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EXACERBATION OF ACUTE ALCOHOL INTOXICATION IN PIGS UNDER HEAT STRESS: AN EXPERIMENTAL STUDY

Jury Ju. Ivnitsky[✉], Olga A. Vakunenkova, Ekaterina A. Zolotoverkhaja, Semen S. Gaft, Natalya V. Lapyna, Vladymir L. Rejniuk

Golikov Research Center of Toxicology, St. Petersburg, Russia

Introduction. The hypothesis that ambient temperature influences the manifestations of alcohol intoxication was proposed long ago; however, the exacerbation of acute alcohol intoxication by heat stress remains empirically unconfirmed. The mechanisms underlying this phenomenon have likewise not been described in the literature.

Objective. To assess the impact of heat stress on metabolism, thermal status, and neurological status in pigs with moderate acute alcohol intoxication.

Materials and methods. In two- to three-month-old male Landrace pigs weighing 30–40 kg, kept at ambient temperatures of 24 °C and 40 °C, the neurological status was assessed, and rectal temperature, external respiration parameters, circulatory parameters, arterial blood hemoglobin oxygen saturation, acid-base status, blood gas composition, and venous blood biochemical parameters were determined within 3 h after intravenous administration of ethanol at a dose of 1.2 g/kg. Statistical analysis was performed using OriginPro software.

Results. All animals in the control group retained responses to auditory and painful stimuli but lost them in the experimental group. At an ambient temperature of 40 °C, rectal temperature increased by 2.4 °C, whereas a tendency toward its decrease was observed in the control group (24 °C); tachypnea developed. At 40 °C, venous blood oxygen tension decreased by 22% and hemoglobin oxygen saturation decreased by 20%, while in the control group these parameters increased by 42% and 15%, respectively. Bicarbonate levels decreased by 16%; base deficit and metabolic acidosis developed, with a 0.1-unit drop in pH. Lactate levels increased by 186%, pyruvate by 68%, ammonia by 152%, and bacterial endotoxin by 40%, whereas no significant changes in these parameters were observed in the control group.

Conclusions. Moderate acute alcohol intoxication in pigs under heat stress differed qualitatively from that under comfort thermal conditions as evidenced by the development of acute cerebral insufficiency (equivalent to coma in humans), tachypnea, venous hypoxemia, metabolic lactate acidosis, pyruvatemia, and endotoxemia, which included hyperammonemia and endotoxemia. The occurrence of such effects in humans would require refinement of the currently used methods for predicting and assessing the severity of alcohol intoxication, which are based on data regarding the ethanol dose, its concentration in blood, and its levels in exhaled air.

Keywords: alcohol intoxication; heat stress; coma; tachypnea; metabolic acidosis; lactic acidemia; pyruvic acidemia; hyperammonemia; endotoxemia; endotoxemia; pigs; animal study

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✉ Jury Ju. Ivnitsky neugierig@mail.ru

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ОТЯГОЩЕНИЕ ОСТРОЙ АЛКОГОЛЬНОЙ ИНТОКСИКАЦИИ У СВИНЕЙ ПРИ ТЕПЛОВОМ СТРЕССЕ: ЭКСПЕРИМЕНТАЛЬНОЕ ИССЛЕДОВАНИЕ

Ю.Ю. Ивницкий[✉], О.А. Вакуненко, Е.А. Золотоверхая, С.С. Гафт, Н.В. Лапина, В.Л. Рейнюк

Научно-клинический центр токсикологии им. академика С.Н. Голикова Федерального медико-биологического агентства, Санкт-Петербург, Россия

Введение. Предположение о влиянии температуры окружающей среды на проявления алкогольной интоксикации сделано давно, однако отягощение острой алкогольной интоксикации тепловым стрессом остается гипотезой. Механизмы этого феномена в литературе также не освещены.

Цель. Оценка влияния теплового стресса на метаболизм, тепловой и неврологический статус свиней при острой алкогольной интоксикации средней степени.

Материалы и методы. У двух-трехмесячных самцов свиней породы ландрас массой 30–40 кг, содержавшихся при температуре воздуха 24 и 40 °C, в течение 3 ч после внутривенного введения этанола в дозе 1,2 г/кг оценивали неврологический статус, определяли ректальную температуру, показатели внешнего дыхания, кровообращения, сатурацию кислородом гемоглобина артериальной крови, кислотно-основное состояние, газовый состав и биохимические показатели венозной крови. Статистический анализ выполняли с помощью программного обеспечения OriginPro.

