# CORRELATION OF MICROEMBOLISM RISK FACTORS WITH AGE IN THE ISCHEMIC STROKE RECOVERY PERIOD

Orlova EV ✉, Berdalin AB, Lelyuk VG

Federal Center of Brain and Neurotechnologies of the Federal Medical Biological Agency, Moscow, Russia

Identification of the age-related features of interaction between the risk factors of microembolism can improve understanding of the mechanisms underlying the development of ischemic stroke (IS). The study was aimed to assess the effects of age and other risk factors of stroke on the biophysical characteristics of microembolic signals (MES) recorded during the ischemic stroke recovery period. Transcranial Doppler ultrasound (TCD) involving microembolus detection (MED) was performed in 515 people, the data of 28 patients having a history of ischemic stroke, among them 9 women (32%) and 19 men (68%) aged 33–78 (average age 58 ± 13 years), were included in the study. Using the mixed-effects linear model it was found that age and interaction between age and atrial fibrillation affected the power of MES. The increase in the power of the recorded MES with age is observed, that is especially evident in patients with atrial fibrillation ($p < 0.0005$). As for cardioembolic IS variant, the power and duration of MES turn out to be significantly higher in elderly patients ($p < 0.0005$). The power of MES gradually increases with age in patients with no atherosclerosis and gradually decreases in patients with atherosclerosis, while MES power in patients with atherosclerosis in general (all age groups) is significantly higher ($p < 0.0005$) than that observed in patients with no atherosclerosis.

**Keywords:** ischemic stroke, age, atrial fibrillation, atherosclerosis, microembolism

**Funding:** State Assignment No. 388-00083-22-00 of 30.12.2021, research project No. 122022100113-7 of 21 February 2022

**Author contribution:** Orlova EV — literature review, manuscript writing, working with the database, analysis of the results; Berdalin AB — working with the dataset, statistical processing of the results, part in writing the results and the discussion; Lelyuk VG — study planning and management, search for sources of funding, manuscript editing.

**Compliance with ethical standards:** the study was approved by the Ethics Committee of the Federal Center of Brain and Neurotechnologies of FMBA of Russia (protocol № 01/24-10-22 of 24 October 2022); the informed consent was submitted by all study participants.

✉ **Correspondence should be addressed:** Ekaterina V. Orlova
Ostrovityanova, 1/10, k. A8-008, Moscow, 117513, Russia; ekaterina.shlyk@gmail.com

**Received:** 28.10.2022 **Accepted:** 29.11.2022 **Published online:** 12.12.2022

**DOI:** 10.24075/brsmu.2022.058

# ВЗАИМОСВЯЗЬ ФАКТОРОВ РИСКА МИКРОЭМБОЛИИ С ВОЗРАСТОМ В ВОССТАНОВИТЕЛЬНОМ ПЕРИОДЕ ИШЕМИЧЕСКОГО ИНСУЛЬТА

Е. В. Орлова ✉, А. Б. Бердалин, В. Г. Лелюк

Федеральный центр мозга и нейротехнологий Федерального медико-биологического агентства, Москва, Россия

Выявление сопряженных с возрастом особенностей взаимодействия факторов риска развития микроэмболии может расширить представления о механизмах развития ишемического инсульта (ИИ). Целью исследования было изучить влияние возраста и других факторов риска инсульта на биофизические характеристики микроэмболических сигналов (МЭС), регистрируемых в восстановительном периоде ишемического инсульта. Транскраниальное допплеровское мониторирование с микроэмболодетекцией провели 515 лицам, в исследование были включены сведения о 28 пациентах, перенесших ишемический инсульт, из которых 9 (32%) женщин и 19 (68%) мужчин в возрасте 33–78 лет (средний возраст — 58 ± 13 лет). При помощи смешанной линейной модели выявлено, что возраст и взаимодействие возраста с наличием фибрилляции предсердий оказывали влияние на мощность МЭС. С возрастом наблюдается увеличение мощности регистрируемых МЭС, особенно заметное у пациентов с фибрилляцией предсердий ($p < 0{,}0005$). При кардиоэмболическом варианте ИИ мощность и длительность МЭС оказалась значимо больше у более пожилых лиц ($p < 0{,}0005$). При отсутствии атеросклероза мощность МЭС с возрастом постепенно увеличивалась, а при его наличии — постепенно уменьшалась, при этом мощность МЭС у пациентов с атеросклерозом в целом (во всех возрастных группах) была достоверно выше ($p < 0{,}0005$), чем при его отсутствии.

