ASSESSMENT OF LIPID PROFILE STABILITY IN POSTMORTEM SAMPLES FOR THE DEVELOPMENT OF INTRAOPERATIVE DIAGNOSTIC METHODS

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Intraoperative determination of tumor margins reduces the volume of resected tissue while ensuring complete removal of malignant tissue without increasing the risk of recurrence. The existing approaches, including intraoperative histology or tomography, are highly effective, but they extend the time of the surgery. Therefore, real-time analysis methods are a particularly interesting avenue. One such solution is mass spectrometric profiling based on ambient ionization mass spectrometry. The molecular profile of the examined tissue is compared with a reference database of healthy and pathologically altered tissues. For many human organs, samples for this database can only be obtained from autopsy material. However, due to the unavoidable time delay between the moment of death and sample collection, tissue degradation may change the picture of pathological process. This experimental quantitative study investigated the stability of polar lipid profiles in the liver and brain tissues of healthy BALB/c mice (n = 23) during the early postmortem period (0–72 hours). It has been shown that lysolipids and free fatty acids correlate with the postmortem interval (r > 0.6 overall; r = 0.75 for FA 20:4 and FA 22:6); therefore, they cannot be used as molecular markers in diagnostic models based on autopsy samples. At the same time, the profile of phospholipids in tissue cell membranes remains largely unchanged in the early postmortem period, which preserves their value as biomarkers detectable in both biopsy and autopsy specimens.

Keywords: mass spectrometry, molecular diagnostics, molecular profiling, lipids, postmortem stability, oncometabolites, intraoperative diagnostics

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ОЦЕНКА СТАБИЛЬНОСТИ ЛИПИДНОГО ПРОФИЛЯ ПОСМЕРТНОГО БИОМАТЕРИАЛА ДЛЯ РАЗВИТИЯ МЕТОДОВ ИНТРАОПЕРАЦИОННОЙ ДИАГНОСТИКИ

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Интраоперационное определение границ опухоли позволяет снизить объем резекции, обеспечивая полноту удаления злокачественной ткани без повышения риска рецидива. Существующие подходы, такие как интраоперационная гистология или томография, отличаются высокой эффективностью, но увеличивают продолжительность хирургического вмешательства. Поэтому особый интерес представляет развитие методов анализа в реальном времени. Одним из таких решений является масс-спектрометрическое профилирование, основанное на методах прямой ионизации. Молекулярный профиль исследуемой ткани сопоставляется с референсной базой данных, содержащей профили патологически измененной и здоровой контрольной ткани, получение которой для многих органов человека возможно только с использованием аутопсийного материала. Однако из-за неизбежной задержки между наступлением смерти и отбором образцов, процессы деградации тканей могут вносить вклад в картину изменений, связанных с развитием патологического процесса. Цель проведенного экспериментального количественного исследования — изучить стабильность профилей полярных липидов в тканях печени и головного мозга здоровых мышей линии Balb/c (n = 23) в раннем посмертном периоде (0–72 ч). Показано, что лизолипиды и свободные жирные кислоты коррелируют (r > 0,6 для всех; r = 0,75 для FA 20:4 и FA 22:6) с посмертным интервалом, поэтому не могут быть использованы как молекулярные маркеры для построения диагностических моделей на базе коллекций аутопсийного материала. В то же время фосфолипиды клеточных мембран не претерпевают существенных изменений представленности в тканях в раннем посмертном периоде, поэтому сохраняют потенциал как биомаркеры, подходящие для выявления с использованием не только биопсийного, но и аутопсийного материала.

Ключевые слова: масс-спектрометрия, молекулярная диагностика, метаболическое профилирование, липиды, посмертная стабильность, онкометаболиты, интраоперационная диагностика

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Соблюдение этических стандартов: исследование одобрено комиссией по контролю за содержанием и использованием лабораторных животных центра доклинических исследований центральной научно-исследовательской лаборатории (ЦДИ ЦНИЛ) ФГБОУ ВО СибГМУ Минздрава России (протокол № 1 от 13 октября 2023 г.). Работа выполнена в соответствии с Федеральным законом № 61-ФЗ «Об обращении лекарственных средств», рекомендациями Коллегии Евразийской экономической комиссии 2023 г. «Руководство по работе с лабораторными (экспериментальными) животными при проведении доклинических (неклинических) исследований». Соблюдены санитарно-эпидемиологические нормы, закрепленные в СанПиН 3.3686-21 «Санитарно-эпидемиологические требования по профилактике инфекционных болезней».

