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Original article

CD4$^+$ CELLS MITOCHONDRIAL MEMBRANE POTENTIAL IN MILD AND MODERATE ASTHMA

E.V. Kondratyeva, T.I. Vitkina

Abstract

Background. The pathogenetic mechanisms of bronchial asthma (BA) are based on the processes of changes in the cellular energy status and lipid metabolism, the development of hypoxemia, oxidative stress, and systemic inflammation. A reduction in mitochondrial membrane potential (MMP) is manifested even at the early stages of chronic lung diseases development and can be a key pathological sign of their clinical course aggravation.

Purpose. The aim of this study is to investigate the impact of bronchial asthma on the MMP of CD4$^+$ cells, depending on severity and disease control.

Materials and methods. The study included 289 patients with BA, of whom 151 exhibited mild severity and 138 exhibited moderate severity. The control group consisted of 60 volunteers who were deemed to be practically healthy. MMP was quantified using the JC-1 fluorescent dye and monoclonal antibodies for CD4$^+$ identification by flow cytometry. Five distinct levels of MMP were identified. The calculations were performed using the STATISTICA 10.0 software.

Results. A reduction in the total MMP results in a decline in the number of cells exhibiting very high MMP levels, while the number of cells with high and medium MMP levels increases. As the disease progresses and the level of control declines, the total MMP level reduces, accompanied by an increase in the number of CD4$^+$ cells exhibiting reduced and low MMP.

Conclusions. Patients with mild and moderate BA exhibited a pronounced unidirectional change in MMP levels of CD4$^+$ cells, which is dependent on the degree of severity and level of disease control. The assessment of the redistribution of MMP levels of CD4$^+$ cells provides an opportunity for the early detection of energy metabolism disorders in BA, which will allow optimizing the prevention of pathology progression.

Keywords: mitochondria; mitochondrial membrane potential; bronchial asthma; CD4$^+$ cells

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Научная статья

МЕМБРАННЫЙ ПОТЕНЦИАЛ МИТОХОНДРИЙ CD4$^+$ КЛЕТОК ПРИ БРОНХИАЛЬНОЙ АСТМЕ ЛЕГКОЙ И СРЕДНЕЙ СТЕПЕНИ ТЯЖЕСТИ

Е.В. Кондратьева, Т.И. Виткина

Аннотация

Обоснование. Патогенетические механизмы бронхиальной астмы (БА) основаны на процессах изменения энергетического состояния клеток и липидного обмена, развития гипоксии, окислительного стресса и системного воспаления Снижение митохондриального мембранного потенциала (ММП) проявляется уже на ранних этапах развития хронических заболеваний легких и может являться ключевым патологическим признаком утяжеления их течения.

Цель. Установить особенности нарушения мембранного потенциала митохондрий CD4$^+$ клеток при бронхиальной астме в зависимости от степени тяжести и контроля заболевания.

Материалы и методы. В исследование включено 289 больных БА: 151 легкой степени тяжести, 138 средней степени тяжести. Группу контроля составили 60 практически здоровых добровольцев. ММП оценивали с использованием флуоресцентного красителя JC-1 и моноклональных антител для идентификации CD4$^+$ методом проточной цитометрии. Выделяли 5 уровней ММП. Расчеты были проведены в программе «STATISTICA 10.0».

Результаты. При снижении общего ММП наблюдается снижение количества клеток с очень высоким ММП и повышение количества клеток с высоким и средним ММП. По мере утяжеления БА и снижения степени контроля выявлено уменьшение общего уровня ММП за счет повышения количества клеток CD4$^+$ со сниженным и низким ММП.

Заключение. При БА легкой и средней степени тяжести происходит выраженное однонаправленное изменение уровня ММП CD4+ клеток в зависимости от степени тяжести и уровня контроля заболевания. Оценка перераспределения уровней ММП CD4+ дает возможность раннего выявления

нарушений энергетического обмена при БА, что позволит оптимизировать профилактику прогрессирования патологии.

