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GLAVNI I ODGOVORNI UREDNIK

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**REVIEW**

# Prof. dr Đorđe Joannović, a corresponding member of Serbian Royal Academy, Dean, pathologist and the first Serbian oncologist, one of the world pioneers of the study of autoaggression, the founder and builder of the Institute of Pathology, the most tragic personality in the one-century-long history of the Faculty of Medicine (151 years since birth and 90 years since death)

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**Summary**

Đ. Joannović's greatest scientific achievements, in addition to his participation in the discovery of autoaggression in medicine, were in the field of experimental oncology and pathological morphology of tumors. He was the first oncologist-scientist in Serbia.

Đ. Joannović's death occurred in the night following the incident and humiliation experienced in Petar Živković's cabinet. It was certainly a big emotional blow, a disappointment, and shock for Đj. J. Like old Serbs who used to die for their honor, he committed suicide.

**Keywords:** Faculty of Medicine, Institute of Pathology, Đorđe Joannović, University of Belgrade

## FAMILY BACKGROUND, BIRTH AND LIFE OF ĐORĐE JOANNOVIĆ IN VIENNA 1871-1920.

The family comes from Metohija from where they first moved to the village of Beodra (today a settlement within Novo Miloševo) at Banat district and then to Vienna. Father Hariton was a lawyer and a senator, and he managed the estate of the Viennese baron Sina. Mother Marija's maiden name was Vlahović. The elder brother Simeon was born in 1869. He was engaged in consular affairs and it is him Đorđe Joannović (Đ. J.) was very attached to. Simeon lived in Beodra while Đ. J. was in Belgrade (1-4, 8, 15).

Đ. Joannović was born on June 16, 1871 in Vienna. Đorđe and Simeon were brought up in the spirit of the old Serbian tradition. They had talent for music – Đorđe played the violin and Simeon played the piano. Đ. J. had never got married and had no children. He believed that “science was asking for the whole person”. Z. Levental, a cardiologist and internist from Belgrade, the author of the text on Đ. J. in Yugoslav Medical Encyclopedia published in Zagreb, especially researched Đ. J.'s social life. He claims that he has reliable evidence that Đ. J. loved women. Đ. J. lived in one room in his Institute of Pathology.

Đorđe Joannović was a “typical boy born in Vienna”. This is where he completed his primary and secondary school and the Faculty of Medicine. He was promoted to a doctor of general medicine on July 1, 1895, at the age of 24. He got a job at the Institute of Pathology of the Faculty of Medicine in Vienna. In 1896 he became a lecturer, and then an assistant professor in 1904, an associate professor in 1910, and a full professor in 1919. At that time, Vienna was one of the centers of world medicine, along with Paris, Berlin, London, Padua, Budapest and St. Petersburg. Đ. J. was a Serb with the highest university title in the world at the time (Figure 1).

Oncology and pathology in Vienna were on the highest possible scientific level. They had a famous pathologist Karl von Rokitansky (1804-1878) who held the humoral direction in pathology, in contrast to Rudolf Virchow in Berlin, who advocated cellular pathology. Rokitansky was the rector of the University of Vienna and the president of the Austrian Academy of Sciences. He performed about 30,000 autopsies!

His student and successor Richard Paltauf (1858 – 1924) was Pasteur and Koch's student. He was Joannović's superior, who collaborated with him from 1895 to 1920. Richard Paltauf, Karl Sternberg and Đ. J. established the recognized “Vienna School of Experimental Oncology”. Đ. J. also collaborated with Pick, Paltauf's student, in his scientific papers, as well as with the famous German pathologist Karl Aschoff. (16, 20)



**Figure 1.** Djordje Joannović from his younger days with a signature (Figure courtesy of Dr Nada Kovačev Šljapić, professor of pathology at the Faculty of Medicine in Novi Sad, Đ. J.'s cousin).

Đ. J. knew the Nobel laureates Paul Ehrlich, well-known as a researcher of humoral immunity and the inventor of Salvarzan and Neosalvarzan (anti-syphilis drugs), and Ilya Ilyich Mechnikov, who discovered phagocytosis.<sup>1</sup> He also greatly appreciated the Serbian academician Vladan Đorđević, and he wrote about his honorary PhD thesis and was the author of his obituary when he died.