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Результаты. Все животные сохраняли реакции на звуковой и болевой стимулы в контроле и утрачивали их в опыте. При температуре воздуха 40 °C ректальная температура повышалась на 2,4 °C при тенденции к ее снижению в контроле (24 °C); развивалось тахипноэ. При 40 °C в венозной крови на 22% снижалось напряжение кислорода и на 20% — сатурация кислородом гемоглобина при их повышении в контроле на 42 и 15% соответственно; на 16% снижалось содержание гидрокарбоната, развивались дефицит буферных оснований и метаболический ацидоз с падением pH на 0,1; уровень лактата повышался на 186%, пирувата — на 68%, аммиака — на 152% и бактериального эндотоксина — на 40% при отсутствии их значимых изменений в контроле.

Выводы. Острая алкогольная интоксикация средней степени у свиней в условиях теплового стресса качественно отличалась от таковой при тепловом комфорте развитием острой церебральной недостаточности, эквивалентной коме у человека, тахипноэ, венозной гипоксемии, метаболического лактат-ацидоза, пируватемии и эндотоксемии, включавшей в себя гипераммониемию и эндотоксинемию. Возникновение подобных эффектов у человека потребует уточнения ныне используемых методов прогнозирования и оценки тяжести алкогольной интоксикации, основанных на сведениях о дозе этанола, его содержании в крови и выдыхаемом воздухе.

Ключевые слова: алкогольная интоксикация; тепловой стресс; кома; тахипноэ; метаболический ацидоз; лактацидемия; пируватемия; гипераммониемия; эндотоксемия; эндотоксинемию; свиньи; исследование на животных

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✉ Ивницкий Юрий Юрьевич neugierig@mail.ru

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INTRODUCTION

In the Northern Hemisphere, a positive correlation between per capita alcohol consumption and geographical latitude has been established¹. One possible explanation for this pattern is reduced tolerance to ethanol at lower latitudes, where climatic factors create conditions predisposing the body to overheating. Epidemiological data support this hypothesis, showing an increased mortality rate associated with acute alcohol intoxication both under exposure to extreme temperatures in a sauna [1] and during abnormal heatwaves [2]. However, a PubMed search conducted up to 6 Nov. 2025 using the keywords “heat stress AND acute alcohol intoxication”, “heat stroke AND acute alcohol intoxication”, “heat tolerance AND acute alcohol intoxication”, “acute alcohol intoxication AND body temperature”, or “acute alcohol intoxication AND ambient temperature” yielded no results indicating a direct experimental verification of this hypothesis. The mechanisms underlying the phenomenon of reduced alcohol tolerance under heat stress have not been described in the literature. Studies involving human volunteers have examined only the effect of elevated ambient temperature on the toxicodynamics of ethanol in cases of mild acute alcohol intoxication [3].

For a person engaged in light physical work, heat stress is considered to occur when the wet-bulb temperature (WBT) of the air exceeds 33 °C. Such conditions,

which correspond to an air temperature of approximately 40 °C at low humidity, are not uncommon in the southern regions of Russia. At an air temperature of 33 °C, alcohol contributes to a reduction in the body’s core temperature [3]. However, it remains unknown whether this effect persists under conditions predisposing the body to overheating. Pigs represent a convenient experimental model for studying the influence of microclimatic conditions on the manifestations of acute alcohol intoxication because their anatomical features and ethanol metabolism are similar to those in humans [5].

The aim of the study was to assess the impact of heat stress on metabolism, thermal status, and neurological status in pigs during experimental modeling of moderate acute alcohol intoxication.

MATERIALS AND METHODS

A pilot prospective randomized experimental study with a control group was conducted. The experiment involved two- to three-month-old male Landrace pigs weighing 30–40 kg (from the laboratory animal nursery of LLC “KrollInfo”), which were provided with standard feed and drinking water *ad libitum*. Animals were monitored for 14 days prior to the experiment to exclude sick individuals from the sample. Ten minutes before ethanol administration, they were given an intramuscular injection of tiletamine, zolazepam, and xylazine at a dose of

¹ Global status report on alcohol and health 2018. Geneva: World Health Organization; 2018.

0.5 mg/kg each. This provided a sedative effect lasting up to 15 min, which was sufficient for animal restraint and ethanol administration. The pigs were secured with tape on stretchers in the ventral (prone) position. The experiments were carried out in accordance with the Recommendation of the Board of the Eurasian Economic Commission No. 33 dated 14 Nov. 2023 “On the Guidelines for Working with Laboratory (Experimental) Animals in Preclinical (Nonclinical) Studies”.

