https://doi.org/10.47183/mes.2026-489

PARADOXICAL EFFECT OF FENTANYL ON BODY TEMPERATURE, HEMOGRAM, AND CIRCULATION IN RATS UNDER HYPERTHERMIA

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Introduction. We previously observed that general hyperthermia potentiates the lethal effect of fentanyl in rats. However, the relationship of this phenomenon to indices of vital functions of the organism remains unclear.
Objective. To identify the specific effects of fentanyl on body temperature, blood cell composition, and circulation in rats under heat stress conditions.
Materials and methods. The study was conducted on outbred male albino rats (191–210 g). Two series of experiments were performed on two separate animal samples, each of which was divided into the following groups: “22 °C” (intact), “Fentanyl + 22 °C” (kept at room temperature after fentanyl administration), “40 °C” (placed in a thermal chamber at 40 °C air temperature for 40 min), and “Fentanyl + 40 °C” (placed in the thermal chamber after fentanyl administration). In the first series of experiments, the effect of fentanyl (200 μg/kg) and/or exposure of rats to 40 °C air temperature on mortality over 40 min, body temperature, hemogram parameters, electrocardiogram (ECG), and blood pressure (BP) was studied. In the second series, the effect of fentanyl and/or heat stress on kidney weight, water content, and histological parameters of renal blood filling was studied. Heat stress was modeled by placing perforated restrainers with animals in a thermal chamber for 40 min. Fentanyl solution was administered at a volume of 4 mL/kg and a substance dose of 200 μg/kg into the *v. caudalis lateralis*. Statistical analysis was performed using OriginPro software.
Results. Isolated exposures were non-lethal, whereas their combination resulted in a mortality rate of 50% in the first series and 38% in the second series of experiments. After fentanyl administration, the following significant ($p < 0.05$) differences compared to the control groups were observed. Rectal temperature decreased by 5.6 °C at 22 °C but increased by 5.7 °C at 40 °C. At 22 °C, fentanyl decreased the heart rate of rats by 48%, whereas at 40 °C it increased heart rate by 25%. At 22 °C, fentanyl prolonged the RR interval by 90%, while at 40 °C it shortened the RR interval by 23%. In rats that died in the thermal chamber, the relative wet weight of the kidney was increased by 27% and the relative dry weight by 20%. At 40 °C, but not at 22 °C, fentanyl reduced blood leukocyte count by 47% and platelet count by 33%, increased renal cortical blood filling, activated the juxtamedullary shunt, and induced intravascular hemolysis.
Conclusions. For the first time, it has been established that under heat stress, the effects of fentanyl on body temperature, autonomic balance, and cardiac automaticity are opposite to those observed under thermal comfort. The fentanyl-induced changes in hemogram parameters, BP, and renal blood filling at 22 °C and 40 °C differ in magnitude. These fentanyl effects under hyperthermia represent early manifestations of exotoxic shock.

Keywords: hyperthermia; rats; leukopenia; sympathicotonia; sinus tachycardia; heat stress; thrombocytopenia; fentanyl; shock

For citation: Ivnitsky Ju.Ju., Rozhko M.A., Gajkova O.N., Kubarskaya L.G., Abdrakhmanova A.R., Vakunenkova O.A., Rejniuk V.L. Paradoxical effect of fentanyl on body temperature, hemogram, and circulation in rats under hyperthermia. *Extreme Medicine*. 2026. https://doi.org/10.47183/mes.2026-489

Funding: the study was carried out within the framework of the self-initiated research project of the Golikov Research Center of Toxicology, “Determination of effective doses of pharmaceutical substances of promising medicinal agents upon intranasal administration” (code: “Thermidor”).

Compliance with the ethical principles: the study was performed in compliance with the bioethical rules approved by the European Convention for the Protection of Vertebrate Animals used for Experimental and other purposes. The study was approved at a meeting of the Bioethics Committee of the Golikov Research Center of Toxicology (minutes No. 1/10-25 dated 28.10.2025).

Potential conflict of interest: Vladymir L. Reiniuk is a member of the Editorial Board of the journal Extreme Medicine. The other authors declare no conflict of interest.

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Received: 17 Mar. 2026 **Revised:** 4 May 2026 **Accepted:** 12 May 2026 **Online first:** 16 July 2026

УДК 615.9

ПАРАДОКСАЛЬНОСТЬ ВЛИЯНИЯ ФЕНТАНИЛА НА ТЕМПЕРАТУРУ ТЕЛА, ГЕМОГРАММУ И КРОВООБРАЩЕНИЕ КРЫС ПРИ ПЕРЕГРЕВАНИИ

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Введение. Ранее мы наблюдали потенцирование общим перегреванием летального действия фентанила на крыс. Однако связь этого феномена с показателями витальных функций организма неясна.
Цель. Выявление особенностей влияния фентанила на температуру тела, клеточный состав крови и кровообращение у крыс в условиях теплового стресса.
Материалы и методы. Исследование проведено на беспородных самцах крыс-альбиносов (191–210 г). Выполнено 2 серии экспериментов на двух отдельных выборках животных, каждая из которых была разделена на группы: «22 °C» (интактные), «Фентанил + 22 °C» (после введения фентанила оставленные при комнатной температуре), «40 °C» (помещенные на 40 мин в термокамеру

при температуре воздуха 40 °С) и «Фентанил + 40 °С» (помещенные в термокамеру после введения фентанила). В первой серии экспериментов изучали влияние фентанила (200 мкг/кг) и/или пребывания крыс при температуре воздуха 40 °С на летальность в течение 40 мин, температуру тела, гемограмму, электрокардиограмму и артериальное давление. Во второй серии — влияние фентанила и/или теплового стресса на массу, влагосодержание и гистологические показатели кровенаполнения почек. Тепловой стресс моделировали помещением перфорированных рестрейнеров с животными на 40 мин в термокамеру. Раствор фентанила вводили в объеме 4 мл/кг и дозе субстанции 200 мкг/кг в латеральную вену хвоста. Статистический анализ провели с использованием программного обеспечения OriginPro.