**Ключевые слова:** ишемический инсульт, возраст, фибрилляция предсердий, атеросклероз, микроэмболия

**Финансирование:** Государственное задание № 388-00083-22-00 от 30.12.2021, регистрационный номер НИР 122022100113-7 от 21 февраля 2022 г.

**Вклад авторов:** Е. В. Орлова — работа с источниками литературы, написание статьи, работа с базой данных, анализ полученных результатов; А. Б. Бердалин — работа с массивом данных, статистическая обработка результатов, участие в написании результатов исследования и их обсуждения; В. Г. Лелюк — планирование и руководство исследованием, поиск источников финансирования, редактирование статьи.

**Соблюдение этических стандартов:** исследование одобрено этическим комитетом ФЦМН ФМБА России (протокол № 01/24-10-22 от 24 октября 2022 г.); все участники исследования подписали добровольное информированное согласие.

✉ **Для корреспонденции:** Екатерина Владимировна Орлова
ул. Островитянова, д. 1/10, к. А8-008, г. Москва, 117513, Россия; ekaterina.shlyk@gmail.com

**Статья получена:** 28.10.2022 **Статья принята к печати:** 29.11.2022 **Опубликована онлайн:** 12.12.2022

**DOI:** 10.24075/vrgmu.2022.058

Brain embolism is one of the most common causes of ischemic stroke (IS) [1–4]. However, the sources of embolism and embolic material are extremely heterogeneous [5]. Thus, atrial fibrillation (AF), atherosclerosis of the brain-supplying arteries, and a number of less frequent conditions, such as inferior vena cava thrombosis, heart valve disease, etc., are considered as the sources of emboli [2, 6–8].

It is known that AF results in the five-fold increased risk of stroke and two-fold increased stroke mortality [9]. AF is one of the most common types of arrhythmia [10–12], the prevalence of AF in the entire population reaches 2–4%. AF increases the risk of ischemic stroke by 0.2–20% on average annually [13, 14]. Arterial hypertension is considered the main cause of AF. In the middle and senior age groups, AF is recognized as the most

**Table 1.** Basic information about the subjects enrolled

| Characteristics | Number, abs. | | Share, % |
|---|---|---|---|
| Gender | Male | 19 | 67.90 |
| | Female | 9 | 32.10 |
| | Total | 28 | 100 |
| Age | ≤ 50 years | 9 | 32.10 |
| | >50 years | 19 | 67.90 |
| | Total | 28 | 100 |
| Pathogenetic variant of IS | Atherothrombotic | 7 | 25 |
| | Cardioembolic | 6 | 21.40 |
| | Cryptogenic | 14 | 50 |
| | Lacunar | 1 | 3.60 |
| | Total | 28 | 100 |
| Affected system | Vertebrobasilar | 7 | 25 |
| | Carotid | 21 | 75 |
| | Total | 28 | 100 |
| Affected side | Bilateral | 4 | 14.30 |
| | Left | 9 | 32.10 |
| | Right | 15 | 53.60 |
| | Total | 28 | 100 |
| Arterial hypertension | Present | 5 | 17.90 |
| | Absent | 23 | 82.10 |
| | Total | 28 | 100 |
| Diabetes mellitus | Present | 18 | 64.30 |
| | Absent | 10 | 35.70 |
| | Total | 28 | 100 |
| AF | Present | 23 | 82.10 |
| | Absent | 5 | 17.90 |
| | Total | 28 | 100 |

common cause of cardiogenic brain embolism [10–12]. There is evidence that the risk of stroke increases as a function of AF duration and, accordingly, of age [10, 15].

