.

Patients were classified into the "cardioembolism" sub-category if at least one cardiac source was identified for an embolus in the absence of significant vascular abnormality in the large ipsilateral arteries with cerebral infarction.

Patients were classified into the "undetermined" sub-category when we could not identify specific risk factors after our usual investigation (digital subtraction angiography, electrocardiography, transthoracic echocardiography, 24-hours Holter monitoring). Other rare causes such as vasculitis and dissection were also categorized into this group.

Definition of CE

CE risk factors of ischemic stroke were defined as:

1. electrocardiogram showing atrial fibrillation,
2. a Holter recording showing intermittent atrial fibrillation,

3. an echocardiogram showing a cardioembolic source such as ejection fraction <30%,
4. a thrombus in the left atrial or ventricular thrombus,
5. rheumatic valvular disease,
6. spontaneous contrast passage during echocardiography,
7. recent myocardial infarction (<4 weeks),
8. others (atrial septal aneurysm and/or patent foramen ovale, aortic arch atheromatous plaques, endocarditis), left ventricular wall hypokinesia/akinesia.

Endovascular Stroke Treatment

All patients in the study were treated with mechanical thrombectomy. Device choice and technique were left to operator's discretion.

Statistical Analysis

Mean, standard deviation, median, minimum, maximum and ratios were used in descriptive data statistics. The distribution of variables was measured using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used for the analysis of quantitative independent data. The Chi-square test was used in the analysis of qualitative independent data and the Fisher test was used when Chi-square test conditions were not met. The Statistical Package for the Social Sciences version 23.0 program (IBM Corp., Armonk, NY, USA) was used in the analyses. In all comparisons, a *p*-value <0.05 was considered statistically significant.

Results

Among the 1,169 patients who underwent mechanical thrombectomy, there were 52.6 % males with a mean age of 63.2 ± 12.9 years and 47.4% females with a mean age of 67.4 ± 13.3 years. The average NIHSS score was 15.3 ± 4.8 and the median initial Alberta Stroke Program Early Computed Tomography score was 8.7 ± 1.3. The successful revascularization (mTICI 2b-3) rate was 85.2%, successful first-pass recanalization (mTICI 2c/3) was achieved in 39.8% (466/1,169) patients. The 90-day good functional outcome rate (mRS 0-2) was 39.8%, mortality (mRS 6) rate was 22.9%. The mean time for symptom onset to groin puncture was 230.4 ± 125.9.

Left-hemispheric strokes (51.4%) were more common than right-hemispheric strokes (48.2%; *p*=0.700).

Detailed patients' baseline characteristics, MT procedural parameters, and target vessels are summarized in Table I.

Of the 1,169 patients, 494 (42.3%) patients received combined MT+IV thrombolysis and 675 (57.7%) underwent direct MT.

We identified tandem ICA-MCA occlusion in 187

Table I. Patients baseline characteristics, MT procedural parameters, and target vessels.

n (%)	Cervical Carotid Atherosclerosis	Cardio -embolism	Other and Undetermined	*p*-value
Median age, y (±SD)	66.3±11.4	67.2±12.7	**63.3±13.7**	0.001
Women, n (%)	**61 (11.1)**	252 (45.7)	238 (43.2)	0.007
Median NIHSS (±SD)	**16.2±4.5**	15.2±4.4	15.1±5.3	0.018
Median ASPECT (±SD)	8.7±1.3	8.8±1.1	8.7±1.3	0.620
Symptom onset to groin recanalization, min, (±SD)	301.7±132.1	284.2±131.8	282.1±128.3	0.216
mTICI 2b-3 (%)	78.8	88	84.7	0.013
mRS 0-2 (%)	33.1	42.6	41.4	0.467
mRS 6 (%)	29.8	22.1	24.1	0.001
IV thrombolysis (%)	38.2	47.6	41.1	0.482
Symptomatic ICH (%)	28.2	15.7	16.6	0.481
First pass (%)	32	42.9	39.6	0.001
Atrial fibrillation (%)	5.1	76.3	2.4	0.001
Smoking (%)	30.2	17.3	27.8	0.001
Diabetes Mellitus (%)	31	32.7	30.4	0.732
Hypertension (%)	74	79.8	67.6	0.001
Ishemic stroke (%)	8	9.7	9.3	0.790