Результаты. Изолированные воздействия были нелетальными, а при их комбинации летальность составила 50% в первой и 38% во второй сериях экспериментов. После введения фентанила выявлены следующие значимые ($p < 0,05$) различия с группами сравнения. Ректальная температура снижалась на 5,6 °С при 22 °С и повышалась на 5,7 °С при 40 °С. При 22 °С фентанил снижал частоту сердечных сокращений у крыс на 48%, а при 40 °С повышал ее на 25%. При 22 °С фентанил удлинял интервал RR на 90%, а при 40 °С сокращал на 23%. У павших в термокамере крыс относительная влажная масса почки была повышена на 27% и относительная сухая масса — на 20%. При 40 °С, но не при 22 °С, фентанил снижал содержание в крови лейкоцитов на 47% и тромбоцитов на 33%, повышал кровенаполнение коры почек, активировал юкстамедуллярный шунт и внутрисосудистый гемолиз.

Выводы. Впервые установлено, что при тепловом стрессе влияние фентанила на температуру тела, вегетативный баланс и функции автоматизма сердца противоположны его эффектам при тепловом комфорте. Вызываемые фентанилом изменения гемограммы, артериального давления и кровенаполнения почек при 22 и 40 °С различны по амплитуде. Такие эффекты фентанила при перегревании являются ранними проявлениями экзотоксического шока.

Ключевые слова: гиперпирексия; крысы; лейкоцитопения; симпатикотония; синусовая тахикардия; тепловой стресс; тромбоцитопения; фентанил; шок

Для цитирования: Ивницкий Ю.Ю., Рожко М.А., Гайкова О.Н., Кубарская Л.Г., Абдрахманова А.Р., Вакуненкова О.А., Рейнюк В.Л. Парадоксальность влияния фентанила на температуру тела, гемограмму и кровообращение крыс при перегревании. *Экстремальная биомедицина*. 2026. https://doi.org/10.47183/mes.2026-489

Финансирование: исследование выполнено в рамках инициативной НИР ФГБУ НКЦТ им. акад. С.Н. Голикова ФМБА России «Определение эффективных доз фармацевтических субстанций перспективных медикаментозных средств при назальном введении» (шифр «Термидор»).

Соответствие принципам этики: исследование выполнено с соблюдением правил биоэтики, утвержденных Европейской конвенцией о защите позвоночных животных, используемых для экспериментальных и других целей. Исследование одобрено на заседании биоэтического комитета ФГБУ НКЦТ им. акад. С.Н. Голикова ФМБА России (протокол № 1/10-25 от 28.10.2025).

Потенциальный конфликт интересов: В.Л. Рейнюк — член редакционной коллегии журнала «Экстремальная биомедицина». Остальные авторы заявляют об отсутствии конфликта интересов.

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Статья поступила: 17.03.2026 **После доработки:** 05.05.2026 **Принята к публикации:** 12.05.2026 **Online first:** 16.07.2026

INTRODUCTION

As follows from previously obtained data [1–3], the outcomes of fentanyl effects on the organism critically depend on microclimatic conditions, which must be taken into account when monitoring vital functions and performing resuscitation measures. The relevance of this task is underscored by the possibility of administering opioids to the wounded during first aid and medical care under hot climate conditions and under the influence of other factors that promote hyperthermia, such as high air humidity, wearing occlusive skin protective gear, and immersion-induced hyperthermia.

The study purpose was to identify the specific effects of fentanyl on body temperature, blood cell composition, and circulation in rats under heat stress conditions.

MATERIALS AND METHODS

The study was conducted from January to February 2026 on outbred male albino rats (191–210 g) obtained from the Rappolovo Laboratory Animal Nursery (Kurchatov Institute). The animals were handled in accordance with the “Good Laboratory Practice” regulations[1]. The diet consisted of standard rat chow and drinking water *ad libitum*. Two series of experiments were performed on two separate animal samples, each of which was divided into the following groups: “22 °C” (intact), “Fentanyl + 22 °C” (kept at room temperature after fentanyl administration), “40 °C” (placed in a thermal chamber at 40 °C air temperature for 40 min), and “Fentanyl + 40 °C” (placed in the thermal chamber after fentanyl administration).

In the first series, the effect of fentanyl and/or heat stress on body temperature, hemogram parameters, and overall hemodynamics was studied: rectal temperature, electrocardiogram (ECG), and BP were recorded. The study design is presented in Table 1.

In the second series of experiments, the scheme of which is given in Table 2, the effect of fentanyl and/or heat stress on parameters of regional hemodynamics — relative kidney weight, water content, and histological parameters of renal blood filling — was studied.

Heat stress was modeled by placing perforated restrainers containing the animals into a BMT Stericell

[1] Order of the Ministry of Health and Social Development of the Russian Federation No. 708n dated 23.08.2010 “On Approval of the Good Laboratory Practice Regulations.”

