ISSN: 2754-6667

Journal of Critical Care & Emergency Medicine

Case Report

Open Access

Utilization of Immediate Energy Resources in Critical Care, Emphasis on Phosphocreatine

Sylvia Frisancho-Kiss*, Pavol Šust, István Bodor and Michal Liška

Department of Anaesthesiology, Perioperative Medicine and Intensive Care, Hospital Bory, Penta Hospitals, Slovakia

ABSTRACT

Modern societies heavily rely on sophisticated energy resources, likewise human baseline daily and stress related activity commencing on the molecular and cellular level is essentially dependent on properly functioning energy producing, rebooting and storage conditions.

Adenosine triphosphate (ATP) assumes the role of universal energy currency stored in high energy phosphate bounds, with immediate availability for biochemical processes requiring fuel resources. The intrinsic resources for ATP are mitochondria providing synthesis from ADP mediated by ATPase, and ATP is recycled in significant amounts from high ATP containing organs, like muscles. ICU patients are characterized by low ATP reserves. The reasons are conceivably multifactorial, including increased requirements, mitochondrial damage, catabolism and muscle breakdown, leading to impaired availability and increased demand.

Phosphocreatine (PCr) provides the high energy substrate to promote regeneration of ATP rendering an immediate energy resource bypassing the largely oxygen dependent oxidative phosphorylation. Currently, phosphocreatine substitution is available therapeutically, offering a transient supportive tool to the organism during conditions when demand is enhanced, production may suffer and endogenous resources of creatine or phosphocreatine are relatively low.

Exogenous phosphocreatine supplementation may be beneficial during critical care illness, when energy resource processing and utilization may be dampened by ischemic and inflammatory pathological processes. The significance of supplementary immediate energy substitution is demonstrated on case reports during inflammatory conditions.

***Corresponding author**

Sylvia Frisancho-Kiss, Department of Anaesthesiology, Perioperative Medicine and Intensive Care, Hospital Bory, Penta Hospitals, Slovakia.

Received: October 06, 2024; **Accepted:** October 09, 2025; **Published:** October 21, 2025

Abbreviations

ADP: Adenosine Diphosphate
ATP: Adenosine Triphosphate
B.Fragilis: Bacillus Fragilis
BMI: Body Mass Index
CABG: Coronary Artery Bypass Surgery
cGAS: cyclicGMP-AMP Synthase - Stimulator of Interferon Genes
CK: Creatinine Phosphokinase
CRP: C Reactive Protein
DAMP: Disease Associated Molecular Patterns
DNA: Deoxyribonucleic Acid
E. coli: Escherichia Coli
FADH2: Flavin Adenine Dinucleotide
GM-CSFR: Granulocyte-Macrophage Colony-Stimulating Factor Receptor
GPCR: G Protein Coupled Receptors
GSH/GPX 4: Glutathione/ Glutathione Peroxidase 4
HFpEF HfrEF: Heart Failure with Preserved, Resp. Reduced Ejection Fraction
ICU: Intensive Care Unit
IL-1β: Interleukin One Beta
MI: Myocardial Infarction
MitCK: Mitochondrial Creatine Kinase
NADPH: Nicotinamide Adenine Dinucleotide Phosphate
NFKb: Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells
NLRP3: NLR Family Pyrin Domain Containing 3
OXPHOS: Oxidative Phosphorylation
PCr: Phosphocreatine or Creatine Phosphate
PDH: Pyruvate Dehydrogenase
PCT: Procalcitonine
PMNs: Polymorphonuclears
ROS: Reactive Oxygen Species
RV EF: Right Ventricle Ejection Fraction
SAH: Subarachnoid Hemorrhage
SIRS: Systemic Inflammatory Response Syndrome
SOD: Superoxide Dismutase
TAMAX: Time Averaged Maximum Velocity
TAPSE: Tricuspid Annular Systolic Excursion
TLR4,9: Toll-Like Receptor 4,9
TNF-α: Tumor Necrosis Factor Alpha

Introduction

Essentially all energy resources - carbohydrates, proteins and lipids, upon breakdown terminate in the mitochondria, where they become converted to acetyl-CoA, serving as substrate for Krebs cycle, releasing reduced cofactors NADH and FADH2. The cofactors then donate electrons to the electron transport chain for oxidative phosphorylation, in which energy is produced through the flow of electrons enabled by five large protein complexes localized in the inner mitochondrial membrane, creating an electrochemical gradient culminating in ATP synthase (complex V) mediated conversion of ADP to ATP [1]. Approximately 30 to 36 molecules of ATP are produced during this aerobic process from a molecule of glucose, approximately 100 molecules of ATP are produced upon beta oxidation of a 16-carbon containing fatty acid. The ATP synthase, that lies in inner mitochondrial membranes, utilizes ADP H+ and inorganic P to produce ATP and water. Rising levels of ADP and H+ in the mitochondrial matrix stimulate APTase in this acceptor-controlled pathway. The mitochondrial Oxidative Phosphorylation System (OXPHOS) is responsible for generating ATP, then by the mediation of mitochondrial Creatine Kinase (mit CK), ATP releases its phosphate group to creatine phosphate (or phosphocreatine PCr) which is a small mobile molecule, and able to diffuse to cytoplasm in order for the reverse reaction to take place mediated by cytoplasmic CK.

