

COMMENTARY TO HABILITATION THESIS¹

In the pathogenesis of many diseases, an imbalance between oxidative antioxidants and oxidants leads to the predominance of oxidant molecule production. Reactive oxygen species (ROS) primarily originate from reactions in the mitochondrial respiratory chain, as well as from reactions catalyzed by enzymes such as NADPH oxidase and xanthine oxidase. Additionally, ROS are produced in situations involving intracellular damage, which release active ions of iron and copper. The body responds to these prooxidative conditions through enzymatic and non-enzymatic antioxidant systems that scavenge and neutralize free radicals. However, when free radical production overwhelms antioxidant capacities, oxidative stress ensues. This state is implicated as a key factor in the onset of various pathological conditions, including systemic response syndromes, sepsis, respiratory failure, acute pancreatitis, atherosclerosis, endocrinological disorders, infectious diseases, and others. Oxidative stress has also been linked to the development of chronic pain through processes involving neuroinflammation. Furthermore, chronic medication use, including opioids, may contribute to a negative redox state in the body, promoting the production of molecules with prooxidative potential. Addressing interventions to mitigate this pathological state is particularly crucial in treatment, especially for critically ill patients, where treatment costs are high and patient outcomes are more vulnerable.

Our initial investigation aimed to explore the antioxidant effects of the trace element selenium administered via parenteral infusion at a dosage of 750 µg/day over a period of 6 days in septic patients. Selenium serves as a crucial cofactor for significant selenoenzymes such as glutathione peroxidase (GPx) and thioredoxin reductase (Trx). In this study, we assessed the activities of key antioxidant enzymes involved in detoxifying superoxide and hydrogen peroxide, including GPx, glutathione reductase (GR), and superoxide dismutase (SOD). While our prospective research demonstrated improvements in oxidative status based on plasma measurements, we did not observe a corresponding decrease in mortality rates. A secondary outcome was the observation of enhanced oxygenation function, measured by the Carrico index ($\text{PaO}_2/\text{FiO}_2$), particularly notable among patients with more severe lung damage at the initiation of selenium supplementation. Our published results in *Wiener Klinische Wochenschrift* and *Clinical Biochemistry* have been cited in systematic reviews and meta-analyses across several prominent medical journals, including *Critical Care*, *Medicine*, *Clinical Nutrition ESPEN*, and the *European Journal of Medical Research*.

Pathological changes in lung tissue are evident during severe respiratory impairment, such as in viral COVID-19 infections. Previous data indicates that mechanical ventilation with high inspiratory volumes and pressures in nonhomogeneous lungs leads to a significant increase in local and systemic concentrations of proinflammatory cytokines (TNF- α , IL-1 β , IL-6, IL-8) compared to protective ventilation strategies. The inflammatory response triggered by mechanical trauma to the lungs can exacerbate pre-existing infectious inflammation and propagate apoptotic signals to secondary tissues. We achieved this goal by implementing programmed multilevel ventilation, utilizing three or four pressure levels. The main parameters included varying positive end-expiratory pressures (PEEP, PEEPh1, PEEPh2), pressure control ventilation or pressure support ventilation (Ppc/Pps), and the settings of respiration frequencies.

¹ The commentary must correspond to standard expectations in the field and must include a brief characteristic of the investigated matter, objectives of the work, employed methodologies, obtained results and, in case of co-authored works, a passage characterising the applicant's contribution in terms of both quality and content.

Additionally, we adjusted the frequency of ventilation at the levels of PEEP₁ (fPEEP₁) and PEEP₂ (fPEEP₂), along with other ventilation parameters, to ensure the optimal distribution of gases to differently affected compartments of the lungs. Our previous study revealed promising outcomes in lung recovery following severe damage in cases of H1N1 pneumonia treated with multilevel ventilation. In an ongoing clinical study adhering to current guidelines for the treatment of COVID-19 pneumonia, high-dose vitamin C (1.5g every 6 hours) and vitamin D (10,000 IU daily) have been utilized as the principal antioxidants in adjunctive therapy for patients with COVID-19. This research was funded by two grants from the European Fund for Regional Development – Operational Programme Integrated Infrastructure. The results were recognized with the Technological Transfer Award in the category of Innovation.

The theoretical implications of oxidative stress in the development of chronic pain are extensively explored in the third part of my habilitation thesis. Both preclinical and clinical research highlight the pivotal role of neuroinflammation in this process. It is widely considered that the primary prooxidative enzyme involved is NADPH oxidase, which catalyzes the conversion of oxygen into superoxide anion. Another crucial enzyme is nitric oxide synthase (NOS), which produces reactive nitric oxide (NO). Playing a key role in protecting neuronal tissue integrity is the antioxidant molecule glutathione. Glutathione helps mitigate oxidative damage to neuronal tissue. Additionally, glutamine is implicated in pain modulation and cellular signaling processes. Detailed features and characteristics of these mechanisms are elaborated upon in our article published in the journal *Molecules*.