Atherosclerosis, being the cause of IS, fulfils its potential in different ways: through atherothrombosis, hypoperfusion or arterio-arterial embolism [1, 2]. The frequency of these mechanisms is uncertain, however, we know that hypoperfusion is the least common mechanism of all [5, 6].

Information on the nature and prevalence of brain embolism available from other sources is even more limited [8, 16].

This is largely due to the high rate of situations, in which there is more than one cause of stroke, among stroke survivors, as well as to difficulties in verifying the fact of embolism [1]. Microembolus detection (MED) by transcranial Doppler ultrasound (TCD) is the only option for in vivo detection of emboli and assessment of the embolic signal intensity and type (based on indirect characteristics) by extraction of appropriate signals from the Doppler spectral blood flow waveforms of cerebral arteries [17]. Microembolic signals (MES) recorded by the specified method are regarded as an independent risk factor of IS and transient ischemic attack (TIA) [2–4]. The use of the method is limited by the lack of the temporal acoustic access.

Despite the fact that the results of studies focused on assessing MES and their intensity in patients with various conditions have been broadly published, there is a few data about the factors affecting embolism and its intensity, as well as the biophysical characteristics of MES and their interaction [2–5, 16].

Thus, it has been determined that asymptomatic paroxysmal AF with lower MES intensity is more favorable compared to chronic symptomatic AF, in which a significantly larger number of MES is detected. Further studies are required to confirm, whether MES have some predictive value in patients with chronic AF predisposed to ischemic stroke [16].

The presence of MES that is associated with the greatly increased risk of IS could be considered a predictor of early IS relapse [1].

Due to the fact that IS and TIA in younger patients and patients of the older age groups have different etiology and pathogenesis [6, 18, 19], identification of the age-related features of interaction between the risk factors of microembolism can have practical significance and can also expand understanding of the mechanisms underlying stroke development.

Inability to fully take into account interaction between factors affecting the event (characteristic, parameter) is a well-known limitation of all observational studies. In particular, it is unclear whether AF (or any other risk factor of IS) is associated with the registered MES, or this relationship is questionable and is due to the fact that individuals with AF are older, and microembolism is in fact associated with age. Thus, the use of statistical methods (see Methods) allowing for at least partial separation of interacting factors (for example, AF and age) is promising since it allows us to get closer to understanding of the cause and effect relationships that contribute to the MES occurrence.

The study was aimed to assess the effects of age and other risk factors of stroke on the biophysical characteristics of MES

**Table 2.** Information about the carotid artery stenosis severity in the patients enrolled

| | Median | 1st quartile | 3rd quartile | Maximum | Minimum |
|---|---|---|---|---|---|
| Severity of the right CCA stenosis (%) | 33 | 30 | 40 | 50 | 20 |
| Severity of the left CCA stenosis (%) | 35 | 30 | 48 | 50 | 25 |
| Severity of the right ICA stenosis (%) | 35 | 30 | 40 | 100 | 25 |
| Severity of the left ICA stenosis (%) | 35 | 30 | 50 | 70 | 20 |

recorded in patients with ischemic stroke during the recovery period.

## METHODS

After the peer reviewing the data of the multimodal instrumental study of 1600 clinical cases of IS during the recovery period, the group of experts that included ultrasound and functional diagnostics doctors, radiologists, neurologists, senior researchers and Head of the Department of Ultrasound and Functional Diagnostics selected 515 people, who underwent TCD involving MED in 2019–2021. In terms of design, we performed the cross-sectional observational study as part of the prospective cohort study.

Inclusion criteria: the history of IS, the presence of potential sources of embolism based on the comprehensive ultrasound examination.

Exclusion criteria: no temporal acoustic access for TCD involving MED.

Post-processing of the recordings revealed the signs of MES in 46 patients out of 515 observations (8.9%). After analyzing the MES acquired, we failed to obtain the values of the MES biophysical characteristics in all patients due to accidental technical difficulties. Thus, the data of 28 patients having a history of IS were included in the study. Among them 9 (32%) were women and 19 (68%) were men aged 33–78 years (the average age was 58 ± 13 years).