Phosphocreatine Mechanism of Action

The biosynthesis of the intrinsic phosphocreatine pool occurs chiefly in muscles from creatine transported from the kidney and the liver, where creatine is synthetized. 50% of creatine is replenished by uptake from food resources, meats, eggs and dairy in particular. Creatine is depleted from the body during CRRT. A small proportion is metabolized to creatinine and excreted via kidneys [2].

The available PCr amount is sufficient only for the first five to eight seconds of muscle activity, after that it must be replenished from resources to secure continuing functionality. Such replenishment may be shattered due to heavy reliance on several organ systems that may partially fail during critical illness related multiorgan dysfunction. Hypoxia-ischaemia leads to quick ATP depletion and cell death consequently.

The energy supplementing functions of PCr are diverse: increasing ATP synthase activity, reducing degradation of AMP, enhancing CK activity, preventing ADP degradation, and reducing ROS.

Endogenous PCr serves as a shuttle for ATP transfer from mitochondria to the cytoplasm for exertion. Conversely, in resting state, ATP is utilized for the regeneration of PCr from creatine, catalyzed by creatine kinase. Such regeneration may be suboptimally functioning in critical care related conditions, underscoring the requirement for exogenous PCr substitution, providing energy support particularly for organs with high energy requirements such as the brain, the heart, muscles and the kidneys.

Mitochondrial dysfunction leads to relative PCr depletion, presupposing its substitution [3]. Mice that are deficient in mit PCr show impaired ability to maintain ATP levels particularly under conditions of physical strain. The thyroid hormones aid at increasing phosphocreatine levels and enhancing its regeneration after muscle contraction. In prolonged hypothyroid conditions experimentally, a greater amount of ADP and creatine was required to stimulate mitochondrial function and while PCr levels are normal in hypothyroid patients, cardiolipin, holding mitCK is lower and the PCr shuttle is slower leading to less ATP production. Studies also showed that creatine supplementation decreases ROS formation.

The expectation is that phosphocreatine supplementation enhances ATP production tilting the adenosine/AMP/ADP/ATP cascade towards ATP production and that PCr partially bypasses the chain of oxidative phosphorylation which may be compromised and/ or interrupted or conversely enhanced in SIRS condition, when increased production and defective elimination of reactive oxygen species occurs [4].

Beyond the energy supplementing function, phosphocreatine contributes to the enhancement of lipid cell membrane stability. The lipid components of the cell membrane, phosphatidyl-choline, phosphatidyl-serine and phosphatidyl-etanolamide bind to the ammonia and phosphate groups of creatine phosphate [5,6]. Cellular membrane phospholipids are zwitterions that serve to protect the cells from non-specific interactions, creating a barrier. securing physical integrity. PCr upon low affinity zwitterion interaction prevents phospholipid membrane disintegration and hemolysis, induced by membrane permeabilizers [7]. By stabilizing the mitochondrial membrane, PCr prevents flow of reactive oxygen species to the cytoplasmic membrane [8].

Several experimental studies demonstrate how PCr protects cells from apoptosis. In a in vitro model, treatment of hepatocellular cancer cells and normal mouse liver cells with PCr leads to improved survival, maintained mitochondrial membrane potential, reduced apoptosis, reduced oxidative stress mediated by inhibiting TLR4 and enhancing Akt (protein kinase B) prosurvival pathways [9,10].

The current, locally approbated indications for PCr usage are as constituent of cardioplegic solutions, and during myocardial ischaemia.

Reactive Oxygen Species in Mitochondria and in Phagocytosis

Reactive oxygen species or free oxygen radicals, among them the most potent are hydroxyl radicals, produced physiologically in mitochondria and in phagosomes in small amounts. Under physiological conditions, 99 % of oxygen leads to ATP production and in 1% ROS is generated serving important physiological functions, such as conditioning the immune system.

During pathological circumstances the pathway is skewed towards preemptive closure of the OXPHOS pathway, causing increased ROS production, and when antioxidative mechanisms are overwhelmed or faulty, ROS cumulation takes place leading to pathological processes, by breaking covalent bounds, inducing lipid peroxidation by hypoxia activated phospholipase A2, chromatin and protein denaturation [11]. Due to the presence of an unpaired electron, ROS are unstable and very reactive. They may fuse with reactive nitrogen species (RNS) thus potentiating their destructive effect, such as mitochondrial fragmentation, the inhibition of SOD / superoxide dismutases, the major ROS deactivating enzymes [12].

In phagosomes ROS production serves to intracellular killing of pathogens, and upon extracellular escape of ROS, and during neutrophil apoptosis, ROS may contribute to severe collateral tissue damage [13].The very same mechanisms that lead to cellular and tissue toxicity, including ROS, RNS and metal ions serve to kill engulfed pathogens by neutrophils causing bacterial protein denaturation, lipid peroxidation and nucleic acid fragmentation. They also facilitate NET formation for pathogen trapping. ROS stimulates proinflammatory cytokine production (TNF-α, MIP2) [14].

Inside phagosomes, the NADPHase complex becomes activated upon bacterial engulfment or by pattern recognition receptors. Upon pathogen encounter, integrin and Fc receptor engagement leads to robust ROS pathway activation. TLR and cytokine (TNFR, GM-CSFR) receptor activation further enhances ROS production. Fc receptors and integrins (CD11b/CD18) upon encountering antibody opsonized pathogens initiate a robust ROS production pathway.