There is also an assumption of a prooxidative effect from long-term opioid treatment. Studies indicate a connection between oxidative stress and complications arising from opioid use, especially morphine. This effect applies to semi-synthetic derivatives that metabolize into morphine or its derivatives within the body. Research on morphine has demonstrated decreased levels of glutathione in brain and liver tissue of rodents, as well as human brain tissue. Chronic morphine treatment additionally diminishes the activity of crucial antioxidant enzymes such as SOD, catalase, and GPx, which are essential for antioxidant defense.

The initial findings from our prospective clinical trial on long-term opioid use show consistent intensity of ongoing antioxidant reactions across all patient groups receiving chronic opioid treatment. We observed a significant increase in plasma enzyme activities of GPx and GR, along with a notable rise in plasma glutathione concentrations. Conversely, there was a significant decrease in SOD activity in these patient groups compared to the healthy control group, indicating heightened ongoing antioxidant activity in chronic pain patients after 6 months of opioid treatment. These results suggest the potential presence of oxidative stress in the group receiving opioids.

One of our current medical and scientific efforts is focused on treating acute and chronic pain with the primary objective of reducing opioid use. Our postoperative acute pain research involves evaluating the efficacy of intercostal nerve cryoablation compared to peripheral blocks and standard opioid treatment in patients undergoing thoracotomy procedures. Published results have consistently shown cryoablation to be a superior method, as detailed in the journal *Medical Science*. Recent studies have also demonstrated promising outcomes from sympathetic lysis of the lumbar sympathetic chain in patients with critical limb ischemia. This intervention has resulted in decreased pain intensity, improved tissue perfusion observed via thermography, reduced opioid consumption, and enhanced quality of life. Pilot results were published in the *Vasa - European Journal of Vascular Medicine*. Various interventional pain procedures have been investigated in our multicentre clinical trials, including epiduroscopy for patients with failed back syndrome, endoscopic discectomy for acute sciatica, and radiofrequency or cryoablation of lumbar facet joints for facet joint syndrome. These interventions consistently demonstrate positive effects on pain reduction, improvements in patient quality of life, and

reduced opioid usage. Our results have been published in reputable journals such as Pain Medicine, Wiener Klinische Wochenschrift, Bratislava Medical Journal, and Medicine. Additionally, these findings have been referenced in systematic reviews and meta-analyses published in Pain Practice, Global Spine Journal, and Pain Physician.

[1]² KOČAN, Ladislav, Jozef FIRMENT, Jana ŠIMONOVÁ, Janka VAŠKOVÁ a Juraj GUZY. Suplementácia selénu u pacientov s ťažkou akútnou pankreatitídou. *Rozhledy v chirurgii : měsíčník Československé chirurgické společnosti pro tvorbu domácí a rozhledy po chirurgii zahraniční* [online]. 2010, **89**(8), 518–521. ISSN 0035-9351. Dostupné z: <https://www.medvik.cz/link/bmc10026345>

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20 %	50 %	50 %	40 %

[2] KOČAN, Ladislav, Janka VAŠKOVÁ, Ladislav VAŠKO, Lucia LAKYOVÁ, Hana HOKOVÁ, Jana ŠIMONOVÁ, Róbert ŠIMON a Jozef FIRMENT. Akútne multiorgánové zlyhanie po kolonoskopii s polypektómiou. *Časopis lékařů českých* [online]. 2012, **151**(12), 568–572. ISSN 0008-7335. Dostupné z: <https://www.medvik.cz/link/bmc13004116>

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20 %	70 %	80 %	50 %

[3] KOČAN, Ladislav, Janka VAŠKOVÁ, Ladislav VAŠKO, Hana HOKOVÁ, Miloš MAJERNÍK, Beáta KRIŠTOFOVÁ, Jana ŠIMONOVÁ a Jozef FIRMENT. Ťažký priebeh Stillovej choroby s multiorgánovým zlyhávaním a závažnou pečevnou dysfunkciou. *Anesteziologie & intenzivní medicína* [online]. 2011, **22**(6), 337–342. ISSN 1214-2158. Dostupné z: <https://www.medvik.cz/link/bmc12003018>