The patients enrolled underwent inpatient treatment at the departments of medical rehabilitation of the Federal Center of Brain and Neurotechnologies of FMBA of Russia. The following tests were performed in all patients.

1. Duplex scanning of the brachiocephalic arteries (DS BCA), transcranial duplex scanning (TCD), and transthoracic echocardiography (TTE) were performed using the Epiq 7 scanners (Philips; USA); extracranial sections of the BCA were examined using the 3–12 MHz broadband multi-frequency linear transducers, while TCD and TTE were performed using the 1–5 MHz broadband multi-frequency sector transducers.

2. TCD involving MED was performed with the Angiodin-Universal scanner (NPF BIOSS; Russia) equipped with the 2 MHz pulse wave sensors fixed in the Spencer's helmet. Blood flows in the middle cerebral artery (MCA) and posterior cerebral artery (PCA) were detected simultaneously from two sides using the temporal acoustic access; scanning was performed for 60 min when lying down or sitting [17]. To minimize artifacts during the study, the lowest possible amplification and power values that ensured preservation of Doppler spectrum were used. Automatic MES recording was performed during monitoring using the Bionita Cabinet software (Biosoft-M; Russia), while the subsequent analysis of the results and differentiation between MES and artifacts were performed in the manual mode. The size of the sample volume mark was 20 mm, detection was performed at a depth of 50–60 mm.

In case the signs of embolism were revealed, the embolism intensity was assessed (number of MES/hour). The duration (ms; an indirect characteristic of the embolus size), frequency (Hz; an indirect characteristic of the embolus structure), and power (dB; integral characteristic of the embolus) were defined for each MES.

3. Electrocardiography (ECG) was performed using the Neurosoft ECG monitoring system with the Poly-Spectrum software (Neurosoft; Russia) in accordance with the standard method.

Statistical processing of the results was performed in the SPSS Statistics ver. 26.0 software package (IBM; USA) and R software ver. 4.0.2. (R Core Team; Austria). The null hypothesis was rejected at a significance level of $p \leq 0.05$. The quantitative variables were described using mean and standard deviation or median and quartiles (in case of non-normal distribution), while qualitative variables were described using frequency and share (percentage). The distribution of quantitative variables was tested for normality using the Shapiro–Wilk test. The mixed-effects linear model with nested data was used to assess the effects of AF and intraluminal carotid artery buildup on the biophysical characteristics of MES adjusted for age taking into account every single MES.

## RESULTS

The main data of the patients enrolled are provided in Table 1.

No cases of myocardial infarction, coronary stenting, carotid endarterectomy, brachiocephalic artery dissection were reported.

The data on the extracranial BCA stenosis severity are provided in Table 2.

TCD involving MED revealed MES in all the people enrolled. A total of 938 MES were extracted. General information about the number and characteristics of MES is provided in Table 3.

The differences in the MES biophysical characteristics between patients having and not having AF were significant ($p < 0.05$).

The analysis of the AF impact on the MES characteristics adjusted for age performed using the mixed-effects linear model showed that the impact of the patient's age and