(16%) patients, carotid T occlusion in 173 (14.9%) patients, M1 occlusion in 486 (41.6%) patients, M2 occlusion in 192 (17.3%) patients, basilar occlusion in 68 (5.8%) patients, anterior cerebral artery A1 occlusion in 16 patients (1.4%), and posterior cerebral artery P1 occlusion in 31 patient (2.7%).

Fifty-three patients (4.5%) had symptomatic hemorrhage (NIHSS >4) with type 2 parenchymal hematoma. Ninety patients (7.7%) had asymptomatic type 1 parenchymal hematoma, 77 patients (6.6%) experienced asymptomatic petechial type 1 hemorrhage, and 73 patients (6.3%) had asymptomatic petechial type 2 hemorrhage (4.2%). Thirty-five patient (3%) had asymptomatic SAH.

Most common etiologies of ischemic stroke were cardioembolism in 532/1,169 (45.5%), large vessel atherosclerotic disease was observed in 175/1,169 (15%), undetermined etiology was detected in 461/1,169 (39.5%) of patients. Atrial fibrillation was the most common cause of cardioembolic stroke with a 76.3% incidence among cardiac causes (Table II).

We identified 11 (0.9%) acute stroke patients treated with MT who had recurrent LVO and received repeated MT. A cardioembolic cause was found to cause the recurrent LVO in 7 of the 11 (63.6%) patients. (Five patients with atrial fibrillation, one patient with mechanical aortic valve, and one patient with atrial cardiac thrombus)

Discussion

In our study, among acute stroke patients treated with thrombectomy, the most common stroke etiology was cardioembolism (45.5%). Atrial fibrillation is found to be the most common cause of cardioembolic stroke with 76.3% incidence among all cardioembolic causes. In addition, among patients with recurrent stroke, 63.6% had cardioembolic source.

Table II. Causes of cardioembolic stroke.

n=532 (%)	
Atrial fibrillation	406 (76.3)
Congestive heart failure (EF <30%)	38 (7.1)
Rheumatic valve disease	34 (6.3)
Spontaneous echocardiography contrast	5 (0.9)
Mechanical valve prosthesis	31 (5.8)
Left atrial or ventricular thrombus	3 (0.5)
Coronary artery catheteritaion	3 (0.5)
Recent myocardial infarction (<4 weeks)	4 (0.7)
Other	6 (1.1)

Ischemic stroke subtype is one of the most important predictors of clinical outcome in patients with LVO. It has been shown that patients with cardioembolic strokes had poorer functional outcomes and higher mortality rate than those patients with other stroke subtypes[13]. This may be attributed to poor leptomeningeal and dural collateral flow in cardioembolic stroke compared to patients with large vessel atherosclerosis[14]. In concordance to our study, cardioembolic strokes may show a higher rate of recurrence in the early and late periods, leading to poor prognosis[5,15,16].

Interestingly, the prevalence of stroke subtype may differ depending on the geographical characteristics including ethnicity[17,18]. Small vessel disease, is the most common subtype in some countries such as Pakistan, whereas the cardioembolic stroke is the most common cause in Western countries[19-21]. In Asian countries, cardioembolic stroke is less common compared to other subtypes whereas the prevalence of large vessel atherosclerosis in has been increasing[21-23]. In China, intracranial atherosclerosis is still the predominant cause of stroke[24]. In contrast to previous studies[25], when patients with acute stroke treated with thrombectomy were analyzed, Guglielmi et al[25] found predominance of cardioembolism with a rate of 47%.