Table 1. Scheme for studying the effect of fentanyl and/or heat stress on body temperature, hemogram parameters, electrocardiogram, and blood pressure of rats

Number of rats surviving until the examination	Exposure of rats		Parameters
	Pharmacological	Microclimatic	
8/8	Absent	22 °C for 40 min post-injection	Rectal temperature, electrocardiographic parameters at 40 min; blood pressure, hemogram parameters at 47 min after fentanyl injection
8/8	Fentanyl		
8/8	Absent	40 °C for 40 min post-injection	
16/32	Fentanyl		

Table prepared by the authors based on their own data

Table 2. Scheme for studying the effect of fentanyl and/or heat stress on the relative weight, water content, and histological parameters of renal blood filling in rats

Number of rats surviving until the examination	Exposure of rats		Parameters
	Pharmacological	Microclimatic	
9/9	Absent	22 °C for 40 min post-injection	Relative kidney weight, kidney water content, histological signs of renal congestion at 40 min after fentanyl injection
8/8	Fentanyl		
8/8	Absent	40 °C for 40 min post-injection	
10/16	Fentanyl		

Table prepared by the authors based on their own data

SC 111 ECO thermal chamber (Czech Republic) with a capacity of 111 L, in which the air temperature was maintained at 40 ± 1 °C, relative humidity at 48%, and the air exchange rate at 45 chamber volumes per hour. According to previously obtained data [1], the first cases of death under such exposure occurred no earlier than 90 min of chamber stay.

Fentanyl solution 50 μg/mL (Moscow Endocrine Plant, batch 571123) was administered at a volume of 4 mL/kg and a substance dose of 200 μg/kg into the *v. caudalis lateralis*. Animals kept at room temperature for 40 min after fentanyl administration constituted the "Fentanyl + 22 °C" group, while those placed in the thermal chamber for 40 min constituted the "Fentanyl + 40 °C" group. Rats that did not receive fentanyl and were kept at room temperature formed the "22 °C" group, and those placed in the thermal chamber formed the "40 °C" group. At 40 min after fentanyl administration and/or placement in the thermal chamber, rectal temperature was measured to an accuracy of 0.1 °C using an electrothermometer with an RET-2 sensor (WPI, China), the tip of which was inserted into the rectum to a depth of 3 cm. Body weight was measured to an accuracy of 1 g before and 40 min after fentanyl administration.

ECG recording in an animal freely placed on a table was performed for 2 min using a "Polispectr 8/V" veterinary electrocardiograph (Neurosoft LLC, Russia). Electrodes (sterile atraumatic needles) were inserted subcutaneously at the base of the limbs. Cardiac automaticity was assessed by heart rate (HR), RR interval duration, and RR variability. Atrioventricular conduction was assessed by the PQ segment duration. Intraventricular conduction was assessed by the QT interval duration and the shape of the R wave. Atrial and ventricular contraction strength was assessed by the amplitude of the Q and R waves. After ECG recording, the rat was transferred for 5 min into a 20-L chamber ventilated with air heated to 45 °C.

After warming, the animal was placed in a restrainer, a pneumatic cuff was applied to the base of the tail, and BP was measured at room temperature in the *a. ventrali caudae* using the Korotkoff method over the range of 35–200 mmHg with an NIBP-6 eight-channel monitor (Columbus Instruments, USA). These procedures were performed uniformly for animals in all groups. Preliminary experiments established that HR, BP, and ECG wave amplitudes in intact rats corresponded to reference values [4]: HR 370–580 bpm; systolic blood pressure (SBP) 86–123 mmHg; P-wave amplitude 0–0.2 mV; R-wave amplitude 0.3–0.8 mV. The durations of the PQ segment (37 ms) and QT interval (40 ms) were 7% and 35% shorter than these reference values (40 and 62 ms, respectively), which

may have been provoked by subcutaneous electrode insertion. The total duration of ECG recording, warming, and BP measurement was 7 min. For each animal, the coefficient of variation of the RR interval (CV, %) was calculated:

$$CV = 100\ s / M, \quad (1)$$

where s — standard deviation, ms; M — arithmetic mean, ms.

To assess the ratio of sympathetic to parasympathetic tone, the Kerdo autonomic index (KAI) was used:

$$KAI = 101 - DBP / HR, \quad (2)$$

where DBP — diastolic blood pressure, mmHg; HR — heart rate, bpm.

An increase in the KAI compared to its value in the intact animal group indicates sympathicotonia, whereas a decrease indicates vagotonia. In intact rats, the value of this index ranges 100.79–100.81, and in hemorrhagic shock it reaches 100.92 [5].

After measuring blood pressure, 0.5 mL of blood was collected from the *v. profunda linguae* into tubes containing EDTA. Hematocrit, hemoglobin content, erythrocyte count, platelet count, absolute and relative leukocyte counts, and mean erythrocyte and platelet volumes were determined using a Siemens Advia 2120i hematology analyzer (Germany).

Changes in renal blood flow were assessed by parameters of renal congestion: relative kidney weight and water content, as well as by histological examination. For this purpose, animals (including those that died during the stay in the thermal chamber) underwent laparotomy (those not receiving fentanyl were first anesthetized with sevoflurane). The right kidney was removed and weighed before and after drying at 105 °C until constant weight. The left kidney of surviving rats was fixed in 10% formalin, dehydrated through graded alcohol solutions, embedded in paraffin, and 4 μm sections were prepared. The sections were stained with hematoxylin and eosin and examined using a 3DHISTECH Pannoramic MIDI light microscope (Carl Zeiss LLC, Germany) at × 400 magnification.

Statistical analysis was performed using OriginPro software. Results were presented as the mean and its standard error ($M \pm m$). The Shapiro–Wilk test was used to check the normality of distribution. The effect of the applied treatments on parametric indicators was assessed using one-way ANOVA. In cases where the obtained models were significant, intergroup comparison of the mean values was performed using Tukey's test. The critical significance level α was set at 0.05.

RESULTS

Under isolated exposure to fentanyl or the thermal factor alone, there was no mortality. Following fentanyl administration, mortality during 40 min of stay in the thermal chamber was 50% in the first series and 38% in the second series of experiments. Animals that remained at room temperature after fentanyl administration exhibited hypothermia, whereas those placed in the thermal chamber exhibited hyperpyrexia, which was more pronounced in the presence of fentanyl.