Đ. J. could have taken over the institutes and chairs of pathology in Innsbruck and Prague from Vienna. He even had invitations to come to the USA. Because of his noble patriotism, and a wish to help Serbia and Serbian people, he accepted the invitation to come to Belgrade at the age of 49. Also, he could have succeeded his teacher Paltauf who died in 1925, but he decided not to return to Vienna.

### Đ. JOANNOVIĆ'S ARRIVAL IN BELGRADE (1920). THE ESTABLISHMENT OF THE FACULTY OF MEDICINE THE UNIVERSITY OF BELGRADE (1920). THE CONSTRUCTION OF THE INSTITUTE OF PATHOLOGY (1926)

Following the end of the First World War, Vojislav Subotić (1859-1923) (surgeon), Milan Jovanović - Batut (1847-1940) (hygienist) and Drago Perović (a Serbian

<sup>1</sup>When talking about the results of Tsar Nicholas II Romanov's reign, White Russian emphasized that during his time Russia had the first two Nobel laureates: Ilya Ilyich Mechnikov in Paris and Ivan Pavlov in St. Petersburg (he discovered conditioned reflexes and dealt with higher nervous activity). After their death, he also wrote obituaries about them.



professor of anatomy at the Faculty of Medicine in Zagreb) were supposed to establish the Faculty of Medicine in Belgrade. However, Prof. Drago Perović soon withdrew due to illness.

The first two members of the triumvirate then invited Đ. J., a full professor of pathology at the Faculty of Medicine in Vienna to come to Belgrade. He accepted the invitation, so in 1920, the Faculty of Medicine of the University of Belgrade was founded (Figure 2).



**Figure 2.** The Triumvirate that finally founded the School of Medicine University of Belgrade in 1920. From left to right: Prof Vojislav Subbotić (surgeon), Milan Jovanović – Batut (hygienist) and Djordje Joannović (pathologist and oncologist).

Đ. J. founded the Institute of Pathology and the Department of Pathology in 1922, where he was the first headmaster or director. He gave his first lecture to students in 1923. He was the most popular professor both among students and among his colleagues. After a pro-

fessional trip around the world in order to get to know various institutes of pathology, Đ. J. established the Institute of Pathology in 1926 (Figure 3).

His associates were: Dimitrije Tihomirov (initially the only assistant, who after World War II went to New York, USA), teachers Ksenofon Šahović (his successor as the director of the Institute, later an academician of SASA), Marija Višnjić Frajnd and Živojin Ignjačev. The following associates stayed at the Institute for a short time: Dragoslav Miletić (later professor of pathology in Skopje and Priština), Meljnikov, K. Putilin, D. Stanulov, Mileta Magarašević, Vladimir Spužić (later the dean and an academician of SASA), Aleksandar Simić, Sveta Dimitrijević and others (5, 9, 18).

Đ. J. was the dean of the newly founded Faculty of Medicine in Belgrade for four years (1922/23, 1925/26, 1927/28 and 1928/29) and a vice dean for three years (1923/24, 1926/27, 1929/30) (32-34).

As Đ. J. came to Serbia from the defeated Austria-Hungary, many professors from victorious France and England, the so-called “Serbian current” (professors Milovanović, Antić, Kostić and others), caused certain difficulties for him in his work. (25, 26, 51)