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The procedural speed of ambient ionization mass spectrometry makes it a promising tool for intraoperative decision support in oncology-related elective operations [1]. Such intraoperative diagnostic methods enable the identification of pathological descriptors by comparing the molecular profile of the examined tissue with a reference database containing profiles of diseased and healthy control samples. The selection of control (non-tumor) samples for such a database is particularly important. One common approach is to use tissues from the vicinity of the tumor [2]. However, such samples may contain a certain number of tumor cells, and morphologically normal cells near the tumor margin may exhibit altered metabolic profiles [1]. The use of tissue affected by a different pathology as a control is not an optimal approach in metabolic studies, as the effects of pathological processes on metabolic pathways are highly complex [3]. A possible solution to the problem of availability of control samples is to collect them from healthy tissues obtained at autopsy. Compared to intraoperative biopsy, usage of postmortem tissues also allows obtaining samples from several regions of the organ, and, if necessary, large samples. Such tissues are important in the context of investigation of etiology and pathogenesis of various diseases, especially in the fields of neurobiology [4] and oncology [5]. However, the accuracy of molecular biological studies can be compromised when samples with different postmortem intervals (PMI) are combined, because PMI has a variable and unpredictable effect on tissue molecular profiles [6, 7].

The death of an organism does not immediately lead to the death of its cells. This is illustrated by rigor mortis, in which skeletal muscles continue to metabolize ATP until all reserves are depleted. The continued metabolism of cells after death is the fundamental reason that enables organ and tissue transplantation from deceased donors [5]. In the last decade, there formed thanatotranscriptomics, a new scientific field that studies global changes in gene expression after death [8]. A large-scale analysis of GTEx project data revealed that PMI length influences tissue specificity and gene-specific patterns of mRNA expression and degradation [9]. A significant increase in the transcription of more than a thousand genes, mainly related to stress, immunity, inflammation, and apoptosis, was detected in the tissues of laboratory animals up to 96 hours after death [10]. Investigation of degradation processes in healthy and pathologically altered tissues allows telling the true, physiologically or pathologically caused changes from the artifacts stemming from postmortem phenomena. A comparative analysis of the postmortem dynamics of gene expression showed that by the 24th hour of PMI, the transcription profiles of healthy and tumor liver tissue begin to converge; the initial difference in the expression of individual genes in this work were significant, and the quality of biomaterial was adequate [11]. Thus, healthy and tumor tissues transform differently after death, and the initial differences in the living tissue are masked. Besides nucleic acids, there are studies focuses on postmortem changes in proteins [12] and small molecules — metabolites [13] and lipids — which are the fastest to reflect all changes occurring in the body due to internal and external factors.

Lipids are an essential component of the cell membrane; they are involved in many biological processes, such as energy metabolism, cellular recognition, and the development and resolution of inflammation. Lipids are easy to detect with high-performance mass spectrometry-based method, which makes them suitable as markers in the domains of neurodegenerative and psychiatric diseases [14], as well as some types of oncologies: tumors of the hepatobiliary system [15], brain [16], etc. Unlike nucleic acids and proteins, relatively few studies have examined the postmortem stability of tissue lipid profiles. Forensic studies focus on long PMI and relevant organs and tissues (bones and muscles) [17, 18]. A 2024 systematic review [19] described lipidomic data as a means of determining PMI; however, studies on the lipid composition of organs have been conducted only for muscle, adipose tissue, and blood. It is noted that there are still no equations linking lipid concentrations with PMI. A study of lipid stability in pre-collected human and rodent brain samples showed that only oxidized fatty acids change significantly in a 48-hour PMI [20]. Changes in the conditions of storage of the samples within the first hour from collection do not affect the lipid profile [21]. Thus, a relevant task today is to investigate the postmortem stability of lipids in human autopsy material early after death (within a 72-hour PMI).

This study aimed to describe changes in the lipid composition of liver and brain tissues of a model animal in the early postmortem period by building a molecular profile using ambient ionization mass spectrometry. The brain and liver were chosen because, for the former, the crucial aspect is achieving complete tumor resection with minimal involvement of healthy tissue, which requires intraoperative determination of tumor margins; for the latter, assessing the degree of tumor invasion can help minimize the extent of resection (as liver tumor surgery traditionally involves removing large portions of the organ) without increasing the risk of recurrence. The liver is also relatively homogeneous and exhibits rapid lipid metabolism, making it a suitable organ for assessing postmortem changes in tissue lipid profiles.