The effect of fentanyl on blood cell composition depended on the microclimatic conditions during the subsequent 40 min. In animals placed in the thermal chamber after fentanyl administration, the total leukocyte count, as well as the numbers of lymphocytes and neutrophilic granulocytes, were 47% lower, and the monocyte count was 37% lower than in animals placed in the thermal chamber without fentanyl administration. In animals kept at room temperature after fentanyl administration, no significant changes in these parameters were observed. In rats placed in the thermal chamber after fentanyl administration, the blood platelet count was 33% lower than in animals placed in the thermal chamber without fentanyl administration; in rats kept at room temperature after fentanyl administration, the platelet count showed a tendency to increase. Isolated exposure to the thermal factor alone was associated

Table 3. Rectal temperature of rats after fentanyl administration and/or 40-min exposure to an air temperature of 22 or 40 °C

Group	Temperature, °C		Temperature change, °C
	Baseline	After 40 min	
22 °C (n=8)	37.4 ± 0.1	38.9 ± 0.1	+1.5 ± 0.2
Fentanyl + 22 °C (n=8)	37.5 ± 0.1	31.9 ± 0.2*	-5.6 ± 0.3*
40 °C (n=8)	37.2 ± 0.1	41.4 ± 0.1*♦	+4.2 ± 0.2*♦
Fentanyl + 40 °C (n=16)	37.4 ± 0.1	43.1 ± 0.1*♦■	+5.7 ± 0.1*♦■

Table prepared by the authors based on their own data

Note. Data are presented as mean and standard error of the mean ($M \pm m$); statistically significant difference compared to the groups: * — "22 °C"; ♦ — "Fentanyl + 22 °C"; ■ — "40 °C" , $p < 0.05$.

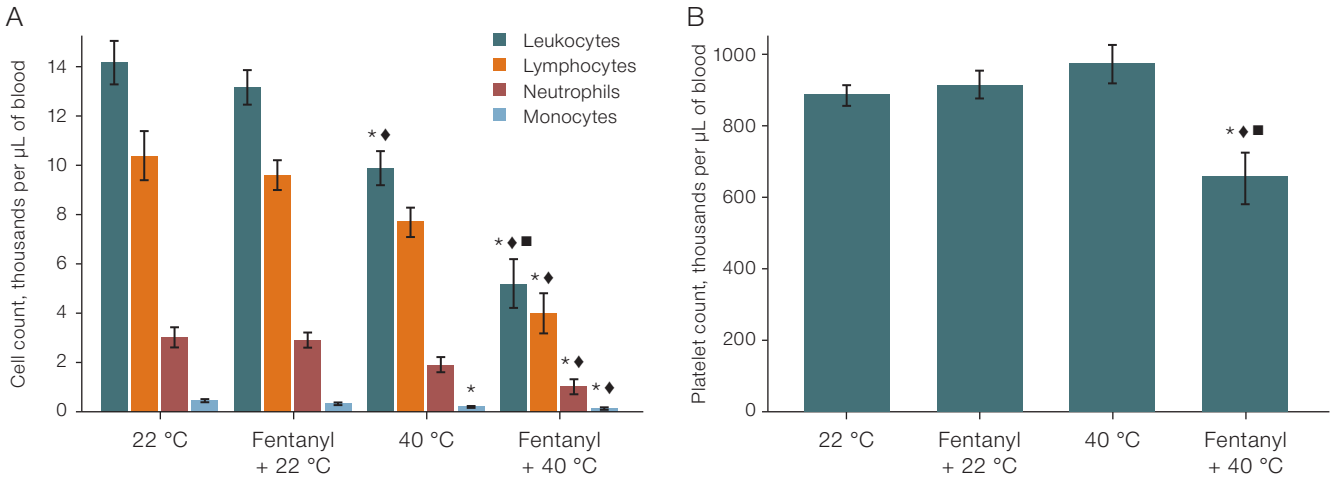

Figure prepared by the authors based on their own data

Fig. 1. Leukocyte (A) and platelet (B) count in venous blood of rats after fentanyl administration and/or 40-min exposure to an air temperature of 22 °C or 40 °C. Data are presented as mean and standard error of the mean ($M \pm m$); statistically significant difference compared to the groups: * — "22 °C" ; ♦ — "Fentanyl + 22 °C"; ■ — "40 °C", $p < 0.05$

with a 29% decrease in leukocyte count, accompanied by a tendency toward an increase in blood platelet count (Fig. 1). Blood hemoglobin levels averaged 160, 166, 167, and 160 g/L; erythrocyte counts averaged 7.14, 7.41, 7.65, and 7.39 thousand per µL; hematocrit levels were 41, 45, 43, and 44% in the "22 °C", "Fentanyl + 22 °C", "40 °C", and "Fentanyl + 40 °C" groups, respectively; intergroup differences in these parameters were present as trends.

In all animal groups, the heart rhythm was sinus. Seven minutes after removal from the thermal chamber of rats that did not receive fentanyl, the parameters of cardiac automaticity and conduction did not differ significantly from those of the intact group. The direction and/or amplitude of fentanyl's effect on these parameters depended on the microclimatic conditions during the 40 min after its administration. At room temperature, fentanyl decreased heart rate by 48%, whereas at 40 °C it increased heart rate by 25% (Fig. 2A). At 22 °C, fentanyl prolonged the PQ segment by 49%, whereas at 40 °C it tended to shorten it (Fig. 2B). At 22 °C, after fentanyl administration, the RR intervals increased on average 1.9-fold (Fig. 2C, 2D); the coefficient of variation of RR values, which did not exceed 10% in the other groups, reached 92%. At 40 °C, after fentanyl administration, the RR interval duration decreased by 23%, and the heart rhythm remained regular (Fig. 2E, 2F). At 22 °C after fentanyl administration, the mean R-wave amplitude increased by 39% (0.38 ± 0.02 vs. 0.28 ± 0.02 mV, $p < 0.05$), whereas at 40 °C a tendency toward a decrease was observed.

