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Platelet Bioenergetics and Associations With Delirium and Coma in Patients With Sepsis:

A Prospective Cohort Study

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Abstract

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BACKGROUND: Acute brain dysfunction during sepsis, which manifests as delirium or coma, is common and is associated with multiple adverse outcomes, including longer periods of mechanical ventilation, prolonged hospital stays, and increased mortality. Delirium and coma during sepsis may be manifestations of alteration in systemic metabolism. Because access to brain mitochondria is a limiting factor, measurement of peripheral platelet bioenergetics offers a potential opportunity to understand metabolic changes associated with acute brain dysfunction during sepsis.

RESEARCH QUESTION: Are altered platelet mitochondrial bioenergetics associated with acute brain dysfunction during sepsis?

STUDY DESIGN AND METHODS: We assessed participants with critical illness in the ICU for the presence of delirium or coma via validated assessment measures. Blood samples were collected and processed to isolate and measure platelet mitochondrial oxygen consumption. We used Seahorse extracellular flux to measure directly baseline, proton leak, maximal oxygen consumption rate, and extracellular acidification rate. We calculated adenosine triphosphate-linked, spare respiratory capacity, and nonmitochondrial oxygen consumption rate from the measured values.

RESULTS: Maximum oxygen consumption was highest in patients with coma, as was spare respiratory capacity and extracellular acidification rate in unadjusted analysis. After adjusting for age, sedation, modified Sequential Organ Failure Assessment score without the neurologic component, and preexisting cognitive function, increased spare respiratory capacity remained associated with coma. Delirium was not associated with any platelet mitochondrial bioenergetics.

INTERPRETATION: In this single-center exploratory prospective cohort study, we found that increased platelet mitochondrial spare respiratory capacity was associated with coma in patients with sepsis. Future studies powered to determine any relationship between delirium and mitochondrial respiration bioenergetics are needed.

Keywords

acute brain dysfunction; bioenergetics; coma; delirium; platelet mitochondria; sepsis

Sepsis affects an estimated 50 million people worldwide each year.[1,2] Patients with sepsis are at high risk of acute brain dysfunction, with up to 50% experiencing delirium or coma.[3] Both are associated with longer periods of mechanical ventilation, prolonged hospital stays, higher health costs, and increased mortality.[4-8] Additionally, sepsis survivors experience long-term cognitive impairment and physical disabilities,[9] the severity of which is predicted by the duration of delirium during sepsis.[10,11] Despite this, the pathophysiologic features of delirium and coma in sepsis and subsequent long-term cognitive impairment after sepsis remain poorly understood.[12]

Mitochondrial function is integral to cellular homeostasis, not only through the production of adenosine triphosphate (ATP) (the energy currency of cells), but also through the generation of mitochondrial reactive oxygen species for signaling and the propagation of apoptotic cell death. Animal models of sepsis show that mitochondrial dysfunction, including decreased ATP production via oxidative phosphorylation, increased reactive

oxygen species production, and dismutation, result in tissue dysfunction and cellular damage and that mitochondrial-specific therapies can limit these changes and can improve outcomes.[13] In humans, mitochondrial dysfunction has been implicated in severe sepsis, sepsis-induced cardiomyopathy, acute kidney injury, and liver dysfunction.[14-18] Dysfunction of mitochondrial electron transport complexes also has been implicated in various neurocognitive disorders, including Alzheimer disease, Huntington disease, and Parkinson disease.[19-22] These studies demonstrate that mitochondrial dysfunction is present in sepsis and neurocognitive pathologic conditions. However, a role for mitochondrial dysfunction in sepsis-induced acute brain impairment has not been explored thoroughly.

Because brain tissue—which could be used to evaluate mitochondrial function if biopsy in this setting were feasible—cannot be safely obtained from most patients with sepsis, we leveraged the measurement of platelet mitochondrial bioenergetics as a measure of systemic mitochondrial function[23-26] to examine associations between mitochondrial dysfunction during sepsis, delirium, and coma. Our objectives were to assess associations between platelet mitochondrial bioenergetics, a surrogate of systemic mitochondrial function, and coma and delirium during sepsis and to generate data-driven hypotheses that can guide the design of future studies examining whether these changes reflect mitochondrial alteration in the brain.