METHODS

The experiments involved 23 male Balb/c mice (weight 19–22 g, age about 2 months). After delivery from the vivarium, the animals were quarantined for 7 days under a natural light/dark cycle, with ad libitum access to food and water. The animals were euthanized with a zoletil solution (Zoletil 100, 200 mg/kg), and their cervical vertebrae were dislocated afterwards.

The mice were randomly assigned to two groups with different post-euthanasia storage conditions: group 1 — storage at +4 °C prior to necropsy; group 2 — storage at +22 °C for the first 4 hours, followed by storage at +4 °C prior to necropsy (Table). The conditions for group 2 were similar to those found in hospital autopsy rooms. Each sample of the necropsy material measured 70 mm^3. The samples were placed in cryotubes, cooled in liquid nitrogen, and stored at –80 °C.

We applied the inline cartridge extraction technique to generate mass spectrometric profiles [22]. The cartridges with integrated disposable electrospray emitters were used as an ion source. The tissue samples were thawed, and three fragments (1–2 mm^3) were excised from each of them for triplicate analysis. The fragments were then washed in 0.9% (w/v) sodium chloride solution. Each fragment was placed into a cartridge and sealed with a solvent injection capillary [22]. The cartridge was connected to the solvent supply line with chromatographic screws, and placed in a purpose-designed holder ensuring the needed three-dimensional positioning and voltage supply from the mass spectrometer. The flow microextraction solution consisted of methanol, isopropanol, acetonitrile, and water in a 3 : 3 : 3 : 1 ratio, with 0.1% (v/v) acetic acid added. This composition ensures effective ionization of polar lipids of various classes [22].

For the experiments was used an LTQ XL Orbitrap ETD hybrid mass spectrometer (ThermoFisher, USA) in full scan mode with m/z 100–2000. The spectra were acquired using a high-resolution mass analyzer (30,000 FWHM at m/z 400) in

Table. Allocation of animals to experimental groups

Group number	Storage time at +22 °C, h	Storage time at +4 °C, h	Total time from euthanasia to necropsy, h	Number of animals
Group 1	0	0	0	2
	0	1	1	1
	0	2	2	1
	0	4	4	2
	0	8	8	2
	0	16	16	1
	0	24	24	1
	0	35	35	1
	0	48	48	1
	0	72	72	1
Group 2	0	1	1	1
	0	2	2	1
	0	4	4	1
	4	1	5	1
	4	2	6	1
	4	4	8	1
	4	16	20	1
	4	26	30	1
	4	46	50	1
	4	65	69	1

both positive and negative ion modes. For each mode, we did two experimental repetitions per sample (cartridge).

The assessment of changes in the tissue lipid profile involved an analysis of behavior of individual glycerophospholipids and potential degradation products — lysophospholipids and free fatty acids (FFA). We examined how postmortem interval length affects the relative intensities of phosphatidylinositols, phosphatidylcholines, and phosphatidylethanolamines containing fatty acid residues FA 16 : 0 and 18 : 0 at the sn-1 position and FA 18 : 2, 20 : 3, 20 : 4, 20 : 5, 22 : 4, 22 : 5, and 22 : 6 at the sn-2 position, which are among the most common lipids in liver and brain tissues [23]. Linear regression was used to detect the presence of a trend (a monotonous dependence of the response value on time).

To construct a matrix of peaks intensity potentially corresponding to lipids from the list, each mass spectrum scan was normalized to total ion current, peaks with a signal-to-noise ratio ≥ 2 were selected, and only peaks with nonzero intensity in