In rats that did not receive fentanyl, staying in the thermal chamber increased SBP, DBP, and pulse blood pressure (PBP). After fentanyl administration, in all animals kept at room temperature, BP values were below the sensitivity threshold of the measuring device. In the "Fentanyl + 40 °C" group, BP in most animals was below 35 mmHg; in the remaining animals, SBP was 57% lower and DBP 60% lower than in intact animals (Table 4).

Table 4. Blood pressure in rats after fentanyl administration and/or 40-min exposure to an air temperature of 22 °C or 40 °C

Group	Blood pressure, mmHg		
	Systolic	Diastolic	Pulse
22 °C (n = 8)	117 ± 2	96 ± 4	21 ± 2
Fentanyl (n = 8)	<35*	<35*	–
40 °C (n = 8)	153 ± 3*♦	119 ± 5*♦	34 ± 3*
Fentanyl + 40 °C (n = 4▲)	50 ± 9*■	38 ± 1	12 ± 8

Table prepared by the authors based on their own data

Note. Data are presented as mean and standard error of the mean $M \pm m$; statistically significant difference ($p < 0.05$) compared to the groups: * — "22 °C"; ♦ — "Fentanyl + 22 °C"; ■ — "40 °C"; ▲ — in the remaining 12 out of 16 rats, blood pressure was below 35 mmHg.

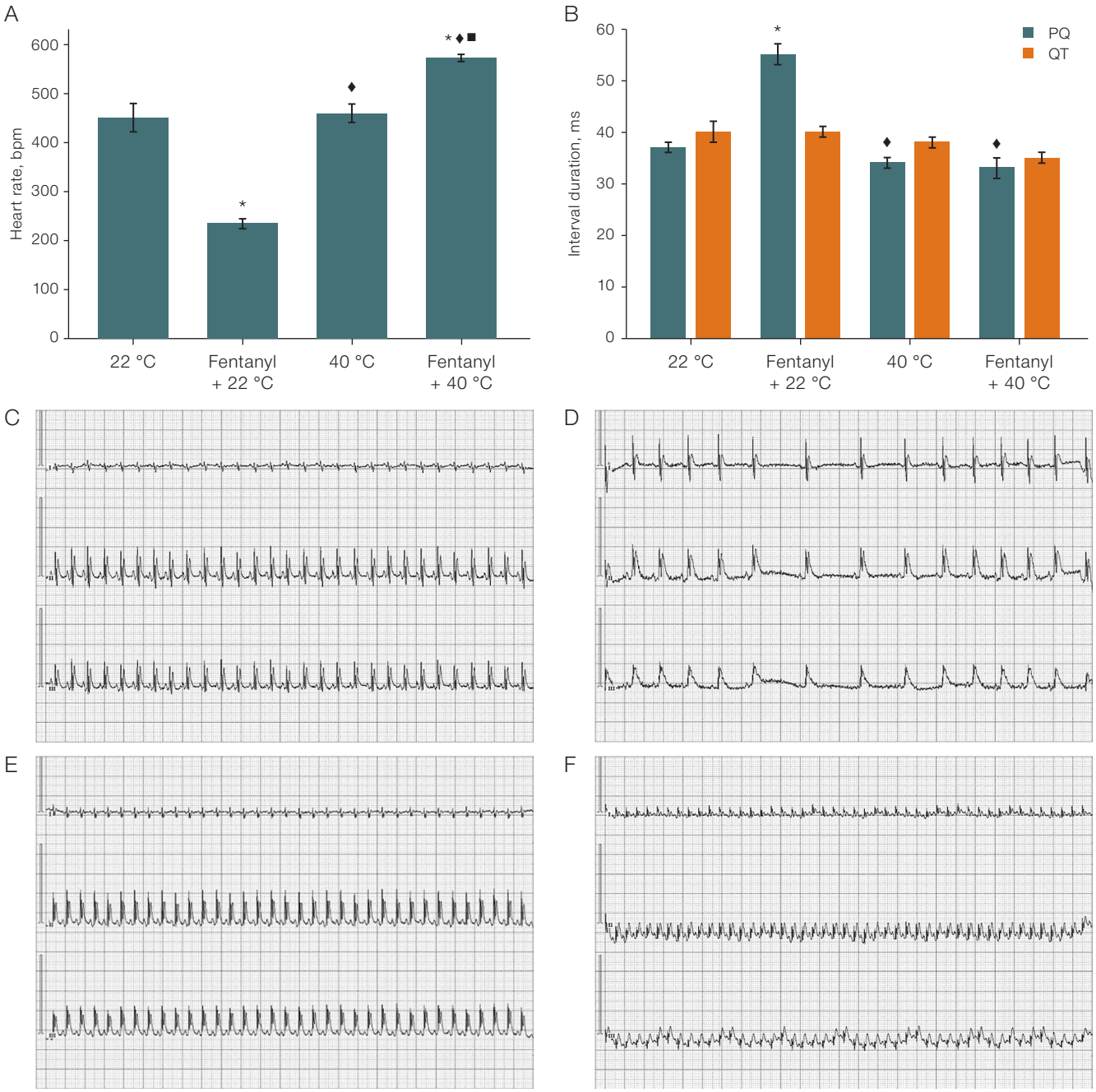

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Fig. 2. Heart rate (A), PQ segment duration and QT interval duration (B) in rats after fentanyl administration and/or 40-min exposure to an air temperature of 22 °C or 40 °C; ECG tracings of rats from the "22 °C" (C), "Fentanyl + 22 °C" (D), "40 °C" (E), and "Fentanyl + 40 °C" (F) groups. Data are presented as mean and standard error of the mean ($M \pm m$); statistically significant difference compared to the groups: * — "22 °C"; ♦ — "Fentanyl + 22 °C"; ■ — "40 °C", $p < 0.05$

The Kerdo autonomic index (KAI) was 100.79 ± 0.02 in intact rats, 100.74 ± 0.02 in rats exposed to the thermal factor alone, and 100.93 ± 0.03 in rats exposed to fentanyl under hyperthermia (the difference between the last group and the first two was significant, $p < 0.05$). Under isolated fentanyl exposure, calculation of the KAI was precluded by the inability to measure DBP.