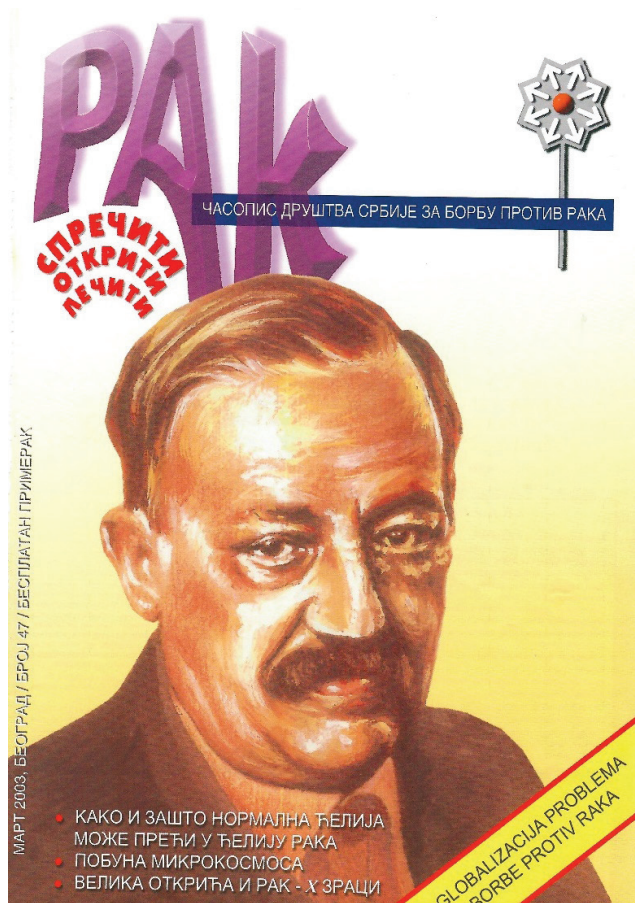
### ĐORĐE JOANNOVIĆ’S NUMEROUS SOCIAL AND MEDICAL FUNCTIONS OUTSIDE THE FACULTY OF MEDICINE AND THE INSTITUTE OF PATHOLOGY

In addition to major responsibilities at the Dean’s Office of the Faculty of Medicine and the Institute of Pathology (i.e. extensive student teaching, education of younger associates, scientific development in the fields of experimental oncology and pathology), Đ. Joannović had numerous other functions (21, 22, 27, 39, 47):

- the founder and the first president (until his death in 1932) (Figure 4) of the Yugoslav Society for the Fight against Cancer (September 27, 1927 in Belgrade) - the



**Fig. 3.** Institute of Pathology “Prof. Djordje Joannović” of the Faculty of Medicine University of Belgrade. Founded by Đ. J. in 1926.



**Figure 4.** The front page of the 47<sup>th</sup> issue of the journal “Cancer” published by the Serbian Society for the Fight Against Cancer from 2003. The picture was made according to Đ. Joannović’s photo at an older age

fourth society of this type in the world. The first society was created in 1910 in Vienna; the second in 1917 in Washington; the third in 1920 in Paris. The Yugoslav Society was under the protection of King Alexander I Karađorđević, with its headquarters in Belgrade in the newly built Institute of Pathology. The General Secretary of the Society was Ksenofon Šahović;

- Đ. J. had an idea to build the Central Institute of Oncology in Belgrade. Its construction began in 1939 under the protection of Queen Marija and Princ Pavle as the main donor<sup>2</sup>;
- lifetime Honorary President of the Association of Yugoslav Students of Medicine and the president of the Humanitarian Aid Fund intended for poor students;
- president of the Serbian Medical Society and its journal Serbian Archives of Medicine 1924/1925 (35-37);
- one of the founders of the international journal Medicinski pregled;
- a contract military doctor and the first medicolegal examiner of the Military Hospital in Belgrade starting from 1920 (45, 46);
- honorary member of Matica Srpska in Novi Sad;

- member of various international medical organizations; he represented Serbia and Yugoslavia at numerous medical congresses in Europe and the USA;
- corresponding member of the Serbian Royal Academy (predecessor of SASA) since February 18, 1926 (13, 35).

#### Đ. JOANNOVIĆ’S CONTRIBUTION TO EXPERIMENTAL ONCOLOGY AND PATHOLOGICAL MORPHOLOGY OF TUMORS

Đ. Joannović’s greatest scientific achievements, in addition to his participation in the discovery of autoaggression in medicine, were in the field of experimental oncology and pathological morphology of tumors. He was the first oncologist-scientist in Serbia.

In the field of pathological morphology of tumors, a German pathologist Prof. Rudolf Virchow (1821-1902) (48, 49), the author of the revolutionary book “Cellular Pathology” in 1858 and the “father of pathological anatomy”, had already achieved great success. (7, 12).