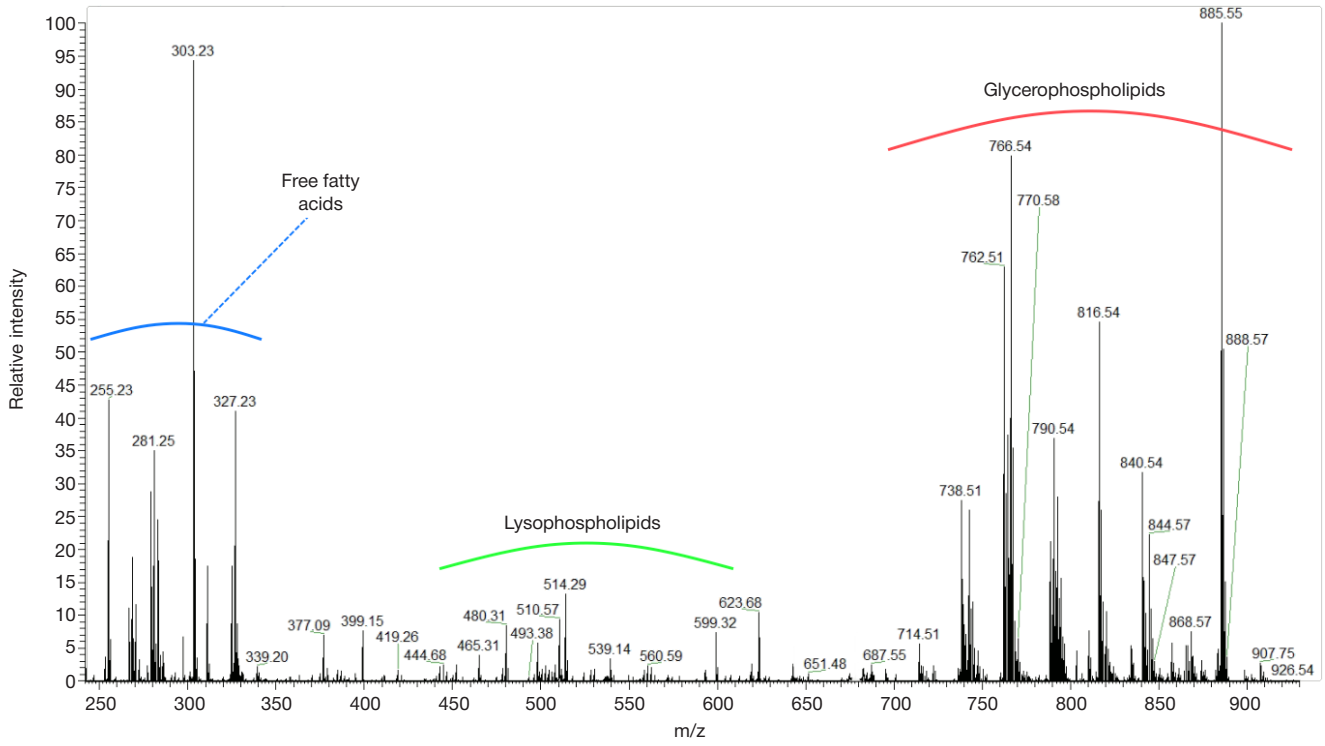

Fig. 1. Mass spectrum of liver tissue samples, negative ion mode

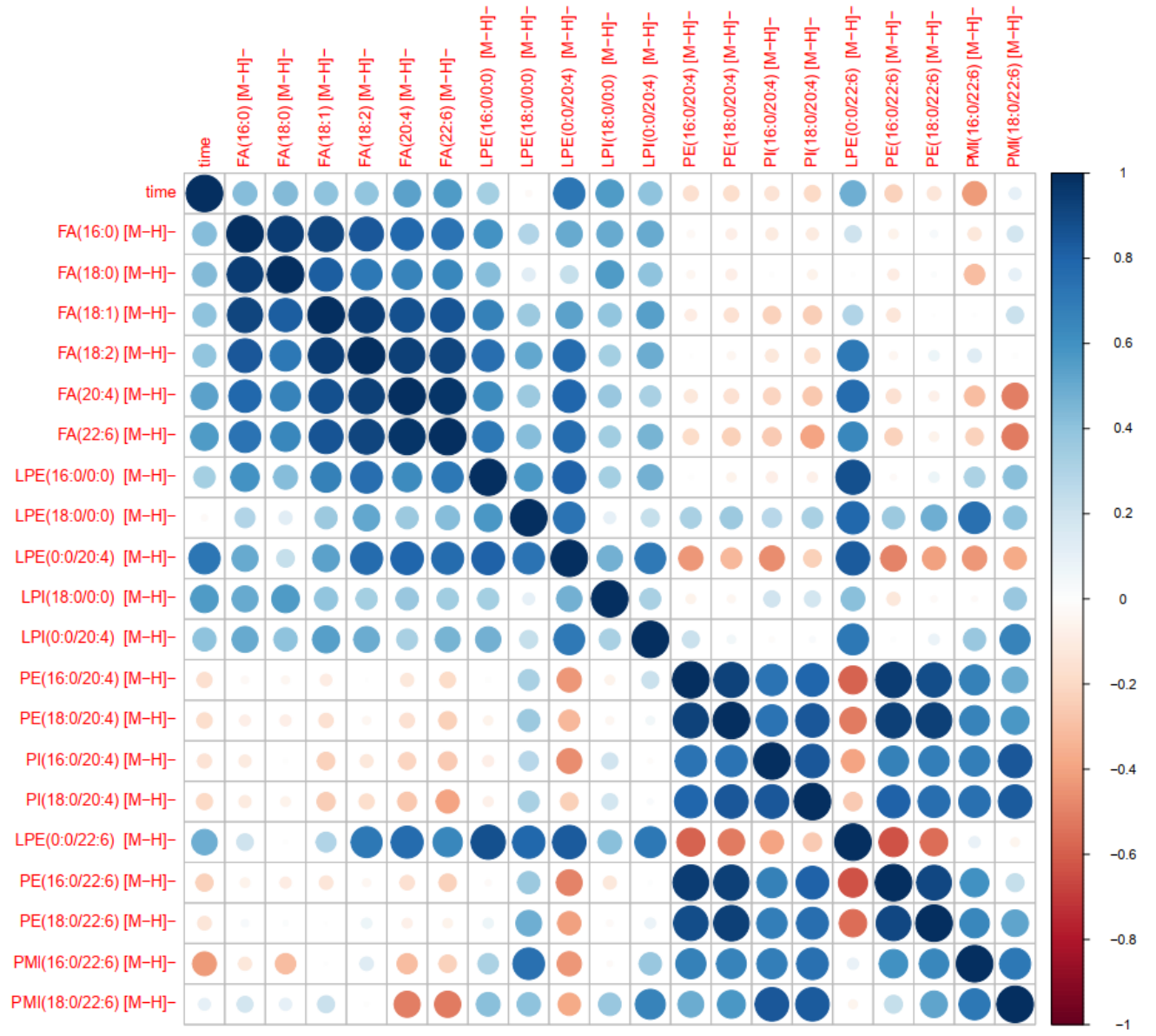

Fig. 2. Spearman's matrix, correlation between lipids and postmortem interval; liver, group 2

at least 25% of spectra were included in the matrix. Then, we selected the columns the m/z value of which differed from the theoretical value by no more than 0.05 Da. Such columns were given names of the corresponding compounds.

RESULTS

The mass spectrometric profiles of liver and brain tissues, acquired in positive and negative ion modes, show two groups of peaks in the m/z 450–600 and 750–900 ranges, corresponding to lysophospholipids and glycerophospholipids, respectively. In the negative ion mode, there is also a cluster of peaks in the m/z 250–350 range, which is attributed to deprotonated ions of FFA (Fig. 1). As the postmortem interval grew longer, the relative representation in the profiles of peaks from the low-mass ranges (up to m/z 600) increased.

Fig. 2 shows Spearman's correlation matrix between lipids and PMI for animal liver tissue samples from group 2 (storage at +22 °C for the first 4 hours, then at +4 °C). A high positive correlation was found between the levels of FFA, lysolipids, and PMI (coefficient > 0.6; the highest correlation coefficient for arachidonic (FA 20 : 4) and docosahexaenoic (FA 22 : 6) acids: r = 0.75), while the correlation between all the above values and the levels of glycerophospholipids was insignificant (modulus coefficient < 0.4) or moderately negative (coefficient < –0.5). For animal liver tissue samples from group 1 (storage at +4 °C), compared with group 2, the correlation of lipid levels with the PMI was weaker, but the correlation between levels of different lipid groups remained at the same level. A similar pattern was observed in animal brain samples from group 2. For animal brain samples from group 1, no significant correlation with PMI (coefficient modulus > 0.5) was found for any lipids from the list; from various classes of lipids, a high positive correlation (coefficient > 0.7) between FFA levels was shown.

Among the lysolipids whose relative intensity increases with increasing PMI are lysophospholipids containing fatty acid residues characteristic of the sn-1 and sn-2 positions in glycerophospholipids. The relative intensities of 1- and 2-lysophospholipids are similar, but approximately one order of magnitude lower than those of phospholipids, their likely precursors (Fig. 3). Therefore, the relative intensities of phospholipids do not change significantly with increasing PMI.