Moderate acute alcohol intoxication was induced by infusion into the veins of the ear pinnae of a mixture comprising 7 parts of physiological saline and 3 parts of 96% ethanol, administered at a volume of 5 mL per kilogram of animal body weight (resulting in an ethanol dose of 1.2 g/kg). Under these conditions, the maximum blood concentration (C) reached 1.7 g/L (Equation 1):

$$C = A / (P \times r), \quad (1)$$

where C is the maximum blood ethanol concentration; A is the mass of ethanol (g); P is the animal's body weight (kg); and r is the distribution factor, assumed to be 0.7 [6]. The infusion method was preferred over intragastric administration to exclude the influence of uncontrolled factors and climatic conditions on the toxicokinetics of ethanol.

Two randomized groups of six animals each were formed using a random number generator². After ethanol administration, the animals were placed for 3 h in rooms with an air temperature of $24 \pm 0.3^\circ\text{C}$ and a relative humidity of $44.3 \pm 0.2\%$ (control) or $40 \pm 0.4^\circ\text{C}$ and a relative humidity of $40.6 \pm 0.2\%$ (experimental). These conditions were monitored using Testo 622 thermohygrometers (Testo, Germany) and VIT-2 psychrometer hygrometers (First Thermometer Plant, Russia); one of the thermometers was wetted.

Respiratory rate (breaths/min) and minute ventilation (L/min) were measured hourly using the Spiro Spectrum hardware software complex (Neurosoft, Russia); heart rate (beats/min) was monitored with the Mindray uMec 12VET patient monitor (Mindray, China); systolic and diastolic blood pressure (mm Hg) were assessed with the PETMAP Graphic II veterinary tonometer (Cardio Command, USA); rectal temperature ($^\circ\text{C}$) was recorded with the MR 402 sensor (Mindray, China); and arterial hemoglobin oxygen saturation (SpO_2 , %) was determined by pulse oximetry using the 562A clip as part of the Mindray uMEC 12 VET patient monitor. Visual observation of the animals with assessment of neurological status was carried out continuously for 3 h after ethanol administration. The absence of a motor response to an auditory stimulus (a hand clap) while preserving the response to a painful stimulus (pinching the ear pinna with fingers) was regarded as stupor; the absence of all sensorimotor reflexes, except for the corneal reflex, was regarded as coma. Upon completion of the exposure period in the thermal chamber, the pigs were released

from restraints and returned to normal microclimatic conditions. A follow-up examination performed 16 h later revealed that motor activity in all animals corresponded to the pre-experimental levels.

Venous blood samples were collected from the ear veins prior to and 3 h after ethanol administration to the animals. A portable EPOC analyzer with an EPOC BGEM cartridge (AG Siemens, Germany) was used to assess energy metabolism status, acid-base balance parameters, blood gases, hemoglobin, and hematocrit.

Plasma glucose and lactate levels were determined using an A-25 biochemical analyzer (BioSystems, Spain) with the Glucose reagent kits (BioSystems, Spain) and Lactate-Vital reagent kits (Medical Innovative Technologies, Russia). Ammonia concentration was measured spectrophotometrically using the “Ammonia Ultra” reagent kit (Sentinel Diagnostics, Italy). Urea content was determined after its hydrolysis to ammonia, employing the Urea UV reagent kit (BioSystems, Spain). Creatinine was simultaneously determined spectrophotometrically via the reaction with picric acid at $\lambda = 500\text{ nm}$, and albumin was measured via the reaction with bromocresol green at $\lambda = 630\text{ nm}$. Endotoxin was detected using the LAL reagent in the gel-clot test format with an ALPYR Test reagent kit (Aligmed Techno, Russia). To enhance the sensitivity of the method, samples were incubated at 65°C for 30 min prior to dilution and mixing with the LAL reagent, followed by centrifugation; this procedure released endotoxin from the bound state into the free state [7]. Pyruvate was determined in the protein-free blood supernatant using the Pyruvate UV-Abris reagent kit (ABRIS+, Russia).

The results are presented as the mean and its standard error ($M \pm m$). Data visualization and assessment of the effect of pathogenic factors on the studied quantitative parameters were performed using two-way ANOVA with OriginPro 8.1 software. When the obtained models were significant, post-hoc pairwise comparisons of group means were performed using Tukey's test. Normality of the distribution was assessed with the Shapiro–Wilk test. The significance of differences in dependent samples (when evaluating the parameter dynamics) was evaluated using the Wilcoxon signed-rank test. The critical significance level α was set at 0.05.