Ключевые слова: митохондрии; митохондриальный мембранный потенциал; бронхиальная астма; $CD4^+$

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Introduction

Bronchial asthma (BA) is a prevalent chronic respiratory disease that affects between 1 and 29% of the global population [6; 12; 16]. The underlying pathogenic mechanisms of BA are attributed to alterations in cellular energy status and lipid metabolism, the development of hypoxia, oxidative stress, and systemic inflammation [11]. $CD4^+$ T cells represent a significant factor in the determination of asthma phenotypes. In individuals with BA, inflammation is driven by cytokine-producing $CD4^+$ T cells, which play a central role in the recruitment and activation of innate immune cells, such as eosinophils, basophils, and mast cells. Furthermore, the pattern of disease progression differs depending on the differentiation of $CD4^+$ T cells, therefore, $CD4^+$ cells are essential in the pathogenesis of BA [13; 14].

One of the organelles involved in the fundamental processes of cellular metabolism and energy production, including the synthesis of adenosine triphosphate (ATP), are the mitochondria. They are responsible for the generation and removal of reactive oxygen species, the activation of the caspases family of proteases, the regulation of intracellular Ca^{2+} homeostasis, and the regulation of apoptotic cell death [7, 9]. Mitochondrial dysfunction is evident at the earliest stages of chronic lung disease development and may serve as a key indicator of disease progression. A reduction in mitochondrial membrane potential (MMP) and an increase in outer membrane permeability result in the release of cytochrome C, which in mitochondria performs the function of regulating energy metabolism. When this protein interacts with proteins in the cytosol, it triggers the activation of caspases, which ultimately leads to apoptosis. It is known that abnormal mitochondrial functioning, including metabolic switching, altered mitochondrial biogenesis and mitophagy, as well as impaired mitochondrial signal transduction plays a significant role in the pathogenesis of BA [10]. However, information regarding MMP changes in individual lymphocyte subpopulations and their role in the pathogenesis of BA is practically non-existent.

Purpose

The objective of this study is to identify the distinctive characteristics of mitochondrial membrane potential disturbance in $CD4^+$ cells at BA in relation to the severity and control of the disease.

Materials and methods

The study included 289 patients with BA. Of these, 151 were classified as having mild BA, including 57 with controlled BA (c.), 74 with partially controlled BA (p. c.), and 20 with uncontrolled BA (unc.). The remaining 138 patients were classified as having moderate BA, including 55 with c. BA, 58 with p. c. BA, and 25 with unc. BA. The control group comprised 60 volunteers who were deemed to be practically healthy. The mean age of the patients was 44.5 ± 4.9 years. The diagnosis of BA was made in accordance with the Global Strategy for Asthma Management and Prevention and the International Classification of Diseases, 10th revision. The study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki (2013) and was approved by the local ethical committee. Each patient participating in the study provided voluntary informed consent. The following exclusion criteria were applied: the presence of acute infectious diseases, chronic diseases of internal organs in the exacerbation phase, chronic heart failure in the decompensation stage, and contact with harmful and hazardous industrial factors.

Peripheral blood samples were collected in tubes containing an anticoagulant (EDTA). A leukocyte suspension was isolated by centrifugation at a density gradient (ficoll verographine).

MMP was evaluated by the percentage of $CD4^+$ lymphocyte cells with altered MMP employing flow cytometry on a BD FACSCanto II cytofluorimeter (USA) with concurrent addition of monoclonal antibodies for the identification of $CD4^+$ lymphocytes using the Mitoprobe JC-1 Assay Kit (Thermo Fisher Scientific, USA). A total of five structured MMP levels were employed to assess the intensity of the abnormalities. The 1st level, MMP-1, was defined as cells exhibiting the highest levels of MMP, characterized by maximum structural and functional integrity. The 2nd level, MMP-2, was defined as cells exhibiting high MMP, characterized by a slight decrease in structural and functional properties. The 3rd level, MMP-3, was defined as cells exhibiting moderate MMP, while processes were reversible. The 4th level, MMP-4, was characterized by cells with reduced MMP, with a transitional form to irreversible damage of the mitochondrial apparatus. The 5th level, MMP-5, was characterized by low MMP with irreversible damage of the mitochondrial apparatus.