In liver tissue samples, the relative intensities of FFA (FA 16 : 0, FA 16 : 1, FA 18 : 0, FA 18 : 1, FA 18 : 2, FA 20 : 3, FA 20 : 4, FA 22 : 4,

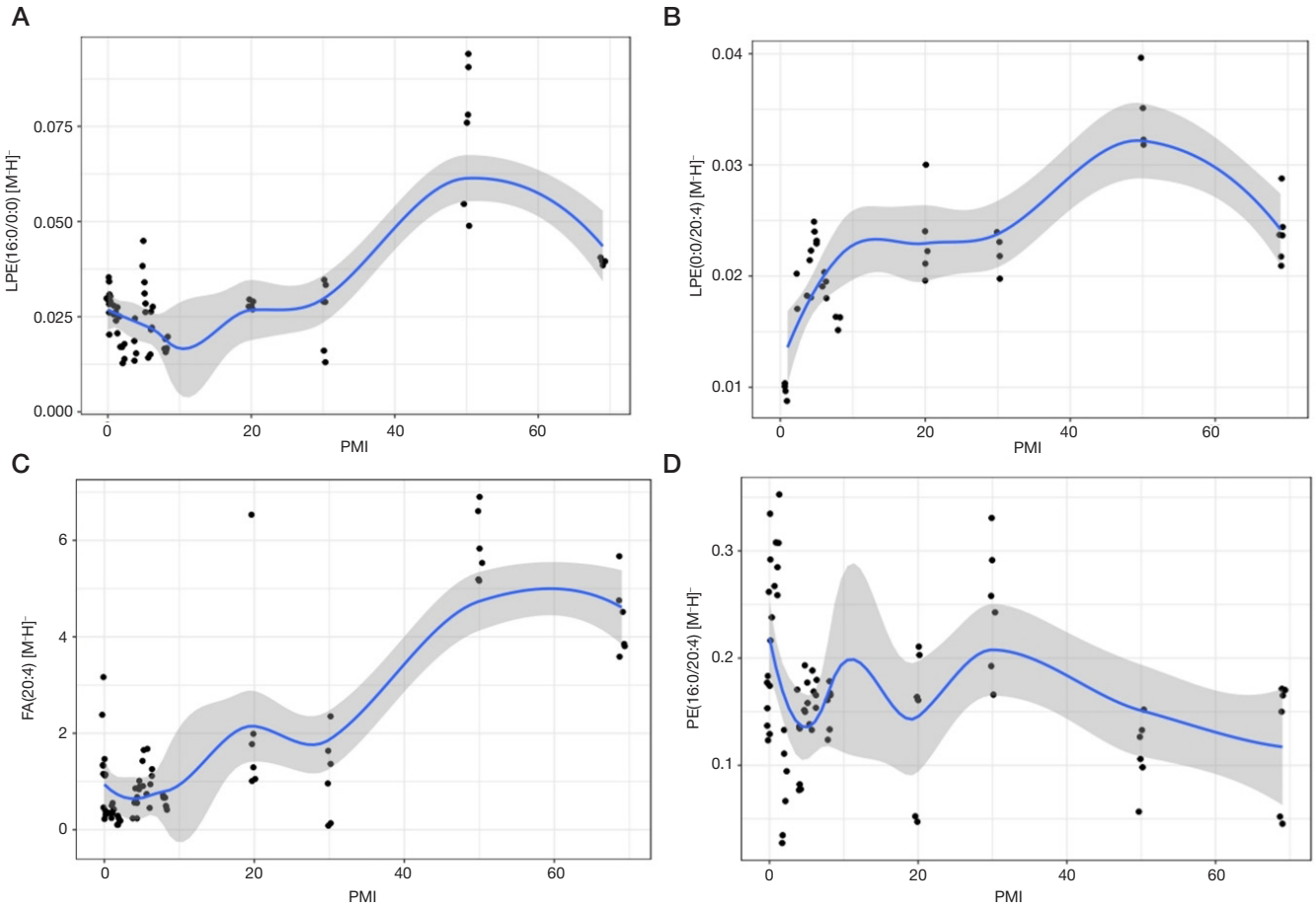

Fig. 3. Relative intensities of PE 16 : 0 / 20 : 4 and its decomposition products as a function of PMI in liver samples, group 2 (storage at +22 °C for the first 4 h, then at +4 °C) **A**. LPE 16 : 0, $p < 0.0001$. **B**. LPE 20 : 4, $p = 0.0001$. **C**. FA 20 : 4, $p < 0.0001$. **D**. PE 16 : 0 / 20 : 4, $p = 0.08$. The blue line shows the LOESS approximation (locally estimated scatterplot smoothing), the gray line shows the 95% confidence interval. Each point is one experimental repetition.

FA 22 : 5, FA 22 : 6) increase with PMI. For group 1 samples, the increase becomes significant when the PMI reaches 36–48 h for all FFA except FA 22 : 5, FA 22 : 6, in which the intensities' growth reaches significance at PMI of 16 h. For group 2 samples, the increase becomes significant when the PMI reaches 10 h. In both groups, the changes between FA 16 : 0 and FA 18 : 0; FA 22 : 4, FA 22 : 5, FA 22 : 6 followed similar patterns within the group (Fig. 4).