Study Design and Methods

Study Design and Population

In this single-center prospective cohort study, from September 2018 through March 2022, we recruited adults admitted to the medical or surgical ICU with sepsis according to the Third International Consensus Definitions for Sepsis and Septic Shock definition. Specifically, patients were eligible who had documented or suspected infection treated with antibiotics and acute respiratory failure, shock, or both. We defined acute respiratory failure as initiation of noninvasive or invasive mechanical ventilation, and we defined shock as the initiation of a vasopressor (eg, any dose of norepinephrine, vasopressin, epinephrine, or > 5 μg/kg/min of dopamine). We recruited patients with these forms of acute organ dysfunction to enrich the study population for those at high risk of delirium and coma. We excluded patients with preexisting dementia or chronic neurologic disease that prevented them from living independently; acute severe neurologic deficit (eg, resulting from acute stroke or anoxic brain injury); moribund state with life expectancy < 24 h; inability to complete delirium assessments because of blindness, deafness, or inability to speak and understand English; or lack of informed consent from an authorized representative or the participant within 48 h of meeting inclusion criteria. This study was approved by the University of Pittsburgh Institutional Review Board Committee A (Identifier: STUDY19020061) before enrollment of participants.

Exposures

We isolated platelets as described previously.[24] Briefly, we collected venous blood samples in citrate-containing cell preparation tubes within 24 h of enrollment, placed the tubes in ice, and transported them to the laboratory within 1 h of collection time. We centrifuged

whole blood at 150*g* for 10 min in the presence of prostaglandin I_2 (measured in micrograms per milliliter), collected plasma, then pelleted platelets from platelet-rich plasma using centrifugation (1,500*g* for 10 min). We then washed platelet pellets with erythrocyte lysis buffer and prostaglandin I_2. Finally, we resuspended samples in modified tyrode buffer (20 mM N-(2-hydroxyethyl) piperazine-N′-2-ethanesulfonic acid, 128 mM sodium chloride, 12 mM bicarbonate, 0.4 mM sodium hypophosphite, 5 mM glucose, 1 mM magnesium chloride, 2.8 mM potassium chloride, pH 7.4).

We then measured the oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) using Seahorse extracellular flux (96XFe; Agilent), as described previously.[24,27,28] We loaded platelets (50 million/well) in unbuffered Dulbecco modified eagle medium into each well of a Seahorse extracellular flux microplate, then centrifuged the microplates after equilibration (10 min at 37 °C). We first measured baseline OCR, which is the result of physiologic turnover of the mitochondrial electron transport chain, in the platelets under basal conditions with no treatment. Next, we sequentially added pharmacologic agents that modulate the electron transport chain (ETC) to facilitate measurement of key parameters of the mitochondrial ETC. The addition of oligomycin A 2.5 μM (a complex V inhibitor) inhibits adenosine diphosphate-to-ATP conversion by the ETC, and thus any OCR remaining after oligomycin A addition is indicative of so-called inefficient respiration and is not linked to ATP production (ie, proton leak). We calculated ATP-linked OCR by subtracting the proton leak from the basal OCR. Next, we added 0.7 μMof carbonyl cyanide p-(trifluoromethoxy) phenyl-hydrazone, a protonophore that uncouples oxygen consumption from ATP production, to dissipate the proton-motive force across completely the inner mitochondrial membrane, enabling the mitochondria to respirate at its maximum capacity (ie, maximum OCR). We calculated spare respiratory capacity, which is indicative of the energy store in the ETC that can be tapped into if the cell requires increased energy, by subtracting the maximum OCR from the basal OCR. We then inhibited complexes I and II by adding rotenone (10 μmol) and antimycin A (10 μmol), which eliminate mitochondrial oxygen consumption entirely (ie, nonmitochondrial OCR). Finally, we added 2-deoxyglucose (100 μM) to inhibit glycolysis completely and measured ECAR as a surrogate for the glycolytic rate. An in-depth review of this methodology is available elsewhere.[28]

Outcomes

To measure mitochondrial function concurrent with delirium or coma, both of which can fluctuate during sepsis, we assessed participants for delirium and coma immediately after collecting blood. Trained study personnel assessed patients for delirium once daily using the Confusion Assessment Method for ICU,[29,30] and they assessed level of consciousness using the Richmond Agitation-Sedation Scale (RASS).[31,32] If the Confusion Assessment Method for the ICU and RASS assessments could not be performed (which occurred only once), we assigned delirium as positive if the clinical nurse-administered Intensive Care Delirium Screening Checklist—which was performed every 12 h and was recorded in the electronic health record—was > 4. We assigned coma as no response to verbal or physical stimulation (RASS score, −5), or no response to voice alone, but a response to physical or painful stimulation (RASS score, −4).