Isolated exposure of rats to the thermal factor had little effect on kidney mass or water content, whereas isolated fentanyl exposure increased kidney water content by 3%. Under hyperthermia, fentanyl increased kidney water content by 3% in rats removed from the thermal chamber alive. In animals that died in the thermal chamber, the fentanyl-induced increase in relative wet mass of the right kidney amounted to 27%, and the increase in relative dry mass of the organ amounted to 20%, with a tendency toward increased water content (Fig. 3).

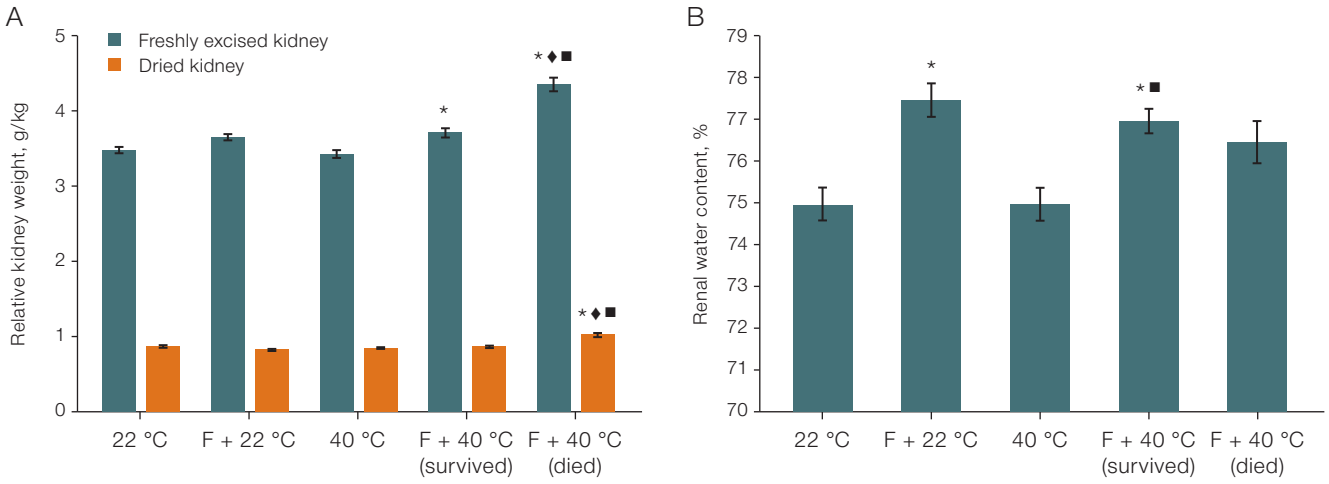

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Fig. 3. Relative wet weight, relative dry weight (A), and water content (B) of the right kidney of rats after fentanyl administration and/or 40-minute exposure to an air temperature of 22 °C or 40 °C. F — fentanyl; data are presented as mean and standard error of the mean ($M \pm m$); statistically significant ($p < 0.05$) difference compared to the groups: * — "22 °C"; ♦ — "Fentanyl + 22 °C"; ■ — "40 °C"