Certain bacteria possess the ability to evade intracellular killing, for example Streptococcus pneumoniae via capsular polysaccharide. Group B streptococcus and Escherichia coli can withstand at least partially the effect of ROS, by applying bacterial Superoxide Dismutases (SOD). In Staphylococcus aureus, manganese protects against ROS mediated killing even in the absence of SOD. Some bacteria, implementing toxin production, deter ROS production for instance streptolysin O from group A streptococci CyaA toxin of Bordetella pertussis. Similarly to humans, certain bacteria can utilize intrinsic GSH to protect against ROS. Listeria monocytogenes prevents phagolysosome fusion. Pseudomonas aeruginosa blocks the oxidative burst in PolyMorphoNuclears (PMNs) [15].

The rare inherited deficiency of NADPHase in phagosomes, Chronic Granulomatous Disease, may manifest from early childhood with severe bacterial and fungal infections due to inability to mount efficient ROS response(16). In analogy, we encounter acquired defects in phagosomal activity, either due to chronic disease induced impairment, or induced by pathogen evasion processes, particularly in chronic substance abusers. These patients typically present with severely impaired ability of bacterial clearance and prolonged ICU stay accompanied by recurrent infections, prolonged antibiotic usage, emerging antibiotic resistance, prolonged clearance, of the primary pathogen.

Ferroptosis

ROS production is particularly harmful during ferroptosis, a leading pathophysiological mechanism during pathological bleeding, particularly in cases of hypertonic, hemostatic dysfunction or traumatic intracerebral, intracranial and subarachnoidal bleeding. [17,18]. Free hemoglobin and ferrous/ferric iron from lysed red blood cells is a strong inducer of ROS production and lipid peroxidation, inducing protein denaturation, DNA fragmentation, and ferroptosis, that is iron dependent non-apoptotic cell death. Ferroptosis significantly contributes to early brain injury and its intensity is associated with mortality during intracerebral bleeding. Lipid peroxidation may increase membrane permeability and brain swelling [19].

ATP and Mitochondria in Sepsis

Sepsis is associated with mitochondrial damage, leading to impaired energy production [20]. Approximately 50% of patients develop septic cardiomyopathy significantly contributing to mortality, induced by TLR4 activation proinflammatory cytokines TNF-α, IL-1β. In a retrospective study of over 500 patients a significant improvement in 28-day mortality was achieved when PCr was added to the conventional treatment protocol. From the immediate indications of efficiency, a significant difference was found in lactate, GAP and nt-pro BNP levels at 72hours, improved extubation, mechanical ventilation and ICU stay time, even though hospitalisation time was not different, which is a variable parameter of success [21].

The many faces of mitochondrial damage were studied under experimental conditions, culminating in increased ROS production and impaired antioxidative mechanisms. A significant decrease in complex I activity of intercostal muscles of septic patients was demonstrated. During sepsis iNOS is produced selectively binding to complex IV, competing with oxygen. Upon binding to ROS peroxynitrite is produced, a highly toxic oxygen radical, irreversibly inhibiting I, CII, CIV, and ATPase.

MIT stress is an ongoing event during sepsis, leading to mtDAMP(Danger Associated Molecular Pattern) release with apoptotic potential and also contribute to SIRS via NLRP3 activation TLR9 and cGAS upregulation, and proinflammatory cytokine release. Each cell contains hundreds, to thousands of MIT, that continuously undergo fusions and fissions to ensure self repair, yet this homeostasis may be breached during severe sepsis [22].

Sepsis leads to impaired mitophagy and MIT turnover, to increased fission and fragmentation, and increased MIT membrane permeability. Sepsis directs pyruvate in cytoplasm towards lactate production, with an impaired PDH and APTase function. Experimentally during caecal puncture and ligation (CPL) induced sepsis pyruvate dehydrogenase (PDH) function had been enhanced to produce AcoA and this led to improved survival [23].

Lactate

During muscle activity and stress, glycolysis is enhanced leading to increased lactate production. Under normal conditions and during physiological strain lactate provides important house keeping functions. Not only pyruvate, but lactate too, serves as a resource for oxidative phosphorylation in mitochondria. Lactate is a major substrate for gluconeogenesis in the liver in the Cori cycle and a hormonal messenger. During sepsis and ischaemia, enhancement of ROS production by aggravated lactate shuttle has harmful consequences. It is the imbalance between production and clearance during sepsis and liver failure that may have deleterious effects and functions as surrogate for mitochondrial dysfunction in septic patients. Lactate levels above 2mmol/l are associated with disease morbidity and mortality in sepsis.

Lactate utilization occurs partly via oxidation in mitochondria (70-80%) during exercise. During sepsis, lactate mediated lactylation(lactate conjugation to proteins via lysine residue) of mitochondria and increased mitochondrial fission leads to mitochondrial dysfunction and energy depletion [24]. Lactylation modifies histones and immune cell functions. Excess lactate enters the mitochondria, directly activates Oxphos, concurrently suppresses glycolysis, and has a blocking effect on fatty acid uptake by mitochondria for beta oxidation [25].

Extracellular ATP utilization by Pathogens

During cell damage, ATP is released extracellularly, similarly bacteria produce ATP during growth phase release extracellularly to facilitate pathogen host interactions [26]. Extracellular ATP may act via several receptors inducing an inflammatory response. The intriguing question is whether PCr may enhance detrimental extracellular ATP production, and this issue warrants further investigation. ATP recovery from PCr however is a rate limiting enzymatic reaction, hence overt ATP levels halt the process.