Covariates

We collected the following covariate data at enrollment: age, preexisting cognitive function, exposure to sedating medications, and severity of illness as measured using a modified Sequential Organ Failure Assessment[33] (SOFA) scale that excluded the neurologic component. We estimated preexisting cognitive function using a short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE),[34,35] a validated surrogate questionnaire, and the proxy-completed 8-item Interview to Differentiate Aging and Dementia.[36] We excluded patients with preexisting mild cognitive impairment using the following definitions: short-form IQCODE score of > 3.4, 8-item Interview to Differentiate Aging and Dementia score of > 2.0, or both.

Statistical Analysis

We examined baseline demographics and clinical characteristics using median and interquartile range (IQR) for continuous variables and proportions for categorical variables. We used the Kruskal-Wallis test to evaluate unadjusted differences between mental status groups (eg, normal, delirium, or coma) and the Dunn test for pairwise comparisons. In a priori-planned analysis, we used multinomial logistic regression to analyze adjusted associations between platelet bioenergetics and mental status (delirium, coma, and normal). In all regression models, we included the following covariates, which we selected a priori based on existing literature and clinical judgment: age, exposure (yes or no) to sedative medication, modified SOFA score (with the neurologic component excluded), and preexisting cognitive function as estimated by the short-form IQCODE. In a post hoc sensitivity analysis, we fit the same models, but replaced the dichotomous covariate for sedative exposure (yes or no) with three covariates reflecting the cumulative doses of propofol, benzodiazepines (in midazolam equivalents), and opioids (in fentanyl equivalents) received on the day of specimen collection. In a separate post hoc analysis, we further assessed the association between platelet bioenergetics and coma that was seen in the initial model using an ordinal logistic regression model with the outcome of RASS, a more granular assessment of the level of consciousness, measured on the day of sample collection (study day 1). Finally, we used Spearman rank correlation to determine whether platelet bioenergetics were correlated with C-reactive protein and IL-6 levels, which we measured using commercially available immunoassays. Because we sought to generate hypotheses to be tested in future confirmatory studies, we based sample size on logistical constraints and did not adjust for multiple comparisons. We used Stata SE version 17 software (StataCorp) for all statistical analyses.

Results

From September 2018 through March 2022, we enrolled 63 patients (Fig 1) who had a median age of 64 years (IQR, 52-72 years) and admission modified SOFA score of 10 (IQR, 8-13); 48% were female. All but three participants were White. On the day of enrollment and sample collection, 10 patients (15%) were delirious, 19 patients (30%) were comatose, and 34 patients (54%) demonstrated normal mental status. The median days in the hospital before sample collection was 2 days (IQR, 2-3 days), with a range of 1 to 8 days. Most patients (71%) were receiving one or more sedative medications on the day of sample

collection. The total SOFA score differed among the three groups. This difference was not statistically significant when the neurologic component was excluded (modified SOFA), perhaps because of the small sample size (Table 1).

In unadjusted analysis, platelet basal OCR was similar among the three groups of patients, as were proton leak and nonmitochondrial OCR (Table 2, Fig 2). Alternatively, comatose patients showed higher maximum OCR than those with delirium (pairwise $P = .003$) and those with normal mental status (pairwise $P = .03$). Additionally, spare respiratory capacity was higher in those with coma vs those with delirium (pairwise $P = .003$) and vs those with normal mental status (pairwise $P = .04$). ECAR was higher in those with coma than in those with delirium (pairwise $P = .01$) and those with normal mental status (pairwise $P = .02$), but no significant difference in ECAR was found between those with delirium and normal mental status (pairwise $P = .18$).

After adjusting for age, sedation, modified SOFA score, and preexisting cognitive function, higher spare respiratory capacity was associated with an increased odds of coma as compared with normal mental status (Table 2). Sensitivity analyses that adjusted for doses of sedatives (rather than yes or no exposure) yielded similar results (e-Table 1). Alternatively, no significant associations were found between proton leak, nonmitochondrial OCR, or ECAR and delirium or coma after adjusting for covariates. In additional post hoc analysis of two commonly studied inflammatory biomarkers (C-reactive protein and IL-6), both inflammatory markers were correlated with basal OCR, proton leak, and nonmitochondrial OCR, but not with the bioenergetic measures that were associated with coma (e-Table 2).