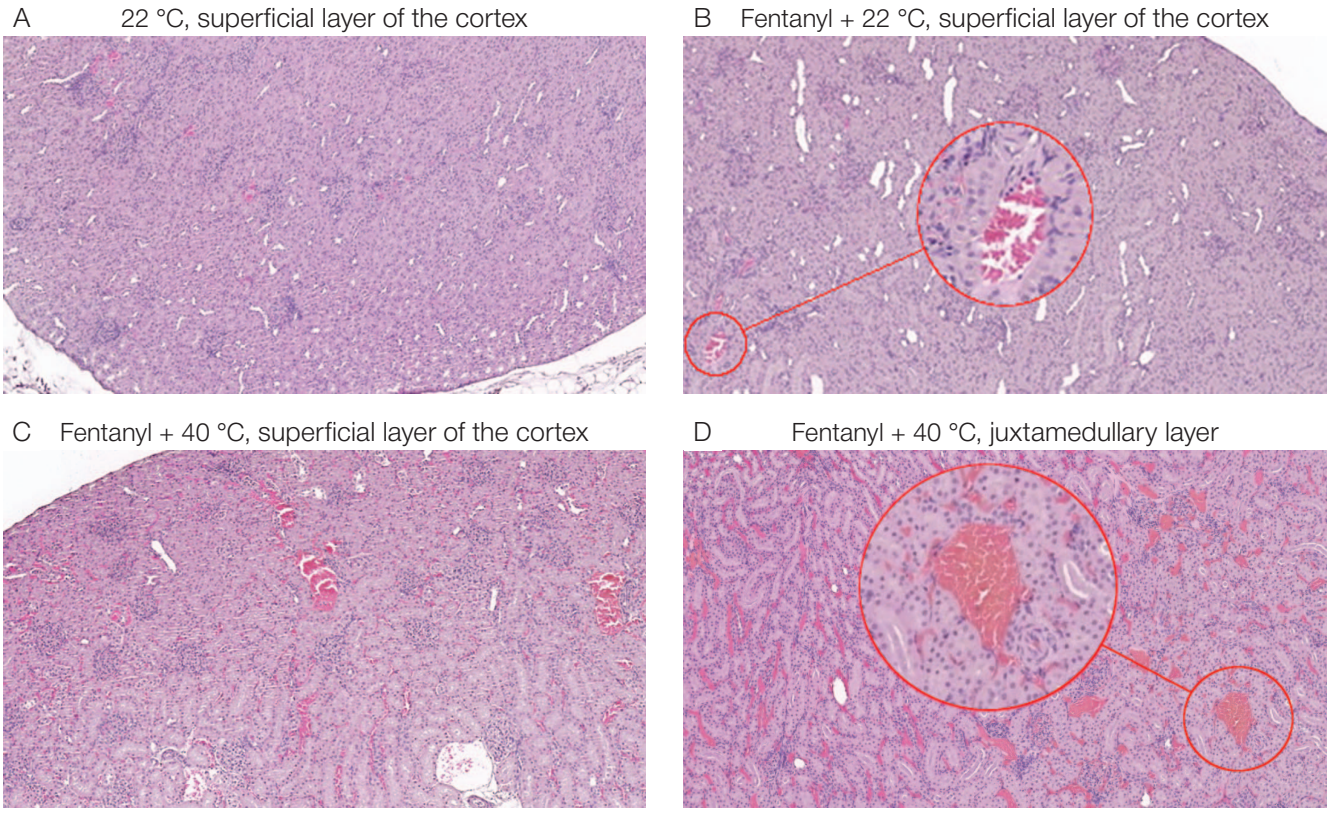

Figure prepared by the authors based on their own data

Fig. 4. Left kidney of a rat. A — "22 °C" group (normal renal cortical blood filling); B — "Fentanyl + 22 °C" group (increased renal cortical blood filling, erythrocytes freely lying in the arteries (inset)); C — "Fentanyl + 40 °C" group (markedly increased renal cortical blood filling); D — "Fentanyl + 40 °C" group (dilated vessels filled with erythrocytes without clear boundaries in the juxtamedullary zone (inset)). Hematoxylin and eosin staining, magnification × 400

In all rats, the structural elements of the nephron (glomeruli, proximal and distal tubules) were clearly visible on histological sections of the renal cortex. In intact animals (Fig. 4A) and animals subjected to isolated hyperthermia, renal cortical blood filling did not differ significantly. After fentanyl administration, blood filling was increased, and intact erythrocytes lay freely in the arteries (Fig. 4B). After the combined exposure to fentanyl and the thermal factor, renal cortical blood filling was increased to an even greater extent (Fig. 4C); the arteries

Table 5. Data on the opioids' effects on body temperature, hemogram parameters, circulatory system function, and autonomic balance under thermal comfort and thermal stress conditions

Parameters	Conditions for assessing the effect of acute opioid exposure		
	Thermal comfort		Heat stress (obtained data)
	Obtained data	Literature data	
Body temperature	Decrease	Decrease due to fentanyl poisoning [6]	Increase
White blood cell count	No effect	Increase during neuroleptanalgesia in pigs [7], opioid poisoning [8], and kratom [9]	Decrease
Blood platelet count	No effect	Decrease due to fentanyl poisoning [10]. No effect of neuroleptanalgesia [11]	Decrease
Cardiac automaticity	Sinus bradycardia	Arrhythmia in fentanyl overdoses [12], bradyarrhythmia in methadone poisoning [13], and morphine poisoning [14]	Sinus tachycardia
Cardiac conduction	First-degree atrioventricular block	PQ and QT prolongation in methadone poisoning [13] and tramadol poisoning [15]	No effect
Blood pressure	Decrease	Decrease in morphine poisoning [14] and fentanyl poisoning [16]	Decrease
Renal circulation	Congestion of the renal cortex	Decrease in renal blood flow in heroin overdose [17]	Marked congestion of the cortex; activation of the juxtamedullary shunt
Autonomic balance	Could not be assessed	Vagotonia (increased vagal tone) after opioid administration in animals [18]	Sympathicotonia

Table prepared by the authors

of the juxtamedullary zone were dilated and overfilled with erythrocytes lacking clear boundaries (Fig. 4D).

DISCUSSION

The results of this work, together with literature data on the effects of opioids on body temperature, blood cell composition, hemodynamics, and autonomic balance, summarized in Table 5, indicate a paradoxical nature of fentanyl toxicodynamics under heat stress conditions. The effects of fentanyl on body temperature, cardiac automaticity, and the sympathovagal balance were directionally opposite depending on the microclimatic conditions, while the amplitude of opioid-induced changes in hemogram parameters, cardiac conduction, blood pressure, and renal blood volume differed between room temperature and elevated ambient temperature. No description of these opioid effects under heat stress conditions was found in the literature. The guidelines[2] stipulate an air temperature 20–24 °C for work with laboratory animals. Therefore, in the absence of any designation of other conditions, the literature data presented in Table 5 were considered to have been obtained at room temperature.

The hypothermic effect of opioids is attributed to a decrease in heat production and an increase in heat loss due to opioid-induced inhibition of hypothalamic thermoregulatory centers mediated through μ-opioid receptor activation [6]. However, cases of opioid-induced malignant hyperthermia have also been described, which is presumably mediated by the interaction between the opioidergic and dopaminergic neurotransmitter systems [19]. The obtained results indicate that, in the presence of fentanyl, elevated ambient temperature may have served as a trigger for such hyperthermia. Impaired heat loss through evaporative water loss from the respiratory tract, resulting from respiratory depression, may also have contributed.