AF is responsible for most cardioembolic strokes, which leads to a five-fold increase in ischemic stroke risk[16]. In a study, AF was detected in 76% of patients with cardioembolic stroke and newly detected AF was responsible for 30.6% cardioembolic stroke[26]. Furthermore, Gladstone et al[27] showed that 47% of stroke patients were related with cardioembolism and AF was associated with cardioembolic stroke in 94% patients. On the other hand, ischemic stroke may be the initial consequence of AF[28]. Both the incidence of AF and stroke increase with age. In some studies[29,30], AF was detected in 6.7% of those between the ages of 50-59, while it was detected in 36.2% of those between the ages of 80-89.

It is demonstrated in one study[31], that among acute stroke patients treated with mechanical thrombectomy and/or thrombolytic treatment, cardioembolic cause is the leading etiology. In this study, cardioembolic stroke was detected in 69.5% of acute stroke patients who underwent mechanical thrombectomy. In another study in which thrombolytic experience was shared, cardioembolic stroke was detected at a rate of 53%[32]. Another study[33] demonstrated a higher rate (49.3%) of cardioembolic stroke among thrombectomy patients.

In parallel to our study, cardioembolic source was the major cause stroke in patients undergoing mechanical thrombectomy. Furthermore, stroke recurrence occurred mostly in patients with cardioembolic etiology. In a study[34], examining patients having recurrent thrombectomy in the last 10 years, demonstrated that 86.5% of them had cardioembolic stroke subtype. Ikenberg et al[35] reported 2% recurrent thrombectomy rate in 697 patients in a period of 4 years. Majority of patients underwent recurrent thrombectomy had cardioembolic stroke (66%), while 19% had large vessel atherosclerosis [36].

In a study, Kim et al[37] observed that 49.3% of stroke patients had cardioembolic source, whereas 26.5% of patients experienced cryptogenic stroke. Clot histolopathology of cardioembolic and cryptogenic strokes were found to be similar, and the authors postulated that most cryptogenic strokes may be in fact cardioembolic. Recent technological advances including long-term Holter monitoring in detecting AF may lead to increased rate of cardioembolic stroke. In addition, performing detailed transthoracic echocardiography and the application of transesophagial echocardiography in indicated cases may contribute to better detection of cardioembolic stroke.

Limitations

Several limitations exist in our study. The retrospective design of the study is one of the limitations. The Holter recording was performed for 24 hours, and transesophageal echocardiography was not performed for every patient with cryptogenic stroke.

Conclusions

This study is one of the studies with the highest number of patients undergoing mechanical thrombectomy for large vessel occlusion focusing on etiology. Among these patients, most common etiologic subtype of large vessel occlusion is cardioembolic stroke. Of paramount importance, future strategies should consider more meticulous methods in detecting AF including long-term Holter monitorization with detailed transthoracic echocardiography. These findings need to be validated in future studies.

Funding
None.

Ethics Approval
This study was approved by of Samsun Training and Research Hospital Institutional Research Ethics Board (approval number TUEK 119-2021 GOKAEK/2-18).

Informed Consent
If the patient is judged to have capacity to give informed consent and able to provide written consent: the patient provides written consent. If the patient is judged to have capacity to give informed consent but unable to provide written consent due to a physical barrier: the patient provides witnessed oral consent and provides later written consent as soon as possible. If the patient lacks capacity to give informed consent, legal guardian is available: the legal guardian acts on behalf of the patient and provides written consent.
If the patient lacks capacity to give informed consent, legal guardian is not available, informed consent by next of kin: next acts on behalf of the patient following the patient's presumed will and provides written consent; patient or legal guardian provides later written consent as soon as possible.

Conflicts of Interest
The authors have no conflicts to disclose.

Authors' Contribution
Concept and design: CKA and EG. Analysis and interpretation: CKA, EG and AOO. Data collection: CKA, EG, OA, AO and AOO. Writing the article: CKA, EG, and AOO. Critical revision of the article: CKA, EG, and AOO. Final approval of the article: CKA and EG. Statistical analysis: CKA. Overall responsibility: CKA, EG, AOO, OA and AO.

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