Figure 3 displays bioenergetic measures according to level of consciousness (measured using RASS) on the day of sample collection. After adjusting for covariates, increased spare respiratory capacity was associated with a decreased level of consciousness, that is, lower RASS (OR, 0.99; 95% CI, 0.97-1.00; $P = .04$). Increased nonmitochondrial OCR also was associated with lower RASS (OR, 0.95; 95% CI, 0.92-0.99; $P = .03$), but maximum OCR (OR, 0.99; 95% CI, 0.99-1.00; $P = .07$), proton leak (OR, 0.97; 95% CI, 0.95-1.00; $P = .07$), and ECAR (OR, 0.93; 95% CI, 0.88-1.00; $P = .052$) were not associated with RASS. In the post hoc analysis when sedation doses were included as covariates, increased maximum OCR also was associated with lower RASS score (OR, 0.99; 95% CI, 0.98-0.99; $P = .03$).

Discussion

This exploratory prospective cohort study is the first, to our knowledge, to examine associations between platelet mitochondrial function and acute brain dysfunction (delirium and coma) in patients with sepsis. After adjustment for covariates, none of the measures of platelet mitochondrial respiration were associated with delirium, but increased spare respiratory capacity was associated with both coma and reduced level of consciousness, a finding that suggests platelet mitochondrial bioenergetics, a surrogate of systemic bioenergetic changes, may provide information about coma during sepsis.

Because both common forms of abnormal mental state during critical illness, delirium and coma often are lumped together and described as *acute brain dysfunction* during sepsis,

but little is known about their pathogenesis. Some have suggested that coma and delirium do not have the same pathophysiologic features.[37] Coma's hallmarks are loss of arousal and awareness. In delirium, however, some level of arousal is retained, but attention is impaired. We found that coma in sepsis was associated with increased spare respiratory capacity, which may be driven by an increased maximum OCR, consistent with an increased requirement for energy use in coma. The association held (and was slightly stronger) after adjusting for doses of sedating medication, indicating that the association is not explained by sedation. Further mechanistic studies are required to determine the underlying mechanisms of increase spare capacity in patients with coma during sepsis.

Alternatively, delirium was not associated with either mitochondrial respiration measures or nonmitochondrial measures, but the small number of patients with delirium at the time of sample collection increased the likelihood of false-negative results resulting from insufficient statistical power. Given that coma is a risk factor for delirium in other studies of critically ill populations, a larger study of patients with sepsis should examine associations between mitochondrial respiration markers measured over time to confirm our findings regarding coma and to re-examine associations with delirium. Indeed, our study was designed to be an exploratory examination to direct future work.

We used peripheral platelet mitochondria in this investigation for a few reasons. First, blood cells display various profiles in sepsis. Monocytes show decreased respiratory capacity and ATP-linked respiration. In contrast, neutrophils show more reliance on glycolysis, which is increased in sepsis.[38-40] Platelets rely more heavily on mitochondria for their ATP needs than do other peripheral blood cells.[38] If increased ATP needs and mitochondrial stress during sepsis underlie the mechanisms of acute brain dysfunction, it is likely to manifest in peripheral platelets. Second, peripheral platelets have been proposed as a viable target when studying systemic mitochondrial bioenergetics in humans.[24-26] Further, prior studies demonstrated that peripheral blood cells (including platelets) potentially reflect brain metabolism. Finally, studies in traumatic brain injury have shown that platelet metabolism may be more sensitive to brain injury than leukocyte metabolism.[41] In light of these data, we sought to explore potential relationships between platelet mitochondrial bioenergetics, a surrogate for systemic mitochondrial bioenergetics, and delirium or coma during sepsis.

Mitochondrial dysfunction has been examined as a mechanism of acute organ dysfunction in sepsis in numerous studies, some of which measured platelet mitochondrial function,[42-46] but no previous study to our knowledge evaluated associations between platelet bioenergetics and acute brain dysfunction during sepsis. Investigations using animal models of sepsis have shown altered brain mitochondrial function in sepsis,[47,48] but studies in humans have been limited, likely because of the difficulty of studying brain mitochondrial function in alive patients with sepsis. Our group showed that platelet mitochondrial respiratory parameters can be a marker of systemic mitochondrial function,[28] and the results from the current study provide a springboard for future mechanistic studies in sepsis.