In small amounts ATP is present physiologically extracellularly with important housekeeping functions. During cell damage eATP may induce NLRP3/IL-1β release via P2X7R, and via the same receptors astrocyte phagocytosis is enhanced [27].

PCr in Chronic Disease Conditions

PCr has been shown to be cardioprotective and neuroprotective, preventing demyelination [28]. Phosphocreatine and ATP levels are decreased in heart failure,they are prognostic markers for mortality in heart failure [29]. Meta-analysis by Landoni showed improved cardiac performance, significantly decreased inotrope requirements, and less arrhythmias upon PCr administration. This analysis included 41 studies with indications of CABG, MI, acute and chronic heart failure [30]. Another meta-analysis of 9 trials showed myocardial protection in viral myocarditis [31]. Significant decrease in high-sensitivity troponin and cardiac creatine kinase (CK-MB) levels was observed. Viral myocarditis, most frequently associated with Coxsackie virus B3 SARS- Cov-2 and Parvovirus 19 infections has no specific treatment, and myocardial protection by restoring the proper energy environment may at least partially prevent apoptosis induced by cytopathic viruses. In an experimental rat model of apoptosis, exogenous PCr alleviated myocardial apoptosis [32]. Heart failure with preserved ejection fraction (HFPeF) upon high-fat diet induction and treatment with nitric oxide synthase (NOS) inhibitor in a mouse mode was associated with impaired mitochondrial mitophagy, ROS cumulation an impaired PDH function and fatty acid oxidation [33].

Studies demonstrate that tumors utilize PCr too. Yet tumors utilize nutrients in general, similarly to healthy cells, unfortunately there isn't a metabolic pathway that would be exclusive to humans and healthy cells as opposed to pathogens and tumors [34].

Particular matter (PM2,5) inhalation has been shown to induce neuronal cell apoptosis, downregulation of energy pathways, including phosphocreatine levels [35].

Endogenous and Exogenous Antioxidants

Several antioxidant systems are deployed by the organism to dampen the deleterious effects of ROS cumulation, such as the GSH/GPX4 glutathione/glutathione peroxidase 4 system, being inhibited during subarachnoid hemorrhage (SAH), further worsening lipid peroxidation. N-acetylcysteine serves as a precursor for cysteine, therapeutically leading to the inhibition of lipid peroxidation in hemorrhagic stroke [36]. Melatonin is produced in pineal gland in small amounts (5%) of total production to regulate sleep and in 95% in mitochondria, one of the most ancient antioxidants with virostatic and bacteriostatic properties. Intramitochondrial melatonin function is multilayered, inhibiting ROS production by preventing electŕon leakage, activating antioxidant enzymes, increasing glutathione production, helps repairing damaged DNA, and binds transition metal ions [37].

PCr and Catecholamines

ICU conditions are frequently associated with the need for circulatory support using catecholamines and inotropes: epinephrine, dopamine, norepinephrine(NE), milrinone levosimendan or dobutamine.

We hypothesize that due to ATP requirement during the intracellular signaling of chief catecholamines used in hemodynamically unstable patients, concomitant PCr administration may lead to enhanced efficacy and decreased overall catecholamine requirements. We demonstrate in case scenarios the immediate effect of PCr administration in vivo on decreased catecholamine (norepinephrine) requirements.

Stressor induced epinephrine release from the adrenal gland provides a signal to distant organs such as liver and muscles by binding to alpha- and beta-adrenergic receptors on the external cell membrane, leading to structural changes, and activation of G-Protein Coupled Receptors (GPCR) [38]. These provide a stimulatory signal for cytoplasmic adenylate cyclase activation which dynamically starts ATP conversion to cyclic AMP (Adenosine Monophosphate). The downstream enzymatic activation cascade leads to the amplification of the signal, ultimately modulating glucose metabolism in a manner that glycogenogenesis halts, glycolysis in the muscles prevails, while glucogenesis in the liver is the dominant feature, providing glucose, carried in blood to organs as energy resource.

Vasodilation and increased vasopermeability are hallmarks of sepsis, according to guidelines prompt antibiotics, increased fluid intake, vasopressors (norepinephrine, argipressine) and corticosteroids are the major therapeutic modalities [39]. While maintenance of blood pressure and vascular tone are essential for survival alpha or beta overstimulation may disrupt metabolism and hormonal secretion. Therefore, it is desirable to minimize catecholamine usage and achieve a homeostasis in which endogenous or low-level extrinsic catecholamine support will be sufficient.

The immune response is also influenced by NE via beta adrenergic receptors leading to overall antiinflammatory effect. In higher doses beta adrenergic activation inhibits NfKb and cytokine production (TNF-α, IL-6,IL-10), in vitro NE decreases natural killer cell cytotoxicity. These effects can be partially reversed by beta blockers. Experimental studies are limited showing support to gram positive and gram-negative bacterial growth in vitro, reduction in CD11b/CD18 expression. It is plausible, that some of the unequivocally lifesaving effect of catecholamine administration in sepsis may contribute to a later immunosuppressive role, overt catabolism, which should be prevented by tampering exogenous catecholamines in timely manner [40]. Creatine supplementation improves neutrophil function by increasing intracellular ATP production [41].