RESULTS

At room temperature, the alcohol-exposed animals retained all sensorimotor reflexes throughout the entire observation period. Under elevated air temperature conditions, the response to both auditory and painful stimuli was absent in all animals for at least 1 h. In the data presented below, all statements regarding intergroup differences imply statistical significance ($p < 0.05$); if no statistical significance was found, the differences are reported as a trend.

² RandStuff. URL: <https://randstuff.ru/number/>

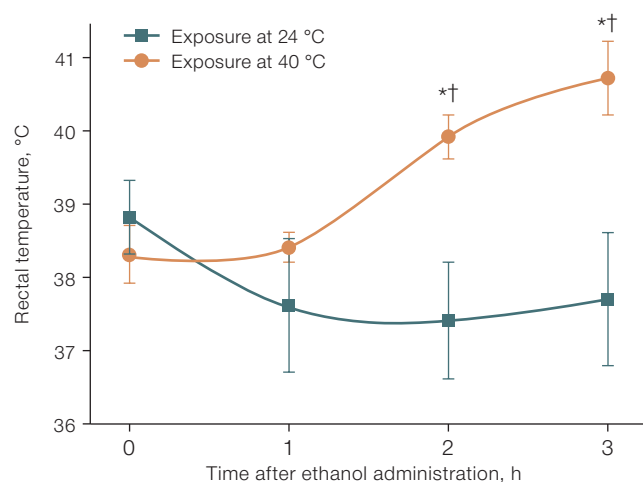


Figure prepared by the authors using their own data

Fig. 1. Dynamics of rectal temperature in pigs exposed to different air temperatures for 3 h after ethanol administration. Data are expressed as mean $\pm$ standard error ($M \pm m$); $n = 6$. Significant differences ($p < 0.05$): * compared with the baseline value; † compared with the “Exposure at 24 °C” group

At room temperature, rectal temperature tended to decrease after ethanol administration. Under elevated air temperature conditions, it exceeded the baseline value by 2.4 °C and the value in the control group by 3 °C at the 3-h time point (Fig. 1).

At room temperature, the external respiratory parameters did not show significant changes. Under elevated temperature conditions, the animals exhibited dyspnea; the respiratory rate increased by a factor of 2.1, and the minute ventilation exceeded the control value by a factor of 1.7 (Fig. 2).

Heart rate, blood pressure, hematocrit, and hemoglobin levels in the experimental group of animals did

not show significant changes over the 3-h observation period and did not differ significantly from those in the control group: heart rate, 113 ± 4 vs. 115 ± 12 beats/min; systolic blood pressure, 151 ± 10 vs. 132 ± 2 mm Hg; diastolic blood pressure, 95 ± 11 vs. 85 ± 10 mm Hg; hematocrit, 34 ± 1 vs. $32 \pm 1\%$; hemoglobin, 114 ± 2 vs. 105 ± 1 g/L. Arterial hemoglobin oxygen saturation remained within the 90–93% range throughout the entire observation period in all pigs and showed no substantial intergroup differences.

The venous blood acid-base parameters — pH, base excess, and bicarbonate concentration — decreased in both animal groups; the decrease was more pronounced in the animals kept at 40 °C (Fig. 3A, B, F). The blood oxygen tension in pigs kept at 40 °C decreased by 22%, whereas it increased by 42% in the control group (Fig. 3C). Venous hemoglobin oxygen saturation decreased from 83.2% to 66.7% at 40 °C, while it increased from 79.5% to 91.3% in the control group (Fig. 3E). Blood carbon dioxide tension tended to decrease in both groups; this trend was statistically significant in the animals kept at 24 °C and amounted to a 15% reduction (Fig. 3D).

Under elevated air temperature, against a background of a tendency toward hypoglycemia, lactic acid accumulated in the blood, with its level being 186% higher than the baseline value; in the control group, similar directional changes did not reach statistical significance. Under heat stress, the lactate level exceeded the glucose level by 54%, whereas prior to ethanol administration, the ratio was reversed in both groups (Fig. 4A, C). Pyruvic acid accumulated only in the blood of pigs kept at elevated temperature; its level was 68% higher than the baseline value in these animals. The lactate-to-pyruvate concentration ratio increased by 114% in animals kept at 24 °C and by 68% in those kept at 40 °C (Fig. 4B, C).