Our study has important limitations. First, this was an exploratory study designed to generate preliminary data and novel hypotheses that will guide the design of future studies. As such, we did not adjust for multiple comparisons, an approach that increases possibility

of chance associations. Second, the number of patients in the study was small because of the availability of the laboratory to process samples on the day of collection and the cessation of laboratory procedures during the height of the COVID-19 pandemic. Third, the number of patients who were delirious at the time of sample collection was small. This limited our ability to detect potentially important differences in platelet mitochondrial bioenergetics when comparing delirium with normal mental status. Using our results as preliminary data, future studies designed to address this question can be powered appropriately to detect important differences between the groups. Fourth, because of the unplanned and unpredictable onset of sepsis, we were not able to assess cognitive function before sepsis directly. To account for this, we used two validated, proxy-administered tools (the short-form IQCODE and 8-item Interview to Differentiate Aging and Dementia) to estimate preexisting cognitive function. Fifth, we collected blood samples for platelet mitochondrial bioenergetics only once during the study, and the timing of sample collection relative to sepsis onset likely varied. Repeated sample collection likely would provide important insight into the associations between platelet mitochondrial bioenergetics and delirium and coma (as well as related downstream outcomes) during sepsis, for example by allowing an analysis of how changes in bioenergetics over time are associated with recovery from delirium or coma. Sixth, the cohort was predominantly White, and we were unable to examine race as a modifier of the associations examined. Seventh, because this was an observational study, we did not require a pause in sedation during the assessment of delirium or coma and cannot distinguish sedative-induced acute brain dysfunction from that driven by critical illness. Finally, as with any observational study, these associations do not prove causation. The changes seen in platelet mitochondria may be a result of coma, rather than a mechanism. However, as previously noted in animal studies, mitochondrial therapies can reverse organ dysfunction in sepsis, suggesting that altered mitochondrial function is a pathologic process during sepsis.[13]

Interpretation

These preliminary findings have important clinical applications. The study of platelet mitochondrial respiratory bioenergetics during sepsis provides information on the processes occurring during acute brain dysfunction in sepsis. The brain has high energy requirements and relies heavily on mitochondria to meet its energy needs. Mechanistic studies exploring the underlying role mitochondria play in acute brain dysfunction during sepsis may yield greater understanding of this phenomena and eventually could support the study of interventions, which may include low-cost supplements that could be personalized based on blood tests. Indeed, mitochondrial-targeted therapies in animal studies already have shown benefits of improved survival and organ function.[13] The addition of substrate or cofactor (eg, ATP-MgC12, cytochrome c, coenzyme q) in humans has shown some efficacy in the management of heart failure[49] and in hepatitis C[50] and may be beneficial during sepsis.

In conclusion, we found that increased platelet mitochondrial spare respiratory capacity is associated with coma in patients with sepsis. Future research should examine the relationship between mitochondrial respiration bioenergetics and brain function during sepsis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS:

ATP	adenosine triphosphate
ECAR	extracellular acidification rate
ETC	electron transport chain
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
IQR	interquartile range
OCR	oxygen consumption rate
RASS	Richmond Agitation-Sedation Scale
SOFA	Sequential Organ Failure Assessment

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Take-home Points

Research Question:

Are altered platelet mitochondrial bioenergetics associated with acute brain dysfunction during sepsis?

Results:

Various measures of platelet mitochondrial respiratory bioenergetics were associated with coma during sepsis, and after adjusting for multiple covariates, spare respiratory capacity remained associated with coma.

Interpretation:

The study of platelet mitochondrial respiratory bioenergetics provides information that may inform and guide future mechanistic studies on the role of mitochondrial function in acute brain dysfunction during sepsis.