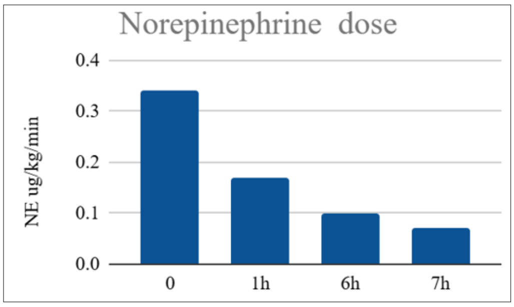
Case Presentation

We present a 34 years old patient with necrotizing pancreatitis, secondary septic insult on norepinephrine and vardessin, with ongoing systemic inflammatory reaction and pyrexias for consecutive three weeks. Upon emerging septic insult sedation had to be increased and catecholamine requirements increased. Cardiac contractility and intracranial arterial flow conduction had been evaluated prior creatinine phosphate administration, one and seven hours after administration. In an attempt to minimize collateral confounders, the time lapse between administration and measurements was minimized. Concomitantly antibiotics were administered for ongoing three days already.

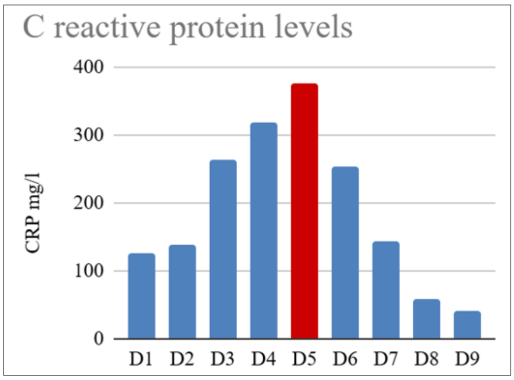
TAPSE (Tricuspid Annular Systolic Excursion) (Figure 2a), S´(tricuspid annulus systolic velocity) (Figure 2c), and diastolic left ventricular parameters E(early diastole peak velocity)(2b) were increased and mitral deceleration time (Figure 2d) decreased. Measurements were provided according to the guidelines advised in the literature (42). TAPSE correlates strongly with the radionuclide angiogram, Simpson right ventricle ejection fraction (RV EF) and RV fractional shortening with good specificity and low sensitivity. The measurement of systolic annular velocity (S´) further underscores vertical right ventricle function, as it is the dominant direction of contractile motion of the right ventricle.

We measured arterial flow through median cerebral arteries bilaterally by using transcranial doppler sonography to assess peripheral effects of cardiac performance and change in vessel reactivity. Time averaged maximal velocity (TAMAX) (Figure 1c) over cerebral medial arteries bilaterally was evaluated and depicted at typical timepoints (0-1-6-7 h). PCr was administered in doses of 2 grams for 30 minutes intravenously six hourly.

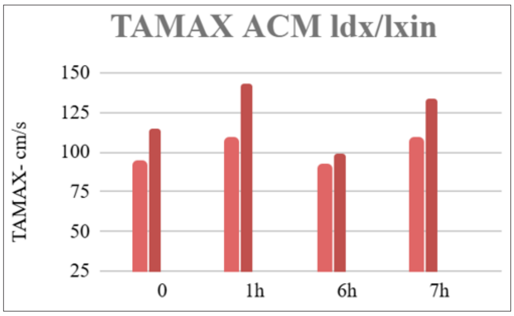
Our measurements were reproducible upon repeated dosing. During the subsequent 12 hours upon phosphocreatine commencement norepinephrine doses (Figure 1a) could be significantly decreased.



(a)



(b)



(c)