**Table 3.** Biophysical characteristics and the number of MES

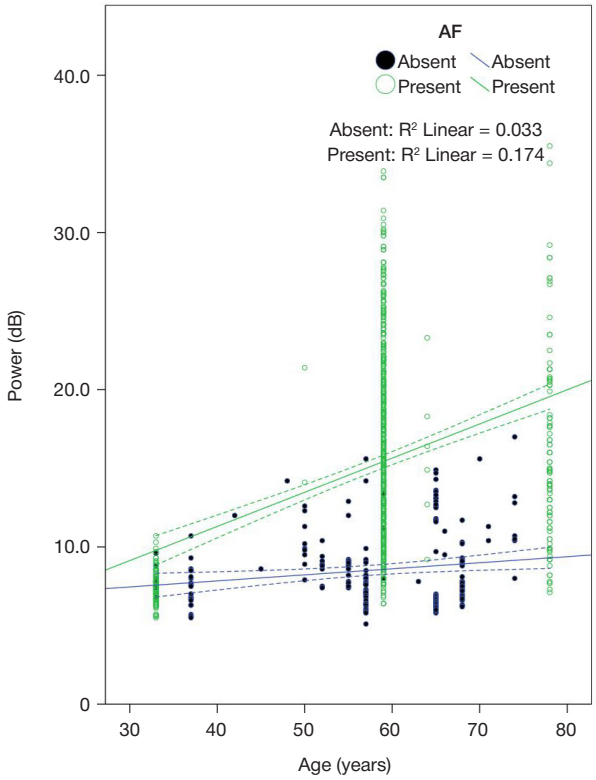
| | Mean | Standard deviation | Median | 25th percentile | 75th percentile | Maximum | Minimum |
|---|---|---|---|---|---|---|---|
| Total number of MES per patient | 34 | 105 | 3 | 1 | 10 | 532 | 1 |
| Average MES power (dB) | 11.06 | 3.32 | 10.22 | 8.31 | 14.2 | 17.75 | 7.28 |
| Average MES duration (ms) | 9.06 | 4.86 | 7.09 | 6 | 11.33 | 23.66 | 4.67 |
| Average MES frequency (Hz) | 528.19 | 241.8 | 475.92 | 328 | 750 | 968 | 230.5 |

**Table 4.** Biophysical characteristics of MES in patients having or not having AF

| | | AF | |
|---|---|---|---|
| | | Absent | Present |
| Adjusted number if MES per patient | Mean | 8.8333 | 149 |
| | Standard deviation | 13.2588 | 219.7476 |
| Average MES power | Mean | 10.0763 | 14.7022 |
| | Standard deviation | 2.4233 | 4.1322 |
| Average MES duration | Mean | 7.5597 | 15.4918 |
| | Standard deviation | 2.5796 | 6.955 |
| Average MES frequency | Mean | 500.7776 | 612.8418 |
| | Standard deviation | 237.8698 | 223.7408 |
| Average MES Energy Index (EI) | Mean | 0.0803 | 0.2784 |
| | Standard deviation | 0.0449 | 0.1675 |

interaction between age and AF on the recorded MES power was significant ($p < 0.0005$), thus indicating the modifying effect of one parameter on the effect of another one (Fig. 1). However, the isolated effect of AF (adjusted for age) was non-significant ($p = 0.109$). Thus, the recorded MES power increased with age, and this was particularly evident in patients with AF. In other words, AF resulted in the higher MES power only in elderly people, while young people with AF showed no significant differences in the MES power.

The mixed-effects linear model for assessment of the impact of the stroke type (cardioembolic/not cardioembolic) adjusted for age on the power and duration of the recorded




| Source | F-test | Significance, *p* |
|---|---|---|
| Adjusted model | 374,728 | < 0,0005 |
| Age | 24,978 | < 0,0005 |
| AF | 2,571 | 0,109 |
| Interaction between age and AF | 13,718 | < 0,0005 |

**Fig. 1.** Mixed-effects linear model of the impact of age and AF on the MES power

MES showed that such parameters as age ($p < 0.0005$) and interaction between age and IS variant ($p < 0.001$) were significant (Fig. 2). The pattern was broadly similar to the model for AF, i.e. the differences between cardioembolic stroke and stroke of another etiology were significant only in elderly patients with IS.

The constructed mixed-effects linear model of the impact of atherosclerotic plaques (ASPs) in the carotid arteries on the biophysical characteristics of the recorded MES constructed based on age showed that the presence of ASPs in the right and left common carotid artery (CCA) and interaction between these factors and age ($p < 0.0005$) were the significant factors (Fig. 3).