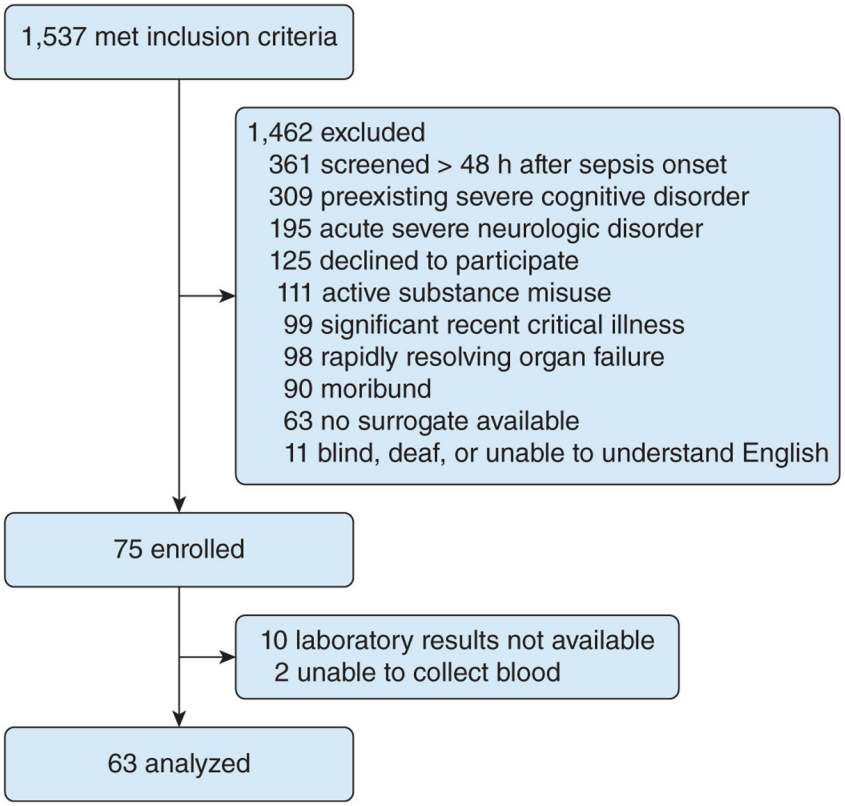

Figure 1 -
Screening and recuirtment flowchart.