The standard software of the flow cytometer was employed to identify the significant region of event fixation on the ordinate scale, which ranged from 0 to 10^5 (100%). Five blocks of equal significance were selected within this region: the lower block, ranged from 0 to 20%, corresponded to MMP-5; the next block, from 21 to 40% corresponded to MMP-4; the following block, from 41 to 60% corresponded to MMP-3; the next block, from 61 to 80% corresponded to MMP-2; and the final block, from 81 to 100% corresponded to MMP-1. The content of cells within these levels and their ratio undergo significant changes in accordance with the state of the organism. However, the conventional use of just two non-detailed levels in accordance with the standard methodology did not permit the revelation of these changes.

The calculations were performed utilizing the STATISTICA 10.0 software. The results of non-parametric descriptive statistics are presented as the median (Me) of the lower and upper quartiles (Q25 and Q75). The Mann-Whitney U test was employed to analyze the differences between the groups. The level of significance for differences was set at $p < 0.05$.

Results

The results of the calculations performed in the groups of patients with mild to moderate BA and the control group are presented in the Table below.

When analyzed according to the standard methodology (according to high and low MMP level), the percentage of cells with reduced mitochondrial membrane potential (MMP-4 and MMP-5) in the control group was 0.15%. In the $CD4^+$ cell population of individuals with mild severity BA, the following figures were observed: in individuals with a controlled (c.) course of disease – 0.45%, in partially controlled (p. c.) course – 1.9%, in uncontrolled (unc.) course – 2.5%, which is 0.3, 1.75, and 2.35% higher than those in the control group. In individuals with moderate severity BA, the relevant indicators for the population of $CD4^+$ cells were as follows: in the c. course – 2.05%, in the p. c. course – 4.4%, and in the unc. course – 6.2%, which is by 1.9, 4.25, and 6.05% higher than those in the control group.

The study of mitochondrial membrane potential using the proposed full-scale technique has led to establishment of the features of cell redistribution between the five MMP levels (Fig.).

A statistically significant decrease in MMP-1 indices by 20.1% ($p < 0.001$), 61.7% ($p < 0.001$), and 79.2% ($p < 0.001$) in the population of $CD4^+$ cells was observed in individuals with mild severity BA in the groups of c., p. c., and unc. course of disease, respectively, in comparison with the control groupA statisti-

cally significant increase in MMP-2 was observed in the groups with c., p. c., and unc. course of disease, respectively, and amounted to 18.8% ($p < 0.001$), 55.2% ($p < 0.001$), and 70% ($p < 0.001$). Similar statistically significant increase for MMP-3 for c., p. c., and unc. course were 1, 4.8, and 6.9%, respectively.

Table.

Membrane potential level in mild and moderate BA

Groups		Indicators, %				
		MMP-1	**MMP-2**	**MMP-3**	**MMP-4**	**MMP-5**
Control group n=25		93.9	5.25	0.7	0.1	0.05
		89.4–95.1	2.2–8.9	0.3–1.2	0.05–0.2	0.03–0.1
Mild BA	c. n=28	73.8***	24.05***	1.7***	0.35*	0.1**
		68.9–76.2	20.7–30.1	1.3–2.1	0.25–0.5	0.08–0.2
	p. c. n=27	32.2***	60.4***	5.5***	1.5***	0.4***
		30.1–37.1	55.1–63.9	4.7–5.9	1.1–1.9	0.35–0.55
	unc. n=20	14.7***	75.2***	7.6***	2***	0.5***
		12.5–17.1	69.4–78.8	5.9–8.6	1.3–2.6	0.35–0.7
Moderate BA	c. n=27	55.25***###	37.4***##	5.3***###	1.65***###	0.4***###
		50.5–57.6	33.2–40.5	4.5–5.7	1–2.2	0.3–0.5
	p. c. n=30	23.5***###	64.3***#	7.8***###	3.3***###	1.1***###
		18.1–25.7	60.7–67.3	7.1–8.8	2.5–4.2	0.5–2
	unc. n=25	3.1***###	75.6***	15.1***###	4.9***##	1.3***###
		2.4–5.5	68.7–78.2	13.2–17.3	2.9–6.3	0.9–1.6