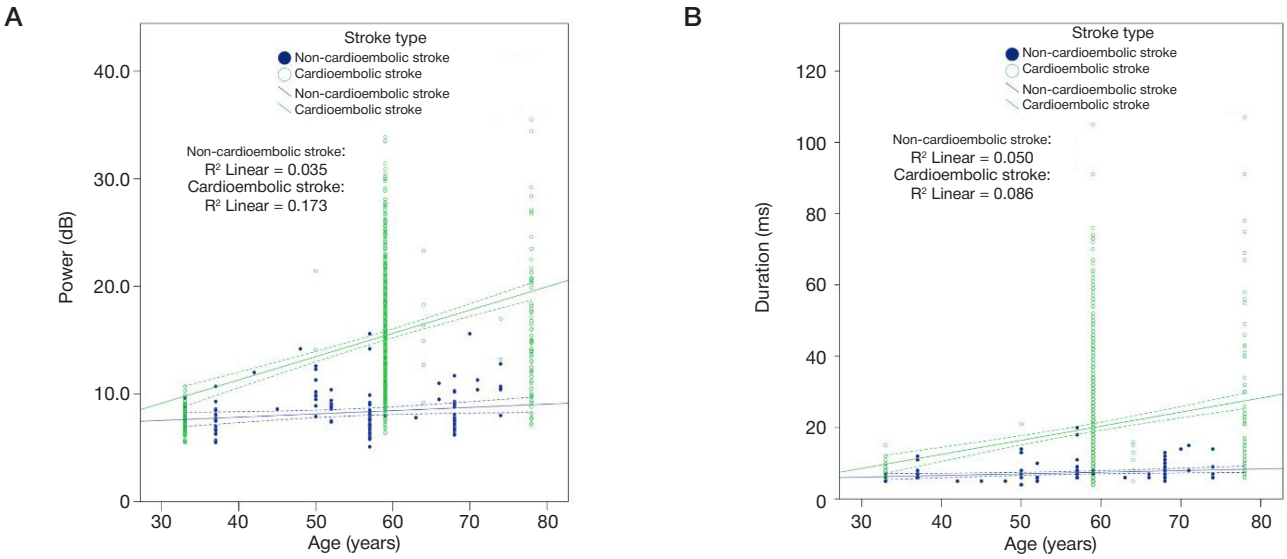
According to the findings, the very fact of the presence of ASPs in the carotid arteries was associated with the higher MES power, while the power-age trends correlated with the presence of ASPs. In other words, when no ASPs were found in the carotid arteries, the power of MES gradually increased with age. In contrast, when ASPs were present, the power of MES gradually decreased.

The mixed-effects linear model taking into account the effects of such risk factors as AF and ASPs in the carotid arteries together with age on the power and duration of MES was constructed in order to assess the competing causes of IS. However, interaction between the aforementioned parameters turned out to be non-significant ($p > 0.05$), i.e. in our study the effects of ASPs and AF on the biophysical characteristics of MES turned out to be unrelated.

## DISCUSSION

The study has a number of limitations. The first one is related to the embolic event, the embolic material intensity and type, while the second one is related to the method of TCD involving MED. Brain embolism is most often discrete, and its intensity is variable [4, 17]. Furthermore, emboli can be represented by the fragments of blood clots of various age, as well as by the fragments of atherosclerotic plaques, valves, components of vascular wall, etc. [1, 5, 16]. Therefore, biophysical parameters of MES may vary significantly in the same case. Methodological determinants result mainly from the flaws of software used for MES extraction from noise [17]. The reported facts show that the results obtained by the applied method cannot be considered as the data giving a comprehensive picture, however, this approach is currently the only available method for in vivo assessment of cerebral embolism.

Given the above limitations, it can be stated that the findings of our study that reflect the correlation of the biophysical




| Source | F-test for the model of impact on the MES intensity | *p* | F-test for the model of impact on the MES duration | *p* |
|---|---|---|---|---|
| Adjusted model | 240.572 | < 0.0005 | 1518.162 | < 0.0005 |
| Age | 19.922 | < 0.0005 | 16.181 | < 0.0005 |
| Stroke type (binary) | 2.226 | 0.136 | 1.913 | 0.167 |
| Interaction between age and stroke type | 11.58 | < 0.001 | 10.801 | < 0.001 |

**Fig. 2.** Mixed-effects linear model of the impact of age and stroke type on the power and duration of MES. **A**. Mixed-effects linear model of the impact of age and stroke type on the power of MES. **B**. Mixed-effects linear model of the impact of age and stroke type on the duration of MES

characteristics of MES with the patient's age and interaction between age and other risk factors of IS require further analysis.