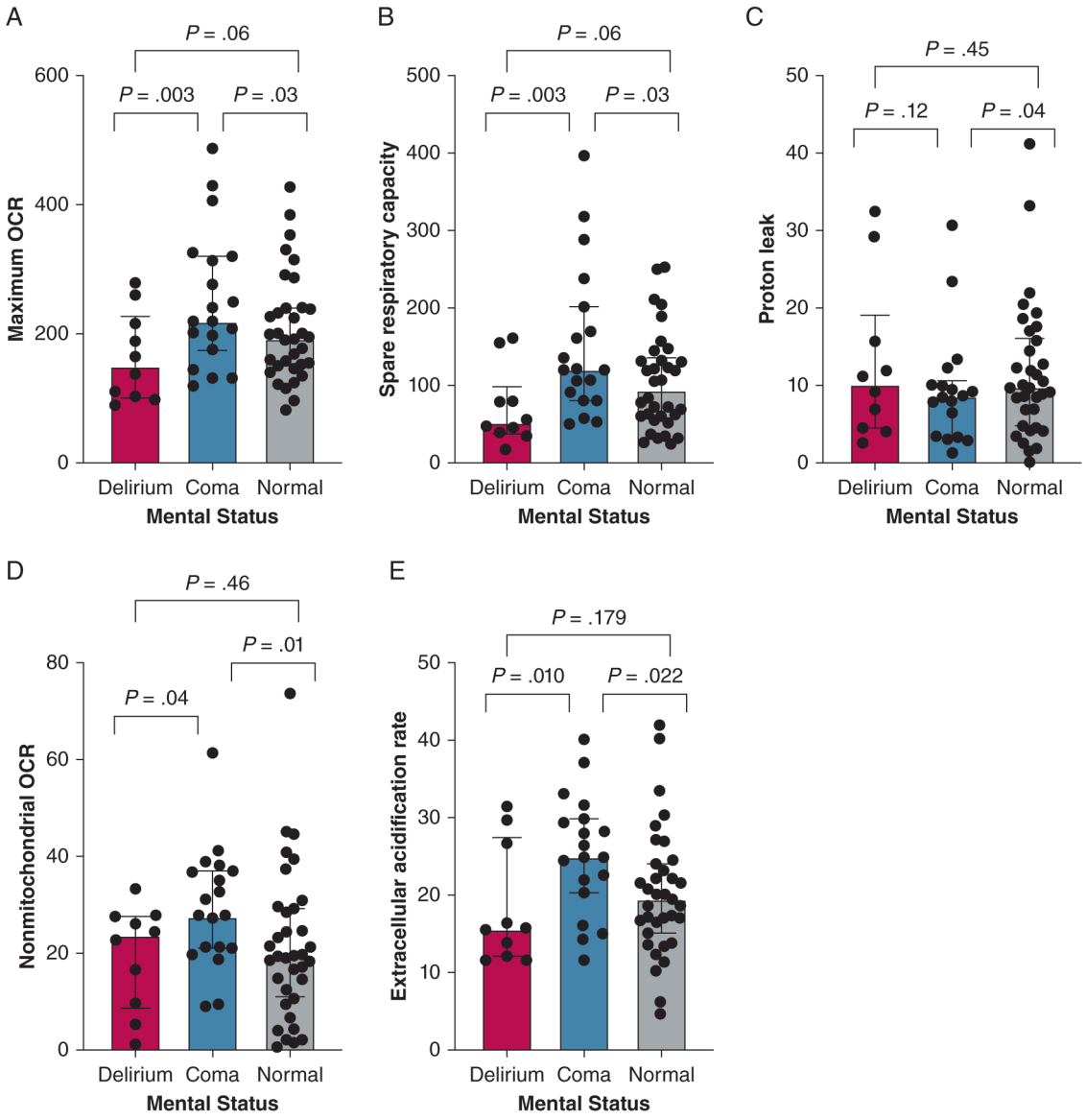

Figure 2 -

A-E, Graphs showing unadjusted comparisons of platelet mitochondrial OCR by delirium, coma, and normal mental status. A, Maximum OCR was significantly different between the coma (n = 19) and normal (n = 34) groups and between the coma and delirium (n = 10) groups. Delirium was not significantly different from normal. B, After removing baseline effect, spare respiratory capacity revealed similar differences among the mental status groups. C, Proton leak was not different among mental status groups. D, Nonmitochondrial OCR was significantly different between those with coma and normal mental status and between those with coma and delirium. No significant difference was found between those with delirium and normal mental status. E, Extracellular acidification rate was significantly different among those with coma and normal mental status as well as among those with coma and delirium. The delirium group did not show significantly different findings than

the normal mental status group. The bar and whisker plots depict median and interquartile range. OCR = oxygen consumption rate.

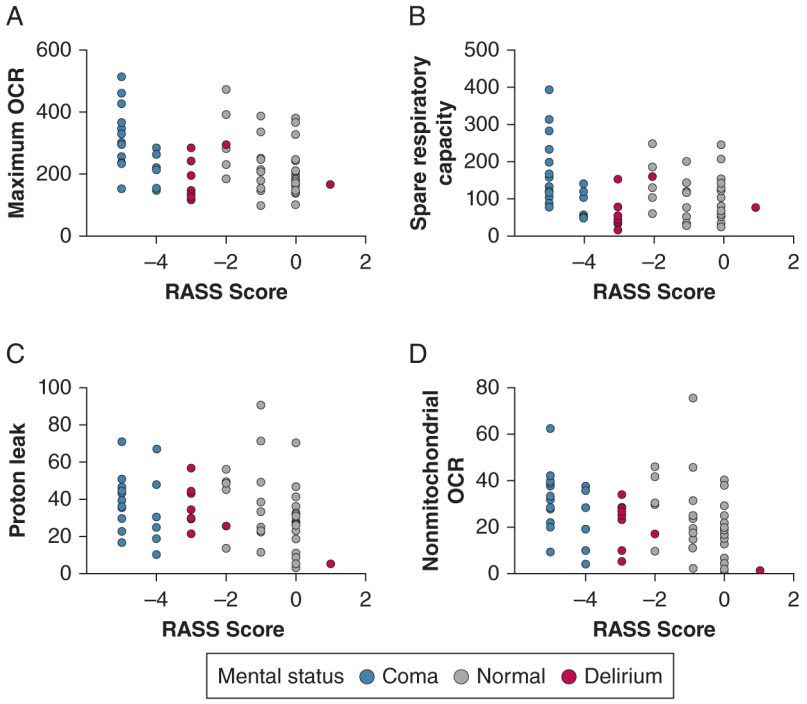

Figure 3 -

A-D, Graphs showing platelet bioenergetic measures according to RASS score. After adjusting for age, sedation, modified Sequential Organ Failure Assessment score, and preexisting cognitive function, increased maximum OCR (A) and spare respiratory capacity (B) were associated with lower RASS scores, whereas proton leak (C) and nonmitochondrial OCR (D) were not associated with RASS scores. OCR = oxygen consumption rate; RASS = Richmond Agitation-Sedation Scale.

TABLE 1]

Participant Characteristics According to Mental Status on the Day of Sample Collection