Figure: 1 a,b,c

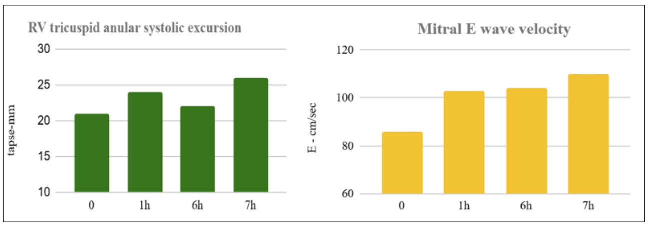


Figure: 2a,b

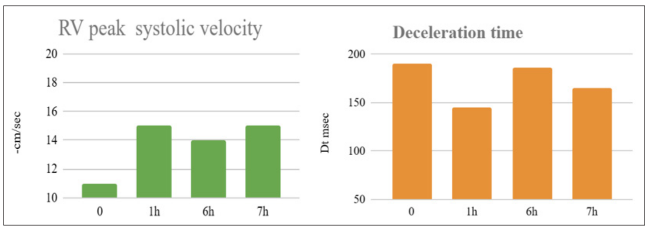


Figure: 2 c,d

The second patient in our case study is a 73years old gentleman with comorbidities, chronic nicotinism, low level chronic alcohol abuse, obesity of BMI 41 due to sedentary lifestyle and limited physical activity, and arterial hypertension. The patient was admitted for acute gangrenous appendicitis and diffuse peritonitis, septic shock and septic atrial tachyfibrillation, after four days of worsening symptoms. Emergency appendectomy and peritoneal lavage were executed. Due to severe hemodynamic instability type one respiratory failure and somnolence the patient was admitted to ICU on analgosedation mechanical ventilation and high dose hemodynamic support (norepinephrine, argipressin, amiodarone and landiolol) with conventional steroid supplementation using hydrocortisone. Invasive hemodynamic monitoring using Edwards Flotrac based on arterial waveform pulse contour analysis, measuring stroke volume, stroke volume variability, cardiac output systemic vascular resistance and parameters calculated to body surface area was implied. Prompt antibiotic coverage using piperacillin tazobactam reinforced with a single dose of amikacin and rehydration according to sepsis guidelines were introduced. Peritoneal secretion microbiology revealed Bacillus fragilis and Escherichia coli. Laboratory measurements revealed high inflammatory markers (CRP, PCT) with impaired phagocytic stimulatory activity (Figure 3c), that may be a consequence of pathogen evasion mechanisms, chronic nicotine and alcohol abuse. B.fragilis impairs phagocytic killing of E. coli [43]. B.fragilis is a normal constituent of the gastrointestinal microbiome, with influence on the immune homeostasis. B. fragilis is inducing a IL-33 dominant immune response in polymicrobial conditions, with pronounced epigenetic modulatory effect [44]. The toxin producing variant of BF is able to elicit colitis and colorectal cancer. BF toxin has a destructive potential on epithelial cells, by cleaving E cadherin destroying cell junctions and has a broad cleavage activity on cellular and extracellular matrices, including C3(complement component 3) [45]. It promotes proinflammatory cytokine expression, and activates oncogenic transcription, increases ROS production and promotes DNA damage. E.coli evasion mechanisms include circumvention of complement mediated killing with serine protease activity, polysaccharide capsule presence and recruitment of complement regulatory proteins [46].

As a supportive measure, phosphocreatine administration was administered, 3 grams for six days. Due to the multitude of contributors unambiguous association between prompt improvement of cardiovascular stability, decrease in septic parameters cannot be drawn. It is important to emphasize that for the patient to improve source control, proper antibiotic coverage, fluid management (Figure 3d,e), catecholamine and antiarrhythmic administration were the priority yet an enhanced and more complete full recovery required immediate energy supplementation. The below graphs demonstrate the improved lactate and base excess (Figure 3a), hemodynamic function, Stroke Volume Variation (SVV), stroke volume index (SVI) (Figue.3b), decreased catecholamine requirements (Figure 3b), which were a result of coherent and combined interventions.

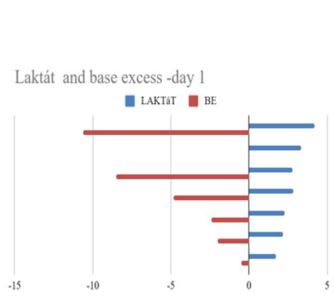


Figure: 3a

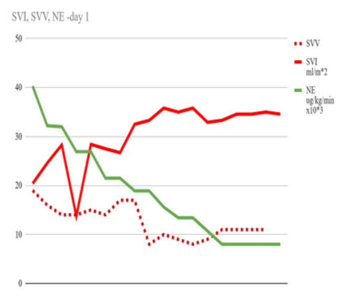


Figure: 3b

immune profile sepsis peak	Column 1
FA	85.8
SI	5.99↓
leu	11.7
neu%/abs	88.5/10.37
ly%/abs	6.3/0.73
CRP	278.5
PCT	19.58
CD25CD4+ treg	5.04
CD4%/abs	42.55/311
CD8%/abs	24.9/182
B%/abs	17.25/126
16/56%	14.9/156
C3	1.42
C4	0.24
IgA	1.52
IgG	6.89
IgM	0.89

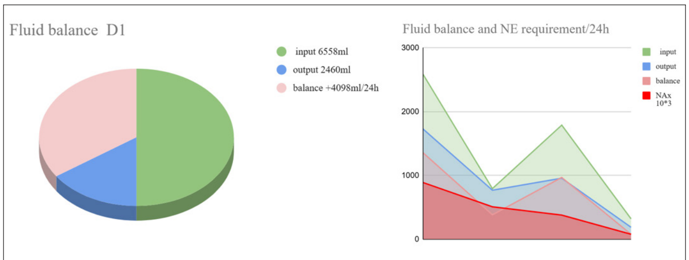


Figure: 3c,d,e

Conclusion

This communication recognizes the importance of the proper maintenance of energy balance upon severe stress inflicted by critical illness.

We highlight the liability of adding immediate energy resources to basic metabolic constituents, at times when synthetic pathways are compromised. In this context creatine phosphate is discussed in greater depth for representing an important adjunct to immediate energy substrate substitution, alleviating the burden on oxidative phosphorylation. PCr evokes diverse functions, enhancing the ATP synthetic pathway, protecting cell membranes and by dampening apoptosis. While PCr competence under ischaemic conditions is well known, ICU related catabolic conditions, sepsis and multiorgan failure, reconvalescence with enhanced energy demands, and recovery upon lengthy surgical procedures are theoretical indications for PCr administration. In case studies we demonstrate the effect of creatine phosphate administration on decreased norepinephrine requirement in septic patients with limited energy reserves.

The effect of phosphocreatine may be direct by enhancing catecholamine activity and indirect by increasing the overall energy level of the organism, by maintaining cell membrane integrity and preventing apoptosis.

Acknowledgement

I would like to express my gratitude to the entire ICU team caring for patients, their encouragement and support.