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30 %	60 %	80 %	50 %

[4] JANKA, Vaskova, Kocan LADISLAV *(corresponding author)*, Firment JOZEF a Vasko LADISLAV. Restoration of antioxidant enzymes in the therapeutic use of selenium in septic patients. *WIENER KLINISCHE WOCHENSCHRIFT* [online]. 2013, **125**(11–12), 316–325 [vid. 2024-06-06]. ISSN 0043-5325, 1613-7671. Available at: doi:[10.1007/s00508-013-0371-x](https://doi.org/10.1007/s00508-013-0371-x)

Document Type: Article; IF = 0,791; median IF MEDICINE, GENERAL & INTERNAL – 1,273; Quartile by IF MEDICINE, GENERAL & INTERNAL Q3; Quartile by AIS MEDICINE, GENERAL & INTERNAL Q3

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
40 %	50 %	30 %	30 %

² Bibliographic record of a published scientific result, which is part of the habilitation thesis.

[5] KOCAN, Ladislav, Janka VASKOVA, Ladislav VASKO, Jana SIMONOVA, Robert SIMON and Jozef FIRMENT. Selenium adjuvant therapy in septic patients selected according to Carrico index. *Clinical Biochemistry* [online]. 2014, **47**(15), 44–50. ISSN 1873-2933. Available at: doi:10.1016/j.clinbiochem.2014.07.004

Document Type: Article; IF = 2,275; median IF MEDICAL LABORATORY TECHNOLOGY – 1,418; Quartile by IF MEDICAL LABORATORY TECHNOLOGY Q2; Quartile by AIS MEDICAL LABORATORY TECHNOLOGY Q2

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
40 %	50 %	40 %	30 %

[6] KOCAN, Ladislav, Jozef FIRMENT, Ingrid PIRNIKOVA, SilviaFarkasova IANNACCONE, Dusan RYBAR, Juliana GNORIKOVA, Jan KORCEK, Hana KOCANOVA, Pavol TOEROEK, Simona RAPCANOVA and Janka VASKOVA. Full recovery of lung tissue after severe viral pneumonia H1N1: A case report with 10 years follow-up. *Medicine* [online]. 2023, **102**(8). ISSN 1536-5964. Available at: doi:10.1097/Md.00000000000033052

Document Type: Article; IF = 1,600; median IF MEDICINE, GENERAL & INTERNAL – 2,700; Quartile by o IF MEDICINE, GENERAL & INTERNAL Q3; Quartile by AIS MEDICINE, GENERAL & INTERNAL Q3 (data from 2022)

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30 %	80 %	60 %	30 %

[7] VASKOVA, Janka, Ladislav KOCAN, Ladislav VASKO and Pal PERJESI. Glutathione-Related Enzymes and Proteins: A Review. *Molecules* [online]. 2023, **28**(3, Article 1447). ISSN 1420-3049. Available at: doi:10.3390/molecules28031447

Document Type: Review; IF = 4,600; median IF BIOCHEMISTRY & MOLECULAR BIOLOGY 3,700; Quartile by IF BIOCHEMISTRY & MOLECULAR BIOLOGY Q2; Quartile by AIS BIOCHEMISTRY & MOLECULAR BIOLOGY Q3 (data from 2022)

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
-	-	15 %	15%

[8] OGURČÁKOVÁ, Daniela, Ladislav KOČAN, Jana ŠIMONOVÁ, Igor MARTULIAK, František SABOL a Janka VAŠKOVÁ. Plasma antioxidant status in patients undergoing long-term opioid treatment. *Medical Science* [online]. 2022, **26**(124, Article ms217e2319). ISSN 2321-7367. Available at: DOI:

<https://doi.org/10.54905/disssi/v26i124/ms217e2319>

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10 %	10 %	10 %	40 %

[9] KOCAN, Ladislav, Viktoria RAJTUKOVA, Maria RASIOVA, Hana KOCANOVA, Simona RAPCANOVA, Robert RAPCAN, Igor MARTULIAK, Radovan HUDAK, Dusan RYBAR, Janka VASKOVA and Marek HUDAK. Thermovision controlled lumbar sympathetic blockade in chronic limb-threatening ischemia treatment - pilot trial. *Vasa-European Journal Of*

Vascular Medicine [online]. 2023, **52**(2), 133–135. ISSN 1664-2872. Available at: doi:10.1024/0301-1526/a001053

Document Type: Letter; IF = 1,800; median IF PERIPHERAL VASCULAR DISEASE - 2,900; Quartile by IF PERIPHERAL VASCULAR DISEASE Q4; Quartile by AIS PERIPHERAL VASCULAR DISEASE Q4 (data from 2022)