*Note: * – statistical significance of differences in comparison with the control group: * – $p < 0.05$; ** – $p < 0.01$; *** – $p < 0.001$;*
 # – statistical significance of differences in comparison with mild BA group: # – $p < 0.05$; ## – $p < 0.01$; ### – $p < 0.001$.

A statistically significant increase in MMP-4 of the $CD4^+$ cell population in individuals with mild BA was observed to be 0.3% ($p < 0.05$), 1.4% ($p < 0.001$), and 1.9% ($p < 0.001$) in the groups of c., p. c., and unc. course of decease, respectively. A statistically significant increase was observed for MMP-5 in the c., p. c., and unc. course of disease, with values of 0.05% ($p < 0.01$), 0.4% ($p < 0.001$), and 0.5% ($p < 0.001$), respectively.

Relative to the control group, in the population of $CD4^+$ cells in individuals with a moderate BA, a statistically significant decrease in MMP-1 was by 38.7% ($p < 0.001$), 70.4% ($p < 0.001$), and 90.8% ($p < 0.001$) in the groups with a c., p. c., and unc. course of the disease, respectively. A statistically significant increase in MMP-2 in the groups with c., p. c., and unc. course of disease, increased by

32.2% ($p < 0.001$), 59.1% ($p < 0.001$), and 70.4% ($p < 0.001$), respectively. In contrast, a statistically significant increase in MMP-3 was observed in the groups with c., p. c., and unc. course of disease, which amounted to 4.6% ($p < 0.001$), 7.1% ($p < 0.001$), and 14.4% ($p < 0.001$), respectively.