References

1. Bonora M, Patergnani S, Rimessi A, Suski JM, Bononi A, et al. (2012) ATP synthesis and storage. Purinergic Signal 8: 343-357.
2. Wallimann T, Tokarska-Schlattner M, Schlattner U (2011) The creatine kinase system and pleiotropic effects of creatine. Amino Acids 40: 1271-1296.
3. Supinski GS, Schroder EA, Callahan LA (2020) Mitochondria and Critical Illness. Chest 2020 157: 310-322.
4. Guimarães-Ferreira L (2014) Role of the phosphocreatine system on energetic homeostasis in skeletal and cardiac muscles. Einstein (Sao Paulo) 12: 126-31.
5. Liu W, Qaed E, Zhu HG, Dong MX, Tang Z (2021) Non-energy mechanism of phosphocreatine on the protection of cell survival. Biomed Pharmacother 141: 111839; Franchini E (2023) Energy System Contributions during Olympic Combat Sports: A Narrative Review. Metabolites 13: 297.
6. Tokarska-Schlattner M, Epand RF, Meiler F, Zandomeneghi G, Neumann D, et al. (2012) Phosphocreatine interacts with phospholipids, affects membrane properties and exerts membrane-protective effects. PLoS One 7: e43178.
7. Li S, Hu Q, Huang J, Wu X, Ren J (2019) Mitochondria-Derived Damage-Associated iMolecular Patterns in Sepsis: From Bench to Bedside. Oxid Med Cell Longlev: 6914849.
8. Gaddi AV, Galuppo P, Yang J (2017) Creatine Phosphate Administration in Cell Energy Impairment Conditions: A Summary of Past and Present Research. Heart Lung Circ 1026-1035.
9. Wang FH, Qaed E, Aldahmash W, Mahyoub MA, Tang Z, et al. (2024) Phosphocreatine ameliorates hepatocellular apoptosis mediated by protecting mitochondrial damage in liver ischemia/reperfusion injury through inhibiting TLR4 and Agonizing Akt Pathway. Tissue Cell 91: 102599.
10. Guerau-de-Arellano M, Piedra-Quintero ZL, Tsichlis PN (2022) Akt isoforms in the immune system. Front Immunol 13: 990874.
11. Muralikrishna Adibhatla R, Hatcher JF (2006) Phospholipase A2, reactive oxygen species, and lipid peroxidation in cerebral ischemia. Free Radic Biol Med 40: 376-87.
12. D'Apolito E, Sisalli MJ, Tufano M, Annunziato L, Scorziello A (2024) Oxidative Metabolism in Brain Ischemia and Preconditioning: Two Sides of the Same Coin. Antioxidants (Basel) 13: 547.
13. Kowalczyk P, Krych S, Kramkowski K, Jęczmyk A, Hrapkowicz T (2024) Effect of Oxidative Stress on Mitochondrial Damage and Repair in Heart Disease and Ischemic Events. Int J Mol Sci 25: 12467.
14. Goh KGK, Desai D, Thapa R, Prince D, Acharya D, et al. (2024) An opportunistic pathogen under stress: how Group B Streptococcus responds to cytotoxic reactive species

