

**THE ROLE OF ENDOTHELIAL DYSFUNCTION IN PNEUMONIA IN PATIENTS
WITH ISCHEMIC STROKE****¹Rasulova Khurshidakhon Abduborievna, ²Achilov Itolmas Khamroevich**^{1,2}Tashkent Pediatric Medical Institute, Tashkent city clinical hospital No. 5<https://doi.org/10.5281/zenodo.8361060>

Abstract. In 78 patients with pneumonia (mean age 59 ± 7 years), serum levels of endothelin-1 (ET-1) were determined. Of these, the first (main) group included 41 patients with pneumonia who had a history of ischemic stroke (IS) for more than six months (P+IS), the second group (comparison) consisted of 37 with pneumonia without a history of stroke (P). In patients with P+IS, compared with patients with P without a history of stroke, the symptoms of the disease were more pronounced due to a more severe course of pneumonia. In all patients, the content of serum ET-1 was significantly higher than the control values, more pronounced in patients with P+IS. Indicators of the content of ET-1 had correlations with the state of lung function. Thus, the course of the disease in patients with pneumonia is characterized by the development of endothelial dysfunction. Their intensity is more pronounced in patients with cardiovascular diseases, in particular with a history of IS.

Keywords: pneumonia, ischemic stroke, endothelial dysfunction, endothelin-1, blood serum.

Аннотация. У 78 больных с пневмониями (средний возраст 59 ± 7 лет) проведено определение уровней эндотелина-1 (ЭТ-1) в сыворотке крови. Из них в первую (основную) группу вошел 41 больной с пневмониями, перенесший ишемический инсульт (ИИ) в анамнезе более шести месяцев (П+ИИ), вторую группу (сравнения) составили 37 с пневмониями без инсульта в анамнезе (П). У больных П+ИИ по сравнению с больными П без инсульта в анамнезе симптомы заболевания были более выраженными в связи с более тяжелым течением пневмонии. У всех больных содержание сывороточного ЭТ-1 было значимо выше значений контроля, более выражено у больных П+ИИ. Показатели содержания ЭТ-1 имели корреляционные взаимосвязи с состоянием функции легких. Таким образом, течение заболевания у больных с пневмониями характеризуется развитием эндотелиальной дисфункции. Их интенсивность более выражена у больных с сердечно-сосудистыми заболеваниями, в частности ИИ в анамнезе.

Ключевые слова: пневмония, ишемический инсульт, дисфункция эндотелия, эндотелин-1, сыворотка крови.

Аннотация. Пневмония билан оғриган 78 нафар беморларнинг (ўртача 59 ± 7 ёш) қон зардобида эндотелин-1 (ЭТ-1) даражаси аниқланди. Улардан биринчи (асосий) гуруҳга анамнезида ишемик инсульт (ИИ) бўлган пневмония билан оғриган 41 бемор (П+ИИ), иккинчи гуруҳ (таққослаш) анамнезида инсульт бўлмаган пневмонияли 37 бемор кирган (П). П+ИИ билан оғриган беморларда анамнезида инсульт бўлмаган беморларга нисбатан пневмония янада оғир кечиши аниқланган. Барча беморлар қон зардобида ЭТ-1 даражаси П+ИИ бўлган беморларда назорат қийматларидан, айниқса таққослама гуруҳдан анча юқори бўлган. ЭТ-1 кўрсаткичлари ўпка функцияси ҳолати билан боғлиқ бўлган. Шундай қилиб, пневмония билан оғриган беморларда касалликнинг кечиши эндотелиал дисфункция ривожланиши билан тавсифланади. Унинг интенсивлиги юрак-қон томир касалликлари, хусусан, инсульт ўтказган беморларда кўпроқ намоён бўлади.

Калим сўзлар: пневмония, ишемик инсульт, эндотелиал дисфункция, эндотелин-1, қон зардобу.

Introduction. According to WHO (2019), over the past decade, the main diseases that claimed the most human lives were diseases of the circulatory system (coronary heart disease and stroke), respiratory infections of the lower respiratory tract and chronic obstructive pulmonary disease (COPD) [28]. The urgency of the problem of pneumonia lies in the fact that in addition to the prevalence, this disease is characterized by high mortality and the presence of comorbid conditions (competing, background and combined diseases), and it is sometimes difficult to determine the cause of death directly related to pneumonia. Pneumonia causes every second death in the geriatric population and 90% of deaths from respiratory infections in people over 64 years of age [12, 28].

There are few works in the literature devoted to the role of pneumonia in the course and prognosis in patients with cardiovascular disasters. There are isolated studies showing that pneumonia was the cause of death in stroke patients – about 5% [20, 27].

According to different authors, the frequency of infectious complications in patients with strokes, both in the acute phase and with consequences, varies significantly (5-65% of cases), which is due to differences between patient samples, study design, methods of infection detection [12, 20], therefore reliable statistical data on the frequency of infections in patients there are no cases with strokes. The literature also discusses the complexity of diagnosing nosocomial pneumonia in patients with cardiovascular catastrophes in intensive care units [12].

The currently used term stroke-associated pneumonia (stroke-associated pneumonia – SAP), or post-stroke pneumonia, includes a spectrum of lower respiratory tract infections that occurred within seven days of the onset of stroke. SAP most often develops during the first week from the onset of stroke, possibly reflecting the period of the highest risk of developing pneumonia due to dysphagia, impaired consciousness, decreased immune response and immobility [25].

For a clearer understanding of the pathogenetic mechanisms of the development and progression of pneumonia, there is a need to monitor markers of endothelial dysfunction and immune response in various stages and forms of the disease, as well as to analyze the relationships between the indicators under consideration and risk factors for this pathology. The search for new sensitive and specific markers that allow us to study the pathomechanisms of the development of the disease, taking into account the comorbid background, will allow us to develop effective methods of pharmacological correction. One of such directions may be the effect on endothelial dysfunction (ED) [2, 8]. It can be assumed that ED may be an early sign of hemodynamic disorders in the small circle of blood circulation. The search for new targets for therapeutic effects in pneumonia, taking into account extrapulmonary disorders, is a promising direction of modern pulmonology and intensive care.

In this publication, we present the results of a study performed at the Department of Internal Diseases, Nephrology and Hemodialysis of TashPMI on the basis of the Tashkent State Clinical Hospital No. 5. **The aim of the work** was to study the content of endothelin-1 (ET-1) as a marker of endothelial dysfunction in pneumonia in patients who have suffered an ischemic stroke (IS).

Materials and Methods. A retrospective, prospective, cohort, case-control study was conducted. A total of 78 patients with community-acquired and nosocomial pneumonia were examined at an average age of 59 ± 7 years (from 38 to 83 years). Of these, 43 (55.1%) are men and 35 (44.9%) are women, the ratio is 1:1.2.

Depending on the presence of a history of stroke, patients were divided into two groups: the first (main) consisted of patients with pneumonia who had a history of IS for more than six months ($n=41$; 52.6%) (P+IS), i.e. late recovery and the period of persistent consequences of stroke, the second (comparison group) – patients with pneumonia without a history of stroke ($n=37$; 47.4%) (P). The control group consisted of 20 healthy donors, comparable in age and gender with the study groups.

All patients were subjected to general clinical (collection of complaints, individual and family history, physical examination, examination of organs and systems, neurostatus, clinical blood analysis with leukocytogram), instrumental (chest X-ray, pulse oximetry), microbiological (microscopic examination of sputum with staining according to standard techniques, isolation of pure cultures of microorganisms from the material taken) research. The severity of pneumonia was assessed on the M.J. Fine scale I - V classes (PSI – Pneumonia Severity Index, or PORT – Pneumonia Outcomes Research Team Scale, 1997). The degree of impaired consciousness was assessed according to the Glasgow com scale (Teasdale G.M., Jennett B., 1974.), the severity of IS was determined according to the Scandinavian Stroke Scale (1985).

The level of ET-1 (1-21) was determined by solid-phase enzyme immunoassay in selected and frozen blood sera of patients using a commercial “Biomedica” kit (Austria) according to manufacturer's instructions.

The data obtained during the study were subjected to statistical processing on a Pentium-IV personal computer using the Microsoft Office Excel-2012 software package.

Results and Discussion.

The results of the study showed the greatest number of cases of pneumonia in the age group of 45-75 years (31%) and in people over 75 years (26%). The lowest proportion of severe pneumonia in young patients (22%), aged 20-39, 40-51 years and over 60 years. Male patients (58.5%) (24 men and 17 women) prevailed in the P+IS group, while female patients (54%) (20 women and 17 men) prevailed among patients with pneumonia without stroke (54%).

The study included patients with pneumonia of various etiologies. Of the total number of patients with pneumonia ($n=68$), the majority were patients with nosocomial pneumonia – 26 patients (38.3%), community-acquired pneumonia – 23 patients (33.8%), aspiration pneumonia – 19 patients (27.9%). Nosocomial (nosocomial) and aspiration pneumonia were more common in patients who underwent IS.

The analysis of the clinical picture of pneumonia in hospitalized patients generally reflected the general patterns of the course of the disease. The symptoms of the disease consisted of the phenomena of intoxication (general weakness, headache, shortness of breath), a general inflammatory reaction (chills, sweating, fever) and syndromes of inflammatory changes in the lungs (cough with or without sputum, pleural pain, shortening of percussion sound, increased vocal tremor, increased bronchophony, weakened breathing, shallow-, medium- and large-bubbly, crepitating wheezes).

Table 1. Analysis of clinical symptoms in patients with pneumonia, depending on the presence of ischemic stroke in the anamnesis, %

Indicator	P+IS (n=41)	P (n=37)
Cough	64.3*	94.0
Shortness of breath	46.0*	60.3
Chest pain	32.9	37.7
Wheezing during chest auscultation	65.0	70.0
Respiratory rate more than 20 per minute	48.0	56.4
Heart rate over 90 per minute	47.2	31.0
Body temperature over 37.7°C	39.0	42.0

Note: * – significant reliability of differences between groups ($P < 0.05$).

The analysis of Table 1 showed that the frequency of cough and shortness of breath in patients with pneumonia who had suffered from IS was significantly lower than in patients without a history of stroke, which may be associated with decrease in the cough reflex and depression of the respiratory center due to neurological disorder.

The next stage of our work was to assess the severity of the clinical course of pneumonia and the relationship with the course and severity of stroke. In 69% of cases, pneumonia developed in severe IS with impaired consciousness, severe neurological deficiency (severe paresis, paralysis, swallowing disorders, bulbar, pseudobulbar syndrome). Depending on the localization of the focus of cerebral infarction, pneumonia was more common in vertebrobasilar (stem) stroke, which may also cause violations of the central regulation of respiratory function, along with hemorheological, microcirculatory and other disorders. Assessment of the severity of pneumonia allowed us to assess the course of pneumonia in patients with IS as a whole as severe. The results of our study showed that among patients with pneumonia after undergoing IS, pneumonia with lesions of more than two lung segments was much more common and hospitalization in the intensive care unit was more often required. In the structure of complications of pneumonia, lung abscesses were noted – 1.7%, pleural empyema – 1.7%, pleurisy – 17%, sepsis, acute respiratory distress syndrome (ARDS) and multiple organ failure syndrome (MOFS) - 19.4%. The proportion of patients with complicated pneumonia in the P+IS group was higher due to the greater number of severe pneumonia in this group. Severe pneumonia, observed in 50% of cases, directly correlated with the severity of stroke, prolonged forced horizontal position and swallowing disorder in patients with IS. Also, in the P+IS group, 2 patients (4.9%) with a prolonged course of pneumonia were noted, where the duration of treatment was 1-1.5 months. Pneumonia was classified as a fatal complication (direct cause of death) in the P+IS group in only 3 (7.3%) cases.

Investigation of endothelial dysfunction in the development of pneumonia. Due to the limited literature data and different ET-1 level norms adopted for various laboratory kits to determine the values of these indicators, in order to obtain the values of the norm, we conducted a survey of a group of relatively healthy donors, as well as a group of patients with acute IS. The level of ET-1 in the blood of practically healthy patients was 9.5 ± 2.87 fmol/ml.

In patients with pneumonia, an increase in the level of ET-1 was determined in comparison with the control group (38.79 ± 7.11 vs. 9.5 ± 2.87 fmol/ml, respectively; $P < 0.01$). The level of ET-1 in the blood serum of patients with P+IS was 45.32 ± 6.18 fmol/ml, which significantly exceeded in 1.4 times the values of patients with P without stroke – 32.26 ± 8.05 fmol/ml ($P < 0.05$).

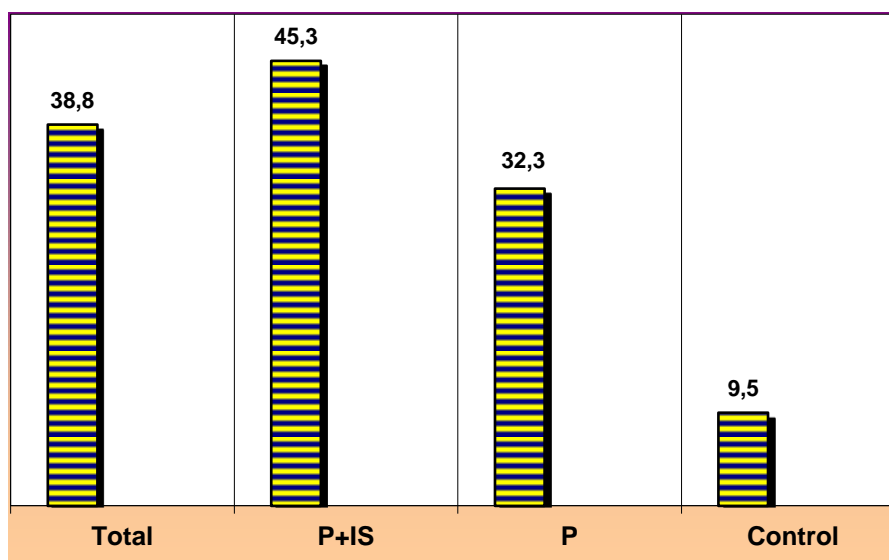


Figure 2. Serum levels of ET-1 in both groups of patients with pneumonia and in healthy donors.

When studying the correlation relationships of the data obtained during the study in patients with pneumonia, significant statistically significant sex and age differences in the levels of the studied ED marker were not revealed. Correlations between the ET-1 level and clinical scores assessing the severity of stroke and pneumonia were very weak (Table 2).

Table 2. Correlations between the endothelial dysfunction factor and the clinical course in pneumonia (r)

Factors	ET-1
Age	0.206
Glasgow coma scale scores	-0.105
Scandinavian scale scores	0.024
Fine scale scores	-0.029

This study showed that the level of ET-1 in the blood of patients with pneumonia is one of the most important indicators of endothelial dysfunction, as well as one of the independent factors for the prognosis of the course of the disease in these patients. The deterioration of the clinical picture of the disease is accompanied by a multiple increase in the level of ET-1. Considering the above, we can conclude about the prognostic value of determining the level of ET-1. The correlation of the ET-1 level with the presence of IS is consistent with the data of other authors on the relationship of this marker of ED with cardiovascular diseases [2, 14, 15].

Thus, the study of ED indicators indicating signs of inflammation is justified and necessary, since it contributes to the early detection and prediction of such a serious and socially significant disease as pneumonia.

Conclusions:

1. Patients with stroke have an increased risk of developing pneumonia due to the frequent development of dysphagia, the presence of aspiration, forced horizontal position, respiratory disorders. However, the diagnosis of pneumonia in this group of patients is difficult due to the frequent absence of signs of the disease in the early stages, which requires a

comprehensive assessment of clinical, laboratory and radiological data, early detection of predictors of development. At the same time, at the beginning of the development of pneumonia in this group of patients, fever, leukocytosis, auscultative data may indicate, which requires a timely start of adequate antibacterial therapy.

2. The course of pneumonia in patients who had suffered ischemic stroke is more severe than in patients without a history of stroke, aggravates the course of the underlying disease, increasing mortality, and in some cases, pneumonia is the direct cause of death of patients.

3. With pneumonia, there is a regular increase in the level of endothelin-1 in the blood serum, which indicates the development of inflammation and dysfunction of the endothelium, as well as a violation of hemodynamics in the small circle of blood circulation. Pronounced and long-term violations of the production of this marker depend on the severity of pneumonia, the presence and severity of ischemic stroke, complications and concomitant diseases.

4. Endothelin-1 levels can be used as a criterion for assessing the severity of the disease, prognosis, the possibility of a prolonged course, the addition of complications and the completeness of recovery.

REFERENCES

1. Авдеев С.Н. Аспирационная пневмония // Клин. микробиол. антимикроб. химиотер. – 2008. – Т. 10, № 3. – С. 216-234.
2. Бедило Н.В., Воробьева Н.А. Эндотелиальная дисфункция у пациентов с внебольничной пневмонией // Актуальные вопросы трансфузиологии и клинической медицины. – 2015. – №1. – С. 161-164.
3. Гребенчиков О.А., Филипповская Ж.С., Забелина Т.С. и др. Определение нитротирозина не позволяет оценить степень выраженности оксидантного стресса и прогнозировать вероятность развития ранних осложнений послеоперационного периода // Патология кровообращения и кардиохирургия. – 2017. – №21 (2). – С. 77-84. DOI: 10.21688-1681-3472-2017-2-77-84
4. Гусаров В.Г., Замятин М.Н., Теплых Б.А. и др. Диагностика и факторы риска нозокомиальной пневмонии у больных тяжелым инсультом // Вестник Национального медико-хирургического Центра им. Н.И. Пирогова. – 2012. – Т.7, №2. – С.63-69.
5. Каминская Л.Ю., Жлоба А.А., Александрова Л.А. и др. Влияние донатора NO нитрозотиола глутатиона на уровень окислов азота и малонового диальдегида в крови крыс // Артериал. гипертен. – 2005. – Т. 11, №1. – С. 5-9.
6. Козина О.В., Огородова Л.М., Геренг Е.А. и др. Вклад токсических метаболитов NO в формирование эозинофильного воспаления при бронхиальной астме // Пульмонология. – 2009. – № 4. – С. 69-73.
7. Комарин А.С., Азимов Р.К. Патофизиология обмена монооксида азота: Метод. рекомендации. – Т., 2005. – 29 с.
8. Кубышева Н.И., Постникова Л.Б., Соодаева С.К., Новиков В.В. и др. Значение растворимых молекул клеточной адгезии, метаболитов оксида азота, эндотелина-1 и их ассоциаций как маркеров прогрессирования воспаления при ХОБЛ // Современные технологии в медицине. – 2017. – Т. 9, №2. – С. 105-117.

9. Мальцева Л.А., Мищенко Е.А., Мосенцев Н.Ф., Мосенцев Н.Н., Голуб А.В. Дисфагия в отделении интенсивной терапии: эпидемиология, механизмы и клиническое ведение // Медицина неотложных состояний. – 2019. – № 6 (101). – С. 30-42.
10. Малявин А.Г., Одинцова Д.В. Роль пневмонии в танатогенезе у больных с инфарктом миокарда и инсультом // Доктор Ру. – 2015. – №3-4 (104-105). – С.17-21.
11. Огородова Л.М., Петрова И.В., Рукин К.Ю. Влияние 3-нитротирозина на формирование субпопуляции Т-регуляторных клеток при воспалении дыхательных путей // Научные ведомости Белгородского государственного университета. Серия: Медицина. Фармация. – 2011. – Т. 15, №16 (111). – С. 78-82.
12. Одинцова Д.В., Малявин А.Г., Зайратьянц О.В. Предикторы развития пневмонии у пациентов с острыми сосудистыми катастрофами // Архив внутренней медицины. – 2017. – № 7 (1). – С. 55-59. <https://doi.org/10.20514/2226-6704-2017-7-1-55-59>
13. Расулова Х.А. Клинико-биохимические особенности острых ишемических инсультов в зависимости от их патогенетической гетерогенности: Дисс. ... канд. мед.наук. – Т.: ТашИУВ, 2010. – 148 с.
14. Расулова Х.А. Нарушение обмена оксида азота при ишемическом инсульте в зависимости от его патогенетических подтипов // Мед. альманах. – 2013. – №1. – С. 111-114.
15. Расулова Х.А. Ангио-церебро-ренальная дисфункция при ишемическом инсульте: прогнозирование, диагностика, лечение: Автореф. дис. ... д-ра. мед.наук. – Т: ТашИУВ, 2018. – 66 с.
16. [Титов В.Ю.](#), [Болдырихин В.С.](#), [Иванова А.В.](#), [Осипов А.Н.](#) Возможный механизм образования нитрита и нитрилатных нитрозосоединений в плазме крови при воспалительных процессах // Бюллетень экспериментальной биологии и медицины. – 2014. – №4. – С. 479-482. <https://rucont.ru/efd/370737>
17. Фархутдинов У.Р., Амирова Э.Ф., Фархутдинов Р.Р. Особенности метаболизма оксида азота при внебольничной пневмонии и ее сочетании с хронической обструктивной болезнью легких // Биорадикалы и антиоксиданты. – 2018. – Т. 5, №3. – С. 247-249.
18. Штабницкий В.А., Чучалин А.Г. Причины отсутствия ответа на ингаляционный оксид азота у больных острым респираторным дистресс-синдромом // Вестник современной клинической медицины. – 2014. – Т. 7, №3. – С. 39-44.
19. Barzegar Amiri Olia M., Schiesser C.H., Taylor M.K. New reagents for detecting free radicals and oxidative stress // Organic & Biomolecular Chemistry. – 2014. – Vol. 45 (40). – P. 6758-67. <http://dx.doi.org/10.1039/c4ob01172d>
20. Chang C.Y., Cheng T.J., Lin C.Y., Chen J.Y. et al. Reporting of aspiration pneumonia or choking as a cause of death in patients who died with stroke // Stroke. – 2013. – Vol. 44, № 4. – P. 1182–1185.
21. Komiya K., Ishii H., Kadota J. Healthcare-associated pneumonia and aspiration pneumonia // Aging Dis. – 2015. – №6 (1). – P. 27-37.
22. Li L., Zhang H., Xu W.P. et al. Risk assessment of ischemic stroke associated pneumonia // World J. Emerg. Med. – 2014. – №5 (3). – P. 209-213.
23. [Rasulova K.](#) Correlation between nitric oxide and cholinesterase levels in blood serum of patients with acute ischemic stroke // European J. Neurol. – 2015. – Vol. 22. – P. 324-324.

24. Sellars C., Bowie L., Bagg J. et al. Risk factors for chest infection in acute stroke: a prospective cohort study // *Stroke*. – 2007. – Vol. 38, № 8. – P. 2284-2291.
25. Smith C.J., Kishore A.K., Vail A. et al. Diagnosis of stroke-associated pneumonia: recommendations from the pneumonia in stroke consensus group // *Stroke*. – 2015. – Vol. 46. – P. 2335-2340.
26. Warusevitane A., Karunatilake D., Sim J. et al. Early diagnosis of pneumonia in severe stroke: clinical features and the diagnostic role of C-reactive protein // *PLoS One*. – 2016. – Vol. 11 (3). – e0150269. doi:10.1371/journal.pone.0150269
27. Westendorp W.F., Nederkoorn P.J., Vermeij J.-D. et al. Post-stroke infection: A systematic review and meta-analysis // *BMC. Neurology*. – 2011. – Vol. 11. – P. 110.
28. World Health Statistics 2016: monitoring health for the SDGs, sustainable development goals. – World Health Organization (WHO) Reports, Geneva, Switzerland. – 2016. – 121 p. www.who.int
29. Zhang Y.H., Jin C.Z., Jang J.H., Wang Y. Molecular mechanisms of neuronal nitric oxide synthase in cardiac function and pathophysiology // *The Journal of Physiology*. – 2014. – Vol. 592 (15). – P. 3189-200. <http://dx.doi.org/10.1113/jphysiol.2013.270306>