Hyperpyrexia, which was significantly more pronounced in fentanyl-treated animals exposed to elevated ambient air temperature, is a vital threat, to which the stereotypical response is activation of the sympathoadrenal system [20]. The occurrence of this response is indicated by a higher KAI in the "Fentanyl + 40 °C" group compared to the other groups, and by the fact that, under heat stress, fentanyl increased heart rate, whereas at room temperature it decreased it. Other manifestations of sympathicotonia included shortening

[2] GOST 33216-2014 "Guidelines for accommodation and care of laboratory animals. Species-specific provisions for laboratory rodents and rabbits".

of the PQ segment (reflecting atrioventricular conduction) and the QT interval (reflecting ventricular myocardial repolarization time). Hyperammonemia, previously demonstrated using a similar experimental model [2, 3], may also have contributed to these effects: ammonia impairs the generation of reducing equivalents in the Krebs cycle for oxidative ATP resynthesis [21], leading to depolarization of the plasmalemma of sinoatrial node cells and tachycardia with the formation of low-output syndrome [22]. Thus, sympathicotonia and hyperammonemia underlay the reversal of fentanyl's effect on cardiac automaticity under hyperthermia. The pathogenetic role of this paradoxical effect is defined by an increased functional load on the heart against a background of deteriorating conditions for its energy supply.

The change in several parameters listed in Table 5 under the combined exposure to fentanyl and the thermal factor was greater in absolute magnitude than their isolated effects. For example, in the "Fentanyl + 40 °C" group, both indirect (increased relative mass) and direct (histological) signs of renal congestion were more pronounced than in the "Fentanyl + 22 °C" or "40 °C" groups. The histological findings in the kidneys of animals in the "Fentanyl + 40 °C" group, revealing arteries distended with erythrocytes, indicate the presence of an obstruction to blood circulation in the tissue compartment of the vascular bed. This obstruction, created by spasm of precapillary and subsequently postcapillary sphincters, is observed in various organs of the visceral zone in the initial phase of shock [23].

The subject of further research is the hypothesis that, at later time points after fentanyl administration, against the background of blood sequestration in the capillary bed, and as a result of fluid extravasation from capillaries into the interstitium, the animals will develop hemoconcentration characteristic of the full-blown clinical picture of shock. Previously [2, 3], using this same experimental model, other shock-related disturbances have also been identified: hyperammonemia, azotemia, lactacidemia, and increased intestinal permeability. In the present study, early signs of shock could include the following observed in animals of the "Fentanyl + 40 °C" group: arterial hypotension, a KAI value characteristic of hemorrhagic shock [5], tachycardia [26], increased renal blood filling, activation of the juxtamedullary shunt in the kidneys, and the histological picture of intravascular hemolysis, which is one of the markers of shock-associated metabolic acidosis [25].

In the present study, the effect of fentanyl under conditions of hyperthermia was manifested by a decrease in peripheral blood leukocyte and platelet counts. The reduction in the circulating pool of lymphocytes, neutrophilic granulocytes, monocytes, and platelets may be attributed to increased adhesiveness, leading to their translocation to the marginal pool. Leukocyte adhesiveness is enhanced in endotoxemia, a condition for which acute intestinal barrier dysfunction — previously identified in rats of the "Fentanyl + 40 °C" group [3] — is a prerequisite. Increased adhesiveness of granulocytes, monocytes [27], and platelets [28], as well as lympho-macrophage infiltration of the intestine, liver, and lungs, have been described in pathological states associated with endotoxemia, including shock of various etiologies *in vitro* [29] and *in vivo* [27]. Hyperthermia contributes to these changes by enhancing the production of the pro-inflammatory cytokine IL-6 and lactic acid [30].

Increased platelet adhesiveness and thrombocytopenia are characteristic of disseminated intravascular coagulation associated with septic shock [31]. Therefore, a likely common mechanism underlying the leukopenic and thrombocytopenic effects of fentanyl under hyperthermia was a systemic inflammatory reaction triggered by endotoxemia — a component of acute intestinal endotoxemia. Thus, the hemogram changes observed in rats following fentanyl administration under hyperthermia represent early manifestations of acute intestinal endotoxemia typical of shock.

Previously [2, 3], using the same experimental model of fentanyl overdose under heat stress in rats, we identified a triad of homeostatic disturbances that provoke energy starvation of biological tissues: hypoxemia and hyperammonemia combined with metabolic acidosis. The present results allow us to add two new phenomena to this triad: arterial hypotension and increased functional load on the heart. The synergistic effect of this pentad on cardiac energy supply is a likely cause of death in some animals before the development of a full-blown clinical picture of exotoxic shock. Testing this hypothesis is the subject of further research.

CONCLUSION

1. Under heat stress, fentanyl-induced hyperpyrexia, sympathicotonia, and sinus tachycardia were opposite to its effects under thermal comfort.
2. Under heat stress, fentanyl decreased the number of circulating leukocytes and blood platelets and activated the juxtamedullary shunt in the kidneys, whereas it had no such effects under thermal comfort.
3. Arterial hypotension, sympathicotonia, tachycardia, reduction of the circulatory pools of leukocytes and platelets, increased renal blood filling, and activation of the juxtamedullary shunt in the kidneys represent early manifestations of the shock that develops in rats during acute fentanyl intoxication under heat stress.

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Authors' contributions. All authors confirm that their contributions meet the ICMJE criteria for authorship. The primary contributions are distributed as follows: Jury Ju. Ivnitsky — conception, development of the research plan, semantics, data interpretation; Mikhayl A. Rozhko — circulatory system studies; Olga N. Gajkova — histological studies; Larisa G. Kubarskaya — hematological studies; Alexandra R. Abdrakhmanova — heat stress modeling; Olga A. Vakunenkova — work with fentanyl; Vladymir L. Reiniuk — experimental model development. All authors participated in the discussion of the results, preparation, and editing of the manuscript.

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