For brain samples, the relative intensity of all the FFA mentioned above does not change with storage time, with the exception of FA 20 : 4 and FA 22 : 4, FA 22 : 5, FA 22 : 6: their relative intensity reaches the maximum within the PMI range of 2–8 h.

DISCUSSION

An increased relative representation of low-mass peaks (up to m/z 600) in the profiles with rising PMI indicates the hydrolysis of glycerophospholipids into lysolipids and FFA. However, the level of possible precursors remains largely unchanged. Changes in the relative intensities of lysolipids and FFA in the liver are more pronounced than in the brain, and in group 2 (storage at +22 °C for the first 4 hours, then at +4 °C), as expected, they are more pronounced than in group 1 (storage at +4 °C). This is consistent with the data confirming better postmortem stability of brain tissues [24] and may be connected to the high content of lipases in the normal liver parenchyma.

A characteristic feature is that relative intensities of polyunsaturated fatty acids exceed those of saturated ones. According to the literature [23], fatty acids with 16 and 18 carbon atoms account for about 25% and 45% of the FA content of liver lipids, respectively, while arachidonic acid accounts for about 13% and docosahexaenoic acid for less than 5%. Generated molecular profiles, however, show greater amounts of released arachidonic and docosahexaenoic acids than the FA characteristic of the sn-1 position in phospholipids. Unlike fatty acids with 16 and 18 carbon atoms, DHA is not a common component of triglycerides, which suggests a conclusion that phospholipids are the source of its release during tissue degradation. Postmortem changes in the lipid profile may be associated with nonspecific lipid degradation as well as with the enzymatic activity of phospholipases in cells undergoing postmortem stress: PLA2 mediates the release of PUFA for the synthesis of eicosanoids and docosanoids [25], while PLA1 contributes to the production of lysophospholipid mediators [26].

Postmortem degradation of phospholipids with the formation of lysophospholipids only slightly affects the level of the initial lipid, and the magnitude of this change can be comparable or only slightly exceed the natural biological variability of the concentration of the respective phospholipid. At the same time, the levels of lysophospholipids change significantly relative to their initial levels, making them a complex marker of the postmortem interval. The relative intensities of FFA, in turn, are comparable, or even an order of magnitude higher than the intensities of phospholipids. This may be due to the variety of sources releasing fatty acids during postmortem tissue degradation. Thus, the high activity of phospholipases in liver tissues, compared with brain tissues, leads to the identification of a number of markers of postmortem degradation associated specifically with enzymatic activity, rather than spontaneous, nonspecific lipid degradation,