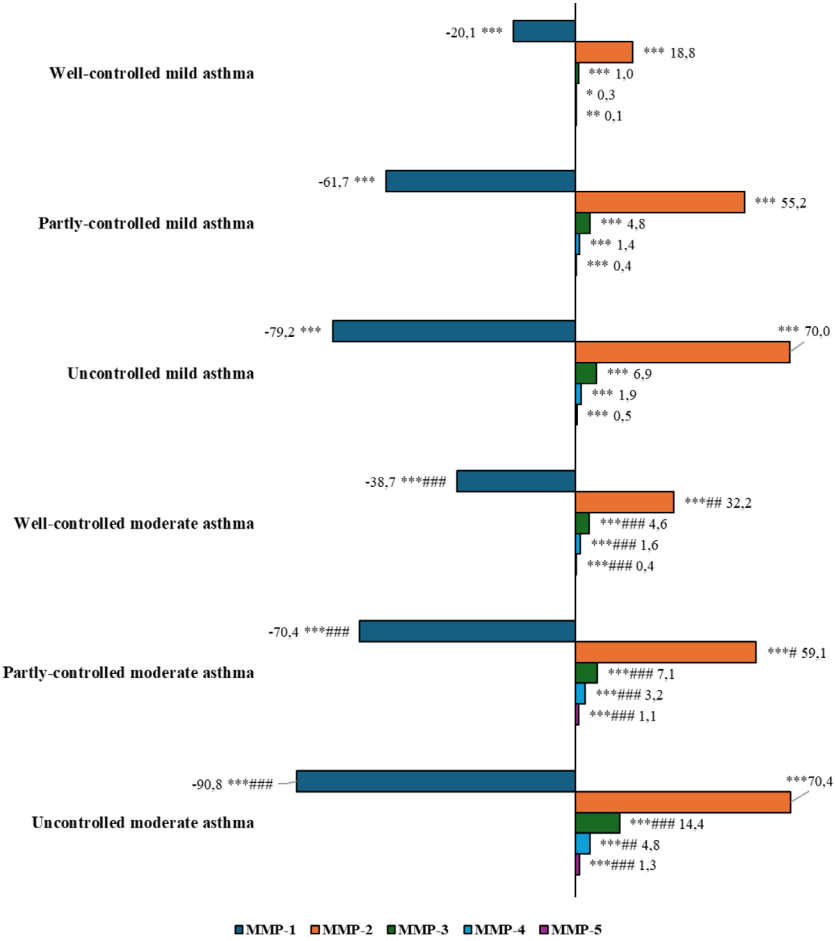

Fig. MMP of $CD4^+$ cell population at BA (comparing with control group, %)

Note: * – statistical significance of differences in comparison with the control group:
* – $p < 0.05$; ** – $p < 0.01$; *** – $p < 0.001$;
# – statistical significance of differences in comparison with mild BA group:
# – $p < 0.05$; ## – $p < 0.01$; ### – $p < 0.001$.

Relative to the control group, in the population of $CD4^+$ cells of individuals with a moderate BA an observed statistically significant increase in MMP-4 was 1.6% ($p < 0.001$), 3.2% ($p < 0.001$), and 4.8% ($p < 0.001$) in the groups with c., p. c., and unc. course of disease. A statistically significant increase in MMP-5 in the above mentioned groups was 0.4% ($p < 0.001$), 1.1% ($p < 0.001$), and 1.3% ($p < 0.001$), respectively.

In addition to the marked differences observed between MMP levels in mild and moderate BA, changes in the distribution of MMP levels were also observed, which were caused by disease control deterioration. Thus, MMP-1 level decreased by 41.6% ($p < 0.001$) and 59.1% ($p < 0.001$), while MMP-2 level increased by 36.4% ($p < 0.001$) and 51.2% ($p < 0.001$) in the p.c. and unc. groups of mild BA compared to c. group of patients with mild BA. In the p. c. and unc. groups of moderate BA, MMP-1 level decreased by 31.7% ($p < 0.001$) and 52.1% ($p < 0.001$), while that in MMP-2 increased by 26.9% ($p < 0.001$) and 38.2% ($p < 0.001$), respectively, compared to c. moderate BA.

Discussion

MMP is an indicator of the energetic state of the cell. It is well established that healthy cells exhibit a high MMP, whereas a reduction in MMP is indicative of the early stages of cellular damage, a process that subsequently progresses through the stages of degradation of the membrane apparatus, ultimately leading to irreversible consequences and cell death [3, 7, 10]. In the majority of cases, the assessment of MMP is based on the evaluation of two distinct indicator areas: cells with elevated membrane potential and cells with depressed membrane potential. This approach does not differentiate between the intensity of the cell damage process or its reversibility, which are crucial characteristics of the functional state of mitochondria [1–3].

During the course of BA, the permeability of the mitochondrial outer membrane increases, resulting in the release of soluble proteins into the cytoplasm and a decrease in MMP [17]. The present study has demonstrated that the most significant alterations in the cellular ratio occur at the levels of MMP-1 and MMP-2. A reduction in the total MMP level results in a redistribution between five levels of cells. The number of MMP-1 cells is observed to decrease, while at this expense the number of MMP-2 and MMP-3 cells increases. Additionally, a reduction in the overall MMP level is associated with an increase in the number of $CD4^+$ cells exhibiting reduced and low MMP levels (MMP-4 and MMP-5). An increase in the number of $CD4^+$ subpopulations of immune-competent cells with MMP-4 and MMP-5 levels and

their prevalence may result in the dysregulation of the immune system and the progression of pathology.