Variable	Delirium (n = 10)	Coma (n = 19)	Normal (n = 34)
Age, y	64 (55-69)	57 (51-69)	66 (52-74)
Female sex	2 (20)	9 (47)	19 (56)
White race	9 (90)	18 (95)	33 (97)
Short-form IQCODE score	3 (2-3.1)	3 (3-3)	3 (2-3.1)
AD8 score	0 (0-0)	0 (0-1)	0 (0-1)
Charlson comorbidity index	2 (1-4)	2 (0-4)	2 (1-3)
BMI, kg/m^2	29 (26-35)	35 (26-40)	29 (25-37)
SOFA score	11 (7-13)	13 (11-14)	9 (7-11)
SOFA score without neurologic	8 (5-11)	10 (7-11)	8 (6-9)
Mechanically ventilated	9 (90)	19 (100)	17 (50)
PaO_2 to FIO_2 ratio	220 (158-313)	149 (96-208)	266 (160-433)
Sedation[a]	9 (90)	18 (95)	18 (53)
Propofol received[b]	3(33)	11 (56)	7 (21)
Fentanyl received[b]	8 (89)	16 (84)	14 (41)
Midazolam received[b]	5 (56)	7 (37)	6 (18)
Vasopressor use			
Norepinephrine	5 (56)	16 (84)	27 (80)
Epinephrine	1(10)	4 (21)	3 (8)
Vasopressin	4 (44)	6 (32)	7 (21)
Highest creatinine[b]	2 (1-2.5)	1.9 (1.1-2.9)	1.7 (.8-2.9)
eGFR ($mL/min/1.73m^2$)[c]	37.4 (22-83.3)	40 (21-101.4)	39.2 (20-76)
Aspirin use[b]	3 (30)	4 (21)	5 (15)
Platelet count, × $1,000/mm^3$	171 (154-203)	208 (58-254)	191 (120-252)

Data are presented as No. (%) or median (interquartile range). AD8 = 8-item Interview to Differentiate Aging and Dementia; eGFR = estimated glomerular filtration rate; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; SOFA = Sequential Organ Failure Assessment.

[a]Received sedating medication on the day of sample collection.

[b]In the 24 h before enrollment.

[c]Calculated by 2021 Chronic Kidney Disease Epidemiology Collaboration equations.

TABLE 2]

Unadjusted Comparisons and Adjusted Associations Between Platelet Bioenergetics and Delirium and Coma During Sepsis From a Multinomial Logistic Regression Analysis

	Unadjusted Comparisons				Adjusted Analysis					
					Delirium vs Normal			Coma vs Normal		
Variable	Delirium (n = 10)	Coma (n = 19)	Normal (n = 34)	*P* Value[a]	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Basal OCR	112.7 (88.1-131.2), 113.9 ± 33.2	125.8 (109.9-150.3), 130.3 ± 33.5	123.0 (95.6-136.9), 125.6 ± 38.2	.43	0.99	0.96-1.02	.45	1.00	0.98-1.02	.83
Proton leak	30.2 (25.9-43.5), 32.3 ± 14.0	39.5 (30.1-48.3), 51.1 ± 53.7	28.42 (23.1-45.4), 33.3 ± 19.5	.20	0.98	0.83-1.04	.53	1.02	0.98-1.06	.33
ATP-linked OCR	78.3 (69.3-87.3), 81.6 ± 34.2	90.4 (79.8-110.5), 79.2 ± 69.9	89.2 (73.1-107.3), 92.3 ± 33.1	.44	0.99	0.98-1.02	.94	0.99	0.98-1.01	.66
Maximum OCR	156.5 (133.0-242.3), 184.3 ± 67.1	257.7 (212.6-346.5), 281.7 ± 106.2	207.4 (169.6-250.6), 229.4 ± 90.9	.02	0.98	0.97-1.00	.06	1.01	0.99-1.00	.09
Spare respiratory capacity	50.4 (39.9-78.4), 70.4 ± 49.5	119.9 (79.4-200.9), 151.5 ± 96.5	93.4 (58.9-130.7), 103.7 ± 62.8	.02	0.98	0.93-1.04	.06	1.01	1.00-1.02	.03
Nonmitochondrial OCR	23.7 (9.7-27.5), 19.5 ± 10.8	27.7 (20.8-36.9), 29.2 ± 12.2	19.4 (12.5-29.1), 21.8 ± 15.2	.07	0.98	0.91-1.04	.47	1.04	0.98-1.09	.17
ECAR	15.7 (12.3-26.8), 18.6 ± 7.7	25.1 (20.5-29.9), 25.4 ± 7.7	19.8 (16.6-24.1), 20.6 ± 8.1	.04	0.99	0.88-1.11	.95	1.09	0.99-1.20	.07

Data are presented as median (interquartile range), mean ± SD. Associations were analyzed using multinomial logistic regression with adjustment for age, sedation, modified Sequential Organ Failure Assessment score, and preexisting cognitive function. ATP = adenosine triphosphate; ECAR = extracellular acidification rate; OCR = oxygen consumption rate.

[a]Unadjusted associations were analyzed using the Kruskal-Wallis test.