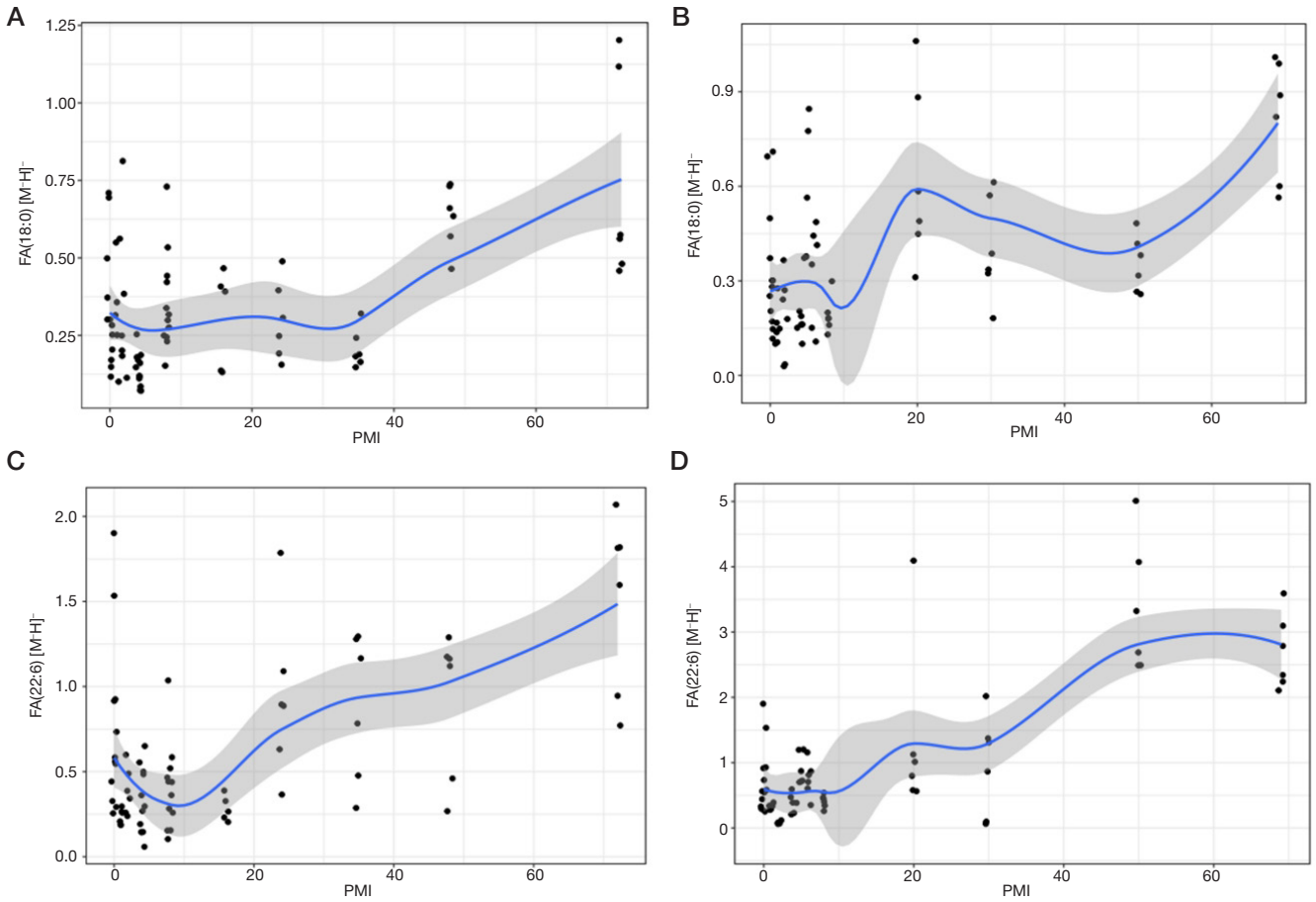

Fig. 4. Relative FFA intensities as a function of PMI, liver samples. **A**. FA 18 : 0, group 1, $p < 0.0001$. **B**. FA 18 : 0, group 2, $p < 0.0001$. **C**. FA 22 : 6, group 1, $p < 0.0001$. **D**. FA 22 : 6, group 2, $p < 0.0001$. The blue line shows the LOESS approximation (locally estimated scatterplot smoothing), the gray line shows the 95% confidence interval. Each point is one experimental repetition

which does not entail a significant increase in concentrations of a narrow set of lipid catabolism products.

A study of postmortem degradation of polar lipids in healthy animal tissues has shown that both lysophospholipids and FFA cannot, in general, be used as molecular markers in generation of diagnostic models referencing collections of autopsy material. A significant change in the content of lysophospholipids and FFA during postmortem tissue degradation will compromise reliability of such models, and the non-monotony of these changes significantly complicates data adjustment, even when using reliable information on the degree of postmortem degradation based on RNA preservation data [27]. At the same time, tissue concentrations of cell membrane phospholipids do change significantly in the early postmortem period, so they remain potentially usable as biomarkers suitable for detection in both biopsy and autopsy material. Thus, the use of autopsy material for the analysis of pathologies of relatively stable organs, such as the brain, is a potentially feasible solution, since phospholipids, rather than lysophospholipids and fatty acids, are the main markers that enable classification of biopsy material as tumor or healthy [16]. However, for constructing diagnostic models to detect tumor cells in samples from rapidly degrading internal organs such as the liver, autopsy material is of limited use and requires monitoring of the PMI.

Study limitations

A limitation of this study is the use of rodent liver tissue; due to differences in hepatocyte lipid metabolism between rodents and humans, we cannot establish the maximum postmortem interval applicable to human autopsy samples for lipid profile analysis.

CONCLUSIONS

For brain lipid profiles, the relative abundance of lysophospholipids and free fatty acids increases with longer postmortem intervals, whereas most glycerophospholipids show no such dependence. This suggests the possibility of using brain autopsy material with a postmortem interval of up to 72 hours to study the molecular mechanisms of the pathological process or to generate diagnostic models in oncology based on a panel of phospholipids. For liver tissue, despite preserved morphology, low molecular stability was observed: significant changes in lipid profiles appear after 3–8 hours. This limits the suitability of autopsy liver material for molecular studies of pathogenesis; however, it still allows the identification of degradation markers, for example to improve assessment of the progression of organ damage during transplantation from postmortem donors.

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