and conditions of metal ion imbalance to survive. FEMS Microbiol Rev 48: fuae009.
15. Nguyen GT, Green ER, Mecsas J (2017) Neutrophils to the ROScue: Mechanisms of NADPH Oxidase Activation and Bacterial Resistance. Front Cell Infect Microbiol 7: 373.
16. Leiding JW, Mathews CE, Arnold DE, Chen J (2025) The Role of NADPH Oxidase 2 in Leukocytes. Antioxidants (Basel) 14: 309.
17. Deng X, Wu Y, Hu Z, Wang S, Zhou S, et al. (2023) The mechanism of ferroptosis in early brain injury after subarachnoid hemorrhage. Front Immunol 14: 1191826.
18. Wan J, Ren H, Wang J (2019) Iron toxicity, lipid peroxidation and ferroptosis after intracerebral haemorrhage. Stroke Vasc Neurol 4: 93-95.
19. Zille M, Karuppagounder SS, Chen Y, Gough PJ, Bertin J, et al. (2017) Neuronal Death After Hemorrhagic Stroke In Vitro and In Vivo Shares Features of Ferroptosis and Necroptosis. Stroke 48: 1033-1043.
20. Hu D, Sheeja Prabhakaran H, Zhang YY, Luo G, He W, et al. (2024) Mitochondrial dysfunction in sepsis: mechanisms and therapeutic perspectives. Crit Care 28: 292.
21. Shi L, Ye G (2025) Evaluating the therapeutic effects of creatine phosphate administration in sepsis-induced myocardial dysfunction. Medicine (Baltimore) 104: e43253.
22. Kakihana Y, Ito T, Nakahara M, Yamaguchi K, Yasuda T (2016) Sepsis-induced myocardial dysfunction: pathophysiology and management. J Intensive Care 4: 22.
23. McCall CE, Zhu X, Zabalawi M, Long D, Quinn MA, et al. (2022) Sepsis, pyruvate, and mitochondria supply chain shortage. J Leukoc Biol 112: 1509-1514.
24. Zhang J, Wu D, Zeng F, Gu H, Li C, et al. (2025) Lactate metabolic reprogramming and histone lactylation modification in sepsis. Int J Biol Sci 21: 5034-5055.
25. Cai X, Ng CP, Jones O, Fung TS, Ryu KW, et al. (2023) Thompson CB. Lactate activates the mitochondrial electron transport chain independently of its metabolism. Mol Cell 83: 3904-3920.e7.
26. Inami A, Kiyono H, Kurashima Y (2018) ATP as a Pathophysiologic Mediator of Bacteria-Host Crosstalk in the Gastrointestinal Tract. Int J Mol Sci 19: 2371
27. Yang SS, Brooks NAH, Da Silva DE, Gibon J, Islam H, et al. (2025) Extracellular ATP regulates phagocytic activity, mitochondrial respiration, and cytokine secretion of human astrocytic cells. Purinergic Signal 21: 485-498.
28. Cambron M, D'Haeseleer M, Laureys G, Clinckers R, Debruyne J, et al. (2012) White-matter astrocytes, axonal energy metabolism, and axonal degeneration in multiple sclerosis. J Cereb Blood Flow Metab 32: 413-424.
29. Schwartz B, Gjini P, Gopal DM, Fetterman JL (2022) Inefficient Batteries in Heart Failure: Metabolic Bottlenecks Disrupting the Mitochondrial Ecosystem. JACC Basic Transl Sci 7: 1161-1179.
30. Landoni G, Zangrillo A, Lomivorotov VV, Likhvantsev V, Ma J, et al. (2016) Cardiac protection with phosphocreatine: a meta-analysis. Interact Cardiovasc Thorac Surg 23: 637-46.
31. Wang L, Chen SF, Huang XW, Wu ZY, Zhang QM (2025) Efficacy and safety of creatine phosphate sodium in the treatment of viral myocarditis: A systematic review and meta-analysis. PLoS One 20: 1-13.
32. Dai H, Chen L, Gao D, Fei A (2019) Phosphocreatine Attenuates Isoproterenol-Induced Cardiac Fibrosis and Cardiomyocyte Apoptosis. Biomed Res Int 2019: 5408289.
33. Yoshii A, McMillen TS, Wang Y, Zhou B, Chen H, et al. Blunted Cardiac Mitophagy in Response to Metabolic Stress Contributes to HFpEF. Circ Res 135: 1004-1017.
34. Yang G, Niu X, Gan J, Yu T, Li M, et al. (2025) Glioblastoma exploits ATP from leading-edge astrocytes to fuel its infiltrative growth revealed by spatially resolved chimeric analysis. Sci Adv 11: 1-14.
35. Silva T, Alves C, Evtyugina MG, Dias AS, Pereira GM, et al. (2025) Cytotoxic and metabolic effects of organic extracts from airborne fine particulate matter (PM2.5) in neuronal cells. Environ Toxicol Pharmacol 116: 104707.
36. Karuppagounder SS, Alin L, Chen Y, Brand D, Bourassa MW, etal. (2018) Ratan RR. N-acetylcysteine targets 5 lipoxygenase-derived, toxic lipids and can synergize with prostaglandin E2 to inhibit ferroptosis and improve outcomes following hemorrhagic stroke in mice. Ann Neurol 84: 854-872.
37. Ates G, Tamer S, Yorulmaz H, Mutlu S, Olgac V, et al. Melatonin pretreatment modulates anti-inflammatory, antioxidant, my, and matrix metalloproteinases in endotoxemic rat lung tissue. Exp Biol Med (Maywood) 247: 1080-1089.
38. Graham RM (1990) Adrenergic receptors: structure and function. Cleve Clin J Med 57: 481-498.
39. Oczkowski S, Alshamsi F, Belley-Cote E, Centofanti JE, Hylander Møller M, et al. (2022) Surviving Sepsis Campaign Guidelines 2021: highlights for the practicing clinician. Pol Arch Intern Med 132: 16290.
40. Thoppil J, Mehta P, gradients B, Sharma D, Farrar JD (2023) Impact of norepinephrine on immunity and oxidative metabolism in sepsis. Front Immunol 14: 1-8.
41. Saito S, Cao DY, Okuno A, Li X, Peng Z, et al. (2022) Creatine supplementation enhances immunological function of neutrophils by increasing cellular adenosine triphosphate. Biosci Microbiota Food Health 41: 185-194.
42. Rudski LG, Wyman WL, Jonathan A, Lanqi H, Mark DH, et al. (2010) Guidelines for the Echocardiographic Assessment of the Right Heart in Adults:A Report from the American Society of Echocardiography Endorsed by the lil, a registered Branch of the European Society of Cardiology and the Canadian Society of Echocardiography. J of Am SocEchocard 23: 685-713.
43. Rotstein OD, Vittorini T, Kao J, McBurney MI, Nasmith PE, et al. (1989) A soluble Bacteroides by-product impairs phagocytic killing of Escherichia coli by neutrophils. Infect Immun 57: 745-53.
44. Heffernan IM, McGeary JE, Chung CS, Ayala A, Heffernan DS (2021) Unmasking Unique Immune Altering Aspects of the Microbiome as a Tool to Correct Sepsis-Induced Immune Dysfunction. Surg Infect (Larchmt) 22: 400-408.
45. Jasemi S, Molicotti P, Fais M, Cossu I, Simula ER, et al. (2025) Biological Mechanisms of Enterotoxigenic Bacteroides fragilis Toxin: Linking Inflammation, Colorectal Cancer, and Clinical Implications. Toxins (Basel) 7: 305.
46. Abreu AG, Barbosa AS (2017) How Escherichia coli Circumvent Complement-Mediated Killing. Front Immunol 8: 452.