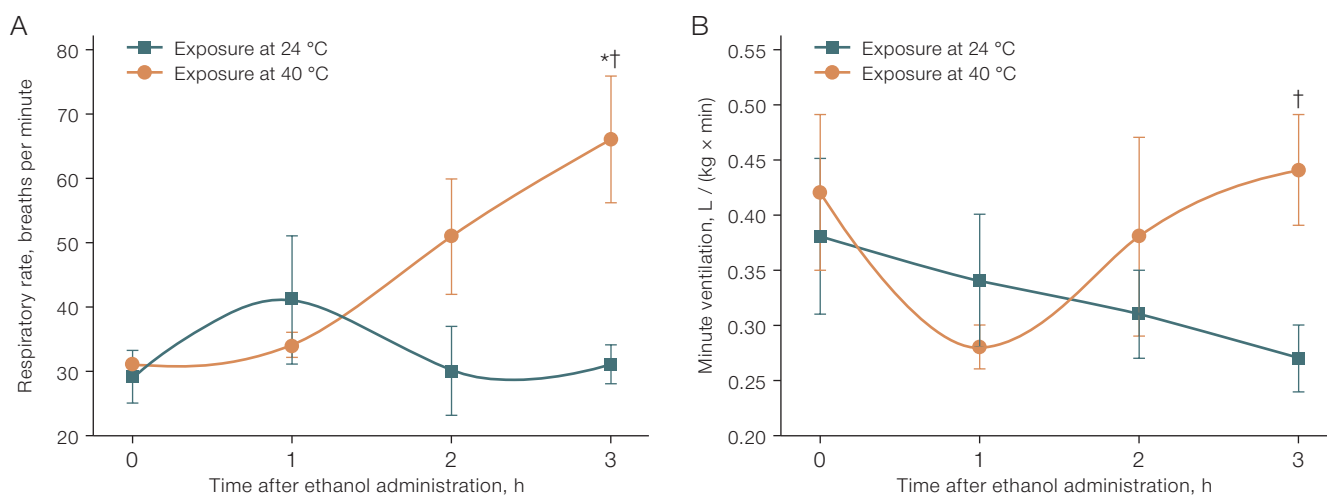


Figure prepared by the authors using their own data

Fig. 2. Dynamics of external respiratory parameters in pigs exposed to different air temperatures for 3 h after ethanol administration. Data are expressed as mean $\pm$ standard error ($M \pm m$); $n = 6$. Significant differences ($p < 0.05$): * compared with the baseline value; † compared with the “Exposure at 24 °C” group