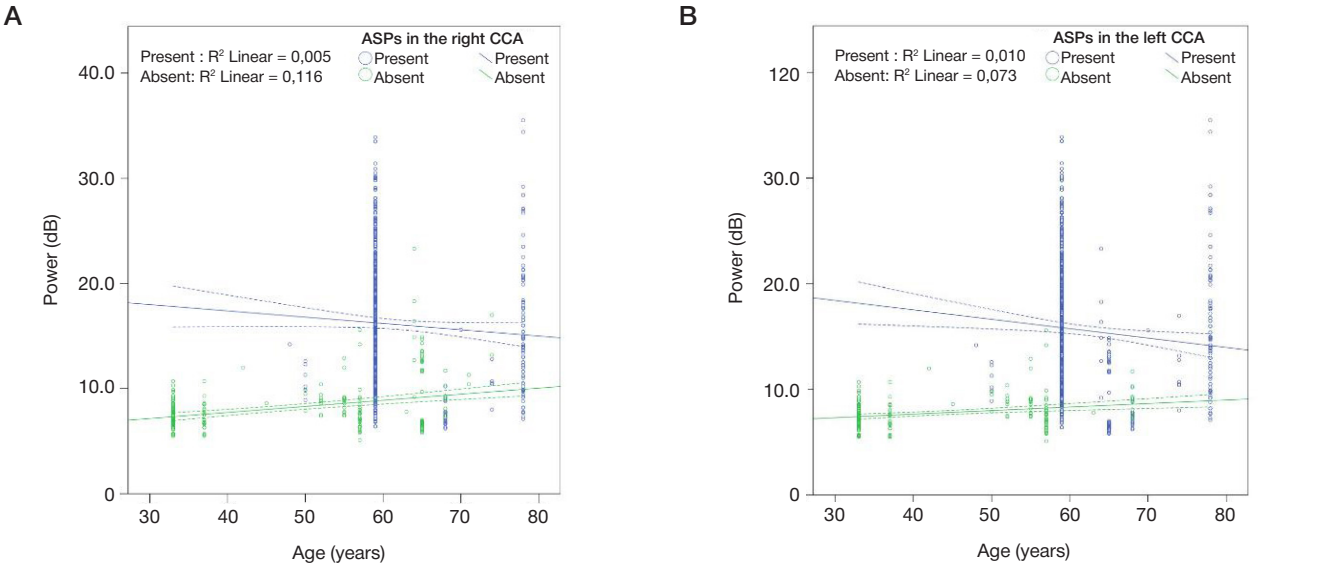
A number of researchers question whether AF itself can be the main cause of cardioembolic complications. They assume that AF is a kind of marker of atrial cardiopathy that can be considered as the proximate cause of cardioembolism [7, 20, 21]. There is also evidence of the relationship between the markers of atrial cardiopathy and IS, regardless of the presence of AF [22, 23].

To date, the literature reports no studies focused on the analysis of the IS risk factor impact on the biophysical characteristics of MES. The results of our study involving creation of the mixed-effects linear model for the impact of age and AF on the biophysical characteristics of MES show that age and interaction between age and AF are significant. MES power, being an integral biophysical characteristic that indirectly reflects both the size and the structure of microemboli, depends on age adjusted for the presence of AF. The data obtained also show that MES power (if any MES recorded) observed in young patients is independent of AF. However, AF affects MES power during ageing, i.e. in older patients. This is probably because of the fact that the pronounced slowing of blood flow, especially in the left atrial appendages of patients with AF, occurs only in elderly patients. Such slowing of blood flow combined with other possible factors results in thrombogenesis and cardioembolism of the brain blood vessels. This is partially confirmed by the literature data showing that the risk of stroke increases with the age-related increase in the atrial ectopic activity. However, the risk could be partially due to prothrombotic endothelial dysfunction developing in patients who develop atrial cardiopathy in addition to arrhythmia [10, 21]. The impact of other unevident factors that simulate such an effect also cannot be excluded. The development of AF resulting from atrial remodeling takes time, and the prevalence of such AF is higher in older people. In younger people, AF can be associated with other factors (genetic predisposition), not with the alterations in atrial wall. This indirectly confirms the increasingly popular viewpoint that cardioembolism is associated not with AF itself, but with alterations in atrial wall, such as inflammation [11, 21, 24]. AF itself is caused by the same remodeling processes. In younger patients, AF that is not associated with atrial remodeling never causes the emergence of MES.