A comparative analysis of the data allows for the identification of more pronounced changes in the ratio of MMP-1 and MMP-2 CD4-positive cells in the context of a loss of disease control. A further significant indicator of this process is an increase in MMP-3 values in T-helper cells.

Recent studies have demonstrated a reduction in MMP levels in lymphocytes, monocytes, neutrophils, and the leukocytes cell population in general, which suggests an imbalance in energy processes in this pathology [2; 5]. The mechanism of MMP reduction in BA patients may be related to the disruption of mitochondrial membrane structure and changes in the qualitative and quantitative composition of fatty acids. These processes result in an increase in mitochondrial membrane permeability and the development of mitochondrial dysfunction [1–4; 8; 14; 15].

The observed trends suggest that disturbances in MMP levels in $CD4^+$ cells may be of significant importance in the context of both the exacerbation of BA and the loss of disease control.

Conclusions

In mild and moderate BA there are unidirectional changes in MMP levels of $CD4^+$ cells, with pronouncement dependent on the degree of severity and level of disease control. Assessment of the redistribution of MMP levels of $CD4^+$ cells may contribute to early detection of energy metabolism disorders in BA, which will allow for the optimization and prevention of pathology progression.

Ethics Committee Approval. The study was conducted in accordance with the principles of the World Medical Association's Declaration of Helsinki and approved by the Ethics Committee of Vladivostok Branch of Federal State Budgetary Scientific Institution "Far Eastern Research Center for Physiology and Pathology of Breathing" — Research Institute of Medical Climatology and Rehabilitation Treatment: Protocol No. 9 dated November 24, 2021.

Informed Consent. Informed consent was obtained from all subjects participating in the study. Written informed consent was obtained from patients for publication of this article.

Conflict of Interest Information. The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

The authors contributed equally to this article.

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DATA ABOUT THE AUTHORS

Elena V. Kondratyeva, PhD, Senior Researcher of Biomedical research Laboratory
Vladivostok Branch of Far Eastern Scientific Center of Physiology and Pathology of Respiration – Institute of Medical Climatology and Rehabilitative Treatment
73g, Russkaya Str., Vladivostok, Russian Federation
elena.v.kondratyeva@yandex.ru
SPIN-code: 8907-2001
ORCID: https://orcid.org/0000-0002-3024-9873
ResearcherID: HLG-7594-2023
Scopus Author ID: 57103185200

Tatyana I. Vitkina, PhD, DSc, Professor RAS, Head of Laboratory of Medical Ecology and Recreational Resources
Vladivostok Branch of Far Eastern Scientific Center of Physiology and Pathology of Respiration – Institute of Medical Climatology and Rehabilitative Treatment
73g, Russkaya Str., Vladivostok, Russian Federation
tash30@mail.ru
SPIN-code: 4578-3522
ORCID: https://orcid.org/0000-0002-1009-9011
ResearcherID: F-5250-2016
Scopus Author ID: 22954655800

ДАННЫЕ ОБ АВТОРАХ

Кондратьева Елена Викторовна, к.б.н., с.н.с. лаборатории биомедицинских исследований
Владивостокский филиал Федерального государственного бюджетного научного учреждения «Дальневосточный научный центр физиологии и патологии дыхания» – Научно-исследовательский институт медицинской климатологии и восстановительного лечения
ул. Русская, 73г, г. Владивосток, 690105, Российская Федерация
elena.v.kondratyeva@yandex.ru

Виткина Татьяна Исааковна, д.б.н., профессор РАН, заведующая лабораторией медицинской экологии и рекреационных ресурсов
Владивостокский филиал Федерального государственного бюджетного научного учреждения «Дальневосточный научный центр физиологии и патологии дыхания» – Научно-исследовательский институт медицинской климатологии и восстановительного лечения
ул. Русская, 73г, г. Владивосток, 690105, Российская Федерация
tash30@mail.ru

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