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50 %	100 %	40 %	100 %

[10] KOČAN, Ladislav, Róbert RAPČAN, Rudolf SUDZINA, Simona RAPČANOVÁ, Dušan RYBÁR, Juraj MLÁKA, Hana KOČANOVÁ, Miroslav BURIÁNEK and Janka VAŠKOVÁ. Radiofrequency denervation and cryoablation of the lumbar zygapophysial joints in the treatment of positive lumbar facet joint syndrome – a report of three cases. *Radiology Case Reports* [online]. 2022, **17**(12), 4515–4520. ISSN 1930-0433. Available at: doi:10.1016/j.radcr.2022.09.010

Document Type: Article; Category: Radiology, Nuclear Medicine and Imaging – SJR Q4

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
25 %	40 %	80 %	20 %

[11] RAPCAN, Robert, Ladislav KOCAN, Juraj MLAKA, Miroslav BURIANEK, Hana KOCANOVA, Simona RAPCANOVA, Michael HESS, Anthony HAMMOND, Martin GRIGER, Michal VENGLARCIK, Miroslav GAJDOS and Janka VASKOVA. A Randomized, Multicenter, Double-Blind, Parallel Pilot Study Assessing the Effect of Mechanical Adhesiolysis vs Adhesiolysis with Corticosteroid and Hyaluronidase Administration into the Epidural Space During Epiduroscopy. *Pain Medicine* [online]. 2018, **19**(7), 1436–1444. ISSN 1526-4637. Available at: doi:10.1093/pm/pnx328

Document Type: Article; IF = 2,764; median IF ANESTHESIOLOGY – 2,734 + MEDICINE, GENERAL & INTERNAL – 1,570; Quartile by IF ANESTHESIOLOGY Q2 + MEDICINE, GENERAL & INTERNAL Q1; Quartile by AIS MEDICINE, GENERAL & INTERNAL – Q1 + ANESTHESIOLOGY Q2

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20 %	70 %	70 %	30 %

[12] RAPCAN, Robert, Ladislav KOCAN, Viktor WITKOVSKY, Juraj MLAKA, Martin GRIGER, Miroslav BURIANEK, Simona RAPCANOVA, Anthony HAMMOND, Lubomir POLIAK, Robert TIRPAK, Jana SIMONOVA, Frantisek SABOL and Janka VASKOVA. EQ-5D-5L questionnaire as suitable assessment of quality of life after epiduroscopy Multicenter randomized double-blind pilot study. *Wiener Klinische Wochenschrift* [online]. 2020, **132**(17), 526–534. ISSN 1613-7671. Available at: doi:10.1007/s00508-019-01590-z

Document Type: Article; IF = 1,704; median IF MEDICINE, GENERAL & INTERNAL – 2,375; Quartile by IF MEDICINE, GENERAL & INTERNAL Q3; Quartile by AIS MEDICINE, GENERAL & INTERNAL Q3

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
40 %	70 %	50 %	30 %

[13] MLAKA, J., R. RAPCAN, M. BURIANEK, S. RAPCANOVA, M. GAJDOS, H. KOCANOVA, M. GRIGER, L. KOVALICOVA, J. VASKOVA and **L. KOCAN *(corresponding author)***. Endoscopic discectomy as an effective treatment of a herniated intervertebral disc. *Bratislava Medical Journal-Bratislavské Lekárske Listy* [online]. 2020, **121**(3), 199–205. ISSN 1336-0345. Available at: doi:10.4149/Bll_2020_030
Document Type: Article; IF = 1,278; median IF MEDICINE, GENERAL & INTERNAL – 2,375; Quartile by IF MEDICINE, GENERAL & INTERNAL Q3; Quartile by AIS MEDICINE, GENERAL & INTERNAL – SCIE Q4

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
25 %	50 %	80 %	25 %

[14] RAPCAN, Robert, **Ladislav KOCAN *(corresponding author)***, Viktor WITKOVSKY, Simona RAPCANOVA, Juraj MLAKA, Robert TIRPAK, Miroslav BURIANEK, Hana KOCANOVA, Janka VASKOVA and Miroslav GAJDOS. Endoscopic discectomy of the herniated intervertebral disc and changes in quality-of-life EQ-5D-5L analysis. *Medicine* [online]. 2023, **102**(26). ISSN 1536-5964. Available at: doi:10.1097/Md.00000000000034188
Document Type: Article; IF = 1,600; median IF MEDICINE, GENERAL & INTERNAL – 2,700; Quartile by IF MEDICINE, GENERAL & INTERNAL Q3; Quartile by AIS MEDICINE, GENERAL & INTERNAL Q3 (data from 2022)

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
35 %	50 %	70 %	80 %