Virchow discovered leukemias: myeloid leukimia (with enlarged spleen) and lymphoid leukimia (with enlarged lymph nodes). He distinguished them from leukocytosis and pyemia. He noticed the local occurrence of cancer and the occurrence of local and distant secondary tumor nodes - metastases. Moreover, he noticed that sarcomas spread hematogenously (he noted pulmonary metastases without the involvement of pulmonary lymph nodes). Enlarged left supraclavicular lymph node is named after him as a site of metastasis of the stomach and ovarian cancer. He described psamoma (Virchow’s tumor). He specified the terminology of certain tumors according to histogenesis: myxoma, myoma, myosarcoma, angioma, lymphangioma, neuroglioma, teratoma, etc.

Đ. Joannović investigated branchiogenic carcinoma (originating from remnants of gill arches), cystic tumors of the neck, calcification and ossification of skin atheroma, the formation of a tumor due to irritation, the multicentric origin of a tumor in an organ, etc.

In experimental oncology, he investigated tumor growth in vivo and in vitro (in tumor tissue cultures). He observed that tumor growth was promoted by the following: castration, splenectomy, rice in the diet. Toluylendiamine intoxication, small doses of morphine, cocaine and quinine, and oats in the diet slowed it down.

He carried out immunological cancer therapy using fermentative extracts from tumor tissue (tumor tissue scraps) from patients themselves.

As indicators of successful immunological treatment of cancer in experimental animals, he marked the following: histopathological finding of lymphectasia, accumulation of plasma cells, and proliferation of connective tis-

<sup>2</sup>Today, in 2022, the director of the Institute of Oncology in Belgrade, Prof. Danica Grujičić, is fighting for a new building for the Institute because of its ever growing needs.

sue with sequestration of groups of cancer cells and their degeneration (13, 29).

Bearing in mind that cancer could be destroyed when erysipelas occurred over skin cancer, Đ.J. by analogy, used bee venom in cancer therapy. He also researched the effects of radiothorium on cancer.

### UNDERSTANDING THE ETIO-PATHOGENESIS OF CANCER BY Đ. JOANNOVIĆ COMPARED WITH CURRENT (2022) KNOWLEDGE

Đ. Joannović believed that the following three things were important in the etio-pathogenesis of cancer: disposition, local changes, and general metabolic disorders. Apart from this, “chronic irritations”, the presence of scattered embryonic cells in tissues where they did not normally belong, and the age of the patient were also of some importance. Of course, these last three factors do not always result in cancer (24, 28, 31).

Cancerology has progressed remarkably since the time of Đ. Joannović. Some essential things concerning the etio-pathogenesis of cancer have been discovered, which promises that cancer will be defeated in the 21st century. The figure which shows that 23% of all deaths are accounted for by cancer will disappear.

Today we know that cancer is a disease of the genes of the individual cell. Mutagenic factors (carcinogenic chemicals, ionizing radiation, oncogenic viruses) lead to mutations of normal cellular genes: proto-oncogenes or tumor suppressor genes (important for cell differentiation and division). Executive proteins, encoded by mutated - cancer genes, change about 100 characteristics of a normal cell.

Cancer cells become immortal. The basis for their immortality includes the following:

1. Action of telomerase enzyme on chromosomal telomeres (“caps” at the ends of chromosomes, which preserve their integrity) preventing their shortening after cell division. When telomeres critically shorten, the cells enter in senium and die. Cancer cells still have the enzyme telomerase, which normal cells have lost during early life;
2. Absence of apoptosis (programmed cell death – “suicide”). Namely, the cells already have a built-in system of caspase enzymes, and when they receive a “molecule of death” from the organism, these enzymes cut the DNA of the cells. In this way excessed and damaged cells of the organism are removed. The process of killing cells is carried out silently, cell remains are phagocytosed and everything passes without an inflammatory reaction and fibrosis. Cancer cells, therefore, do not undergo apoptosis.

The initial cancer cells have to break through the normal “immunological surveillance”. Then, there is favoring one cancer cell clone, which shows uncontrolled

proliferation and invasion of the surrounding normal tissue with its destruction (infiltrative - destructive local growth).

Then, certain cancer cells show a potential to metastasize, i.e., through lymphatic, hematogenous and in other ways, they go to the distant parts of the body, creating secondary cancer nodes, i.e. metastases.

Finally, the so-called “cancer disease of the organism” seems to lead to cachexia - emaciation when the organism is literally skin-and-bones.

Today, in addition to surgical, radiation and chemotherapy, there are also successful attempts of immunotherapy based on prior knowledge of the genetic characteristics of cancer cells and the organism.

### Đ. JOANNOVIĆ'S PAPERS ON GENERAL AND SPECIAL PATHOLOGICAL MORPHOLOGY

With his first paper “On the origin of plasmocytes” Đ. J. attracted the attention of the international scientific community. At the time, nothing was known about the origin of plasmocytes. Đ. J. concluded that plasmocytes arose from lymphocytes (adventitial and degenerated). Many years later, scientists know that they arise from B lymphocytes and that they create antibodies, i.e., participate in humoral immunity.

Đ. Joannović investigated the staining of microorganisms in pathological tissues. He dealt with liver diseases. As an assistant, he participated in the Competition in research of the pathogenesis of icterus and his paper (book) was awarded by the Belgian Royal Academy of Medicine. Some of his experimental research on icterus (“toluylendiamine icterus” disappears after splenectomy) became the basis of today's therapy of hemolytic anemias by splenectomy.

He dealt experimentally and postmortem with pathological morphology of tetanus as well as its prophylaxis. He also investigated anaphylactic shock, problems of transplantation and explantation (tissue culture), and nutrition pathology.

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14. Joannovics G. Paul Ehrlich, 1854-1915. Wiener klin. Wochenschrift 1915; 35:937-42.
15. Joannovics G. Experimentelle Studien zur Frage der Geschwulst-Disposition. Wiener klin. Wochenschrift 1916; 29: 345-9.
16. Joannovics G. Elias Metchnikow. Neue Freie Presse, 18. 07. 1916, 11-12.
17. Joannovics G. Über das Wachstum der transplantablen Mäusetumoren in kastrierten und epinephrektomierten Tieren. Beiträge zur pathologischen Anatomie und Physiologie, 1916; 62:194.
18. Joannovics G. Zum anaphylaktischen Schock im Verlaufe der Tetanusbehandlung. Bruns Beiträge zur klinische Chirurgie, 1917:105.
19. Joannovics G. Zur Wirkung fermentativ gewonnener Spaltungsprodukte aus Geweben und Bakterien ("Ефекат добијен ферментацијом распадних продуката ткива и бактерија"). Wiener klin. Wochenschrift, 1920.; XXXIII (30):649-52 .
20. Joannovics G. Reizgeschwülste. Wiener klin. Wochenschrift 1923; 2:23015.

## PAPERS BY Đ. JOANNOVIĆ WRITTEN IN VIENNA IN SERBIAN, GERMAN AND FRENCH BEFORE HIS ARRIVAL IN BELGRADE IN 1920 AND AFTER HIS ARRIVAL IN BELGRADE (1920 – 1932)

1. Јоанновић Ђ. (у оригиналу погрешно стоји: Јовановић). Нови погледи на постанак и лечење извесних болести. Експерименталне студије (*New views on the origin and treatment of certain diseases. Experimental studies*). Српски архив за целокупно лекарство, новембар и децембар 1920; XXII (11-12); 445 – 55.
2. Joannovics G. Reizgeschwülste. Wiener klin. Wochenschr., 1923; 2 :230-5.
3. Јоанновић Ђ. (У оригиналу погрешно стоји Јовановић). Рак и малигне неоплазме (*Cancer and malignant neoplasms*). Медицинска библиотека (уредник А.Ђ. Костић). Изд. Књијарница "Напредак". Београд, 1924.
4. Јоанновић Ђ. Однос између узрока болести и процеса оздрављења (*The relationship between the cause of illness and the healing process*). Предавање приликом свечаног отварања Патолошког института у Београду, на дан 22.ајрила 1926. године. Београд, Загреб, Љубљана, Софија: Медицински преглед 1926; 1: 2-5. (Први чланак у првом броју интернационалног Медицинског прегледа).
5. Јоанновић Ђ. Théophile-René Laennec као патолошки анатом (*Théophile