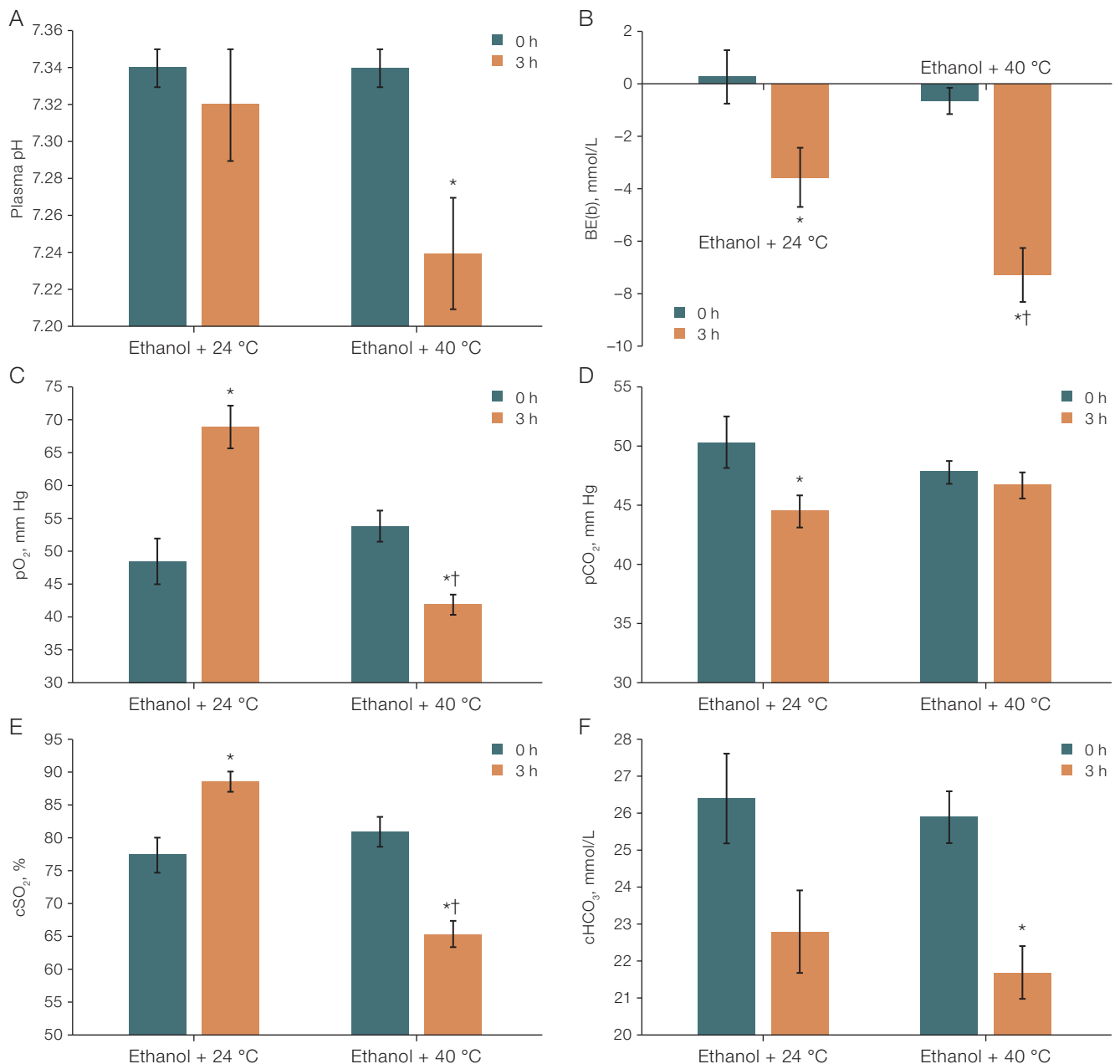


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Fig. 3. Venous blood acid-base status and blood gases in pigs 3 h after ethanol administration and subsequent exposure to air temperatures of 24 °C or 40 °C. A, pH; B, base excess; C, temperature-corrected oxygen tension; D, temperature-corrected carbon dioxide tension; E, oxygen saturation; F, bicarbonate concentration. Data are expressed as mean $\pm$ standard error ($M \pm m$); $n = 6$. Significant differences ($p < 0.05$): * compared with the baseline level; † compared with the “Ethanol + 24 °C” group

The ammonia level in the pigs' blood plasma was approximately one order of magnitude higher than the normal values for humans [8]. Three hours after ethanol administration, it increased by 152% in animals kept at elevated air temperature and, as a trend, by 51% in those kept at room temperature (Fig. 4D). Blood urea (Fig. 4E) and creatinine (Fig. 4F) levels did not change significantly and showed no substantial intergroup differences.

In pigs kept at 40 °C, the plasma endotoxin level 3 h after ethanol administration exceeded the baseline value by 40%, whereas no substantial changes were observed

in the control group (Fig. 4G). Plasma albumin levels did not show substantial changes in either group (Fig. 4I).

DISCUSSION

At a relative humidity of $40.6 \pm 0.2\%$, an air temperature of 40 °C corresponds to a wet-bulb temperature of 29.2 ± 0.1 °C. This is below the heat stress threshold for a human performing light physical work (33 °C) [4]. However, as indicated by the thermometry data, heat stress developed in pigs even under the conditions of

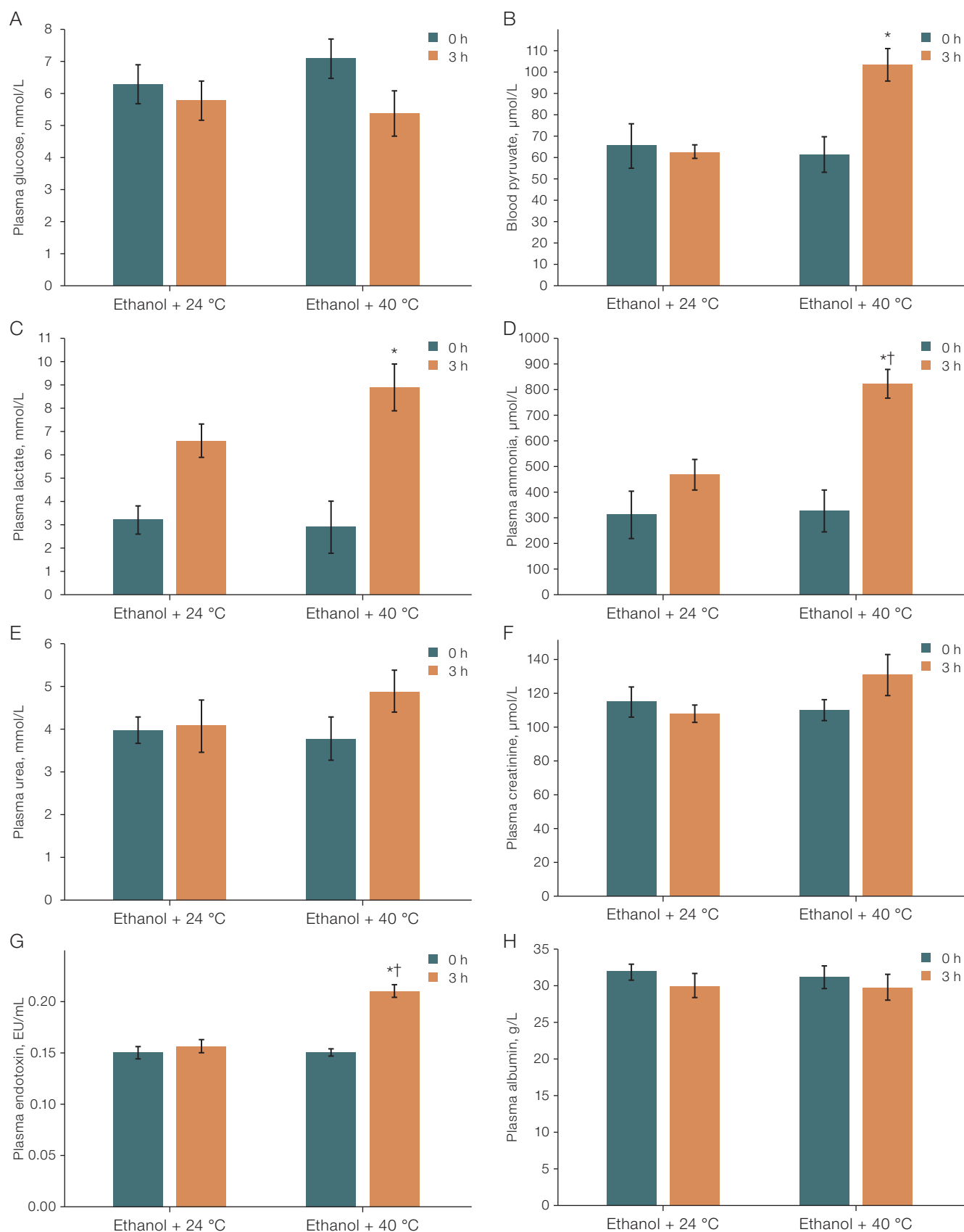


Figure prepared by the authors using their own data

Fig. 4. Energy and nitrogen metabolism parameters and endotoxin levels in venous blood of pigs 3 h after ethanol administration and subsequent exposure to air temperatures of 24 °C or 40 °C. Data are expressed as mean $\pm$ standard error ($M \pm m$); $n = 6$. Significant differences ($p < 0.05$): * compared with the baseline level; † compared with the “Ethanol + 24 °C” group

this experiment (Fig. 1), which may be attributed to the absence of functional sweat glands in their skin, except for the skin of the snout [9]. The rectal body temperature in the experimental group (40.7 °C) did not reach the threshold for irreversible tissue damage (43 °C) [10]. However, ethanol-treated pigs showed signs of metabolic acidosis: depletion of the bicarbonate pool, deficit of buffer bases, decreased plasma pH, lactic acidemia, and pyruvic acidemia. The clinical manifestation of metabolic acidosis — tachypnea — was observed under heat stress conditions but not under heat-comfort conditions.

One of the potential contributors to metabolic acidosis in animals of both experimental groups may have been the accumulation of acetic acid — a product of ethanol oxidation — in the blood. Under isolated ethanol exposure, this factor could have been the primary cause, as pyruvate did not accumulate in the blood, and lactic acidemia was observed only as a trend. In the control group of pigs, no pronounced clinical signs of acute energy deficit were observed: there was no intensification of external respiration or cerebral insufficiency manifested as stupor or coma. The oxygen content in their venous blood increased, while the carbon dioxide content decreased. Given the preservation of normal arterial blood oxygen saturation, this indicated a reduced tissue oxygen demand and, consequently, a lower energy requirement.

Under heat stress at 40 °C, lactic acid and pyruvic acid became significant contributors to acidosis. Their accumulation in the blood reflected the compensation of impaired oxidative phosphorylation by glycolytic metabolism, which was manifested by an inversion of the lactate-to-glucose ratio. The increased intensity of external respiration also indirectly indicated a systemic ATP deficit. Due to the high affinity for NAD⁺ of predominantly cytosolic enzymes — alcohol dehydrogenase and acetaldehyde dehydrogenase — the ATP demand of tissues metabolizing ethanol could not be met by oxidation of cytosolic NADH. The accumulation of NADH in the cytosol is indicated by the increased lactate-to-pyruvate ratio in venous blood. Given the preserved capacity of tissues to utilize oxygen, the efficiency of oxidative phosphorylation was the factor limiting ATP resynthesis in the organism. This possible uncoupling is indicated by the decreased oxygen content in venous blood despite normal arterial oxygen saturation, as well as by the stable carbon dioxide tension in blood, even in the presence of metabolic acidosis. At the same time, due to the dead space in the upper airways, the increased ATP demand could not be fully met by an elevated respiratory rate. This is evidenced by a 0.1 unit drop in blood pH — one of the most stable homeostatic parameters — as well as by the development of coma in the animals.

Acute alcohol intoxication under heat stress conditions was accompanied by endotoxemia, the specific

manifestations of which included hyperammonemia and endotoxemia. These changes were not attributable to hemoconcentration, given the absence of substantial alterations in hematocrit, hemoglobin, plasma creatinine, and albumin levels. The clinical significance of endotoxemia can be accessed via cross-species extrapolation. In humans, a 2.52-fold increase in blood ammonia levels above the upper limit of normal (from 60 µM to 151 µM) would be classified as moderate hyperammonemia³, which is typically associated with acute cerebral insufficiency [8] — a condition that was observed in pigs in this study. A 40% rise in plasma endotoxin levels in humans would lead to cytokine system activation [11], which in pigs may have contributed to the development of hyperthermia and dyspnea.

The intestine is the primary source of blood ammonia and endotoxin. Increased intestinal permeability, combined with dysbiosis, is characteristic of heat stress in both pigs [9] and humans [10]. Under metabolic acidosis, ammonia diffuses from the blood into the brain along the concentration gradient of its neutral form (NH₃), even in the absence of hyperammonemia. This direction of diffusion is driven by the more pronounced decrease in pH (and thus in [NH₃]) in the cytoplasm compared to that in the blood plasma [12]. It can be hypothesized that the resulting intensification of ammonia influx from the blood into the brain led to cerebral swelling due to glutamine accumulation in astroglia [12]. The synergism between ammonia and endotoxin, along with their multiple mechanisms of acute neurotoxicity [13], supports the hypothesis that endotoxemia contributed to the development of the acute cerebral insufficiency observed in the animals. In light of the obtained data, it is of interest to evaluate the effect of interventions for the prevention of acute intestinal endotoxemia — in particular, local abdominal cooling [14] — on the severity of acute alcohol intoxication under heat stress conditions.

Given the exploratory nature of the present study, several limitations should be acknowledged: the limited animal sample size precluded the formation of groups exposed to isolated heat stress or to procedures involving ethanol infusion. In addition, catheterization of the cranial vena cava to assess changes in acid-base status and blood gas composition was not performed. Addressing these limitations defines the prospects for future research.

CONCLUSIONS

Acute moderate alcohol intoxication in pigs under heat stress differed qualitatively from that under heat-comfort conditions as evidenced by the emergence of acute cerebral insufficiency — equivalent to coma in humans — as well as by the development of tachypnea, hypoxemia, pyruvatemias, and endotoxemia, which included hyperammonemia and endotoxemia. Under

³ Lazebnik LB, Golovanova EV, Alekseenko SA, Bueverov AO, Plotnikova EYu, Dolgushina AI, et al. Russian Consensus on Hyperammonemia in Adults (2021 Version). *Experimental and Clinical Gastroenterology*. 2021;187(3):97–118.

heat stress, the metabolic acidosis induced by acute alcohol intoxication was exacerbated. Extrapolation of the obtained data to humans may be complicated by the presence of sweat glands over the entire skin surface in humans, which enables more efficient

evaporative heat loss. If such extrapolation is feasible, methods for predicting and assessing the severity of alcohol intoxication will need to be refined — based on data regarding the dose of ingested ethanol, its concentration in blood, and in exhaled air.

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Authors:

Jury Ju. Ivnitsky, Dr. Sci. (Med.), Professor, ORCID: <https://orcid.org/0000-0002-1057-5356>

Olga A. Vakunenkova, ORCID: <https://orcid.org/0009-0005-9665-9866>

Ekaterina A. Zolotoverkhaja, Cand. Sci. (Biol.), ORCID: <https://orcid.org/0000-0002-9708-2596>

Semen S. Gaft, Cand. Sci. (Chem.), ORCID: <https://orcid.org/0009-0008-5092-8161>

Natalya V. Lapyna, Cand. Sci. (Med.), ORCID: <https://orcid.org/0000-0002-3418-1095>

Vladimir L. Rejniuk, Dr. Sci. (Med.), ORCID: <https://orcid.org/0000-0002-4472-6546>