The analysis of similar model taking into account the variant of stroke (in binary mode: cardioembolic/non-cardioembolic) instead of the presence of AF makes it possible to trace the relationship between two MES characteristics (power and duration) associated with ageing and stroke type. Furthermore, in cases of cardioembolic stroke, the values of these two characteristics are significantly higher in elderly patients. Perhaps, the discovered pattern reflects the occurrence of larger microemboli during realization of factors promoting age-related thrombogenesis. We also should take into account the fact that this could be partially due to almost mandatory assignment of IS to cardioembolic variant based on the TOAST criteria [25] in cases of AF.

The mixed-effects model taking into account both ASPs in the carotid arteries and age allows us to state that the impact of atherosclerosis on MES intensity gradually decreases with age. However, it is obvious that the presence of ASPs in the carotid arteries is associated with the significantly increased MES power compared to patients with no ASPs in both young and elderly patients. It can be assumed that atherosclerosis and arterio-arterial embolism is a major pathogenetic mechanism of acute focal cerebral ischemia, irrespective of age. We also cannot rule out that the cardiac sources may occupy a significant place in the structure of embolic events together with atherosclerosis and age. This explains the gradual increase in MES power with age in patients with no ASPs in the carotid arteries.

There is evidence of the impact of concomitant atherosclerotic vascular disease on the outcomes of ischemic events in patients with AF. Thus, it has been found that burden in the form of the combination of the cerebral artery




| Source | F-test (right CCA) | *p* | F-test (left CCA) | *p* |
|---|---|---|---|---|
| Adjusted model | 63 017.362 | < 0.0005 | 16 882.306 | < 0,0005 |
| Age | 5.723 | 0.017 | 3.851 | 0,05 |
| Presence of ASPs in the CCA | 129.205 | < 0.0005 | 53.639 | < 0,0005 |
| Interaction between age and the presence of ASPs in the CCA | 24.601 | < 0.0005 | 18.659 | < 0,0005 |

**Fig. 3.** Mixed-effects linear model of the impact of age and ASPs in the right and left CCA on the MES power. **A**. Mixed-effects linear model of the impact of age and ASPs in the right CCA on the MES power. **B**. Mixed-effects linear model of the impact of age and ASPs in the left CCA on the MES power

atherosclerosis and AF can be a cumulative marker of the high risk of adverse cardiovascular outcomes [26]. In our study we assessed the impact of AF and atherosclerotic alterations in the carotid arteries on the power and duration of MES taking into account the patients' age. The impact turned out to be non-significant, i.e. the earlier statement [26] was not confirmed.

Thus, the results of using TCD involving MED may be used for implementation of the personalized approach to secondary prevention of IS in the groups of patients with various combinations of risk factors.

## CONCLUSIONS

Age and the association of age with AF affect MES power in patients having a history of IS during the recovery period. The correlation can be traced of the age-related MES power and duration with the stroke variant. Moreover, in cardioembolic variant the values of these characteristics are higher in older patients. Our findings show that MES power gradually decreases with age in patients with ASPs in the carotid arteries, in contrast to patients with no atherosclerosis, while the power of MES in patients with atherosclerosis in general (all age groups) is higher. The impact of AF and ASPs in the carotid arteries, assessed taking into account the patients' age, on the power and duration of MES is non-significant. The findings will make it possible to expand the range of diagnostic information obtained by TCD involving MED in the groups of patients with various combinations of risk factors during the IS recovery period, thus contributing to the strategy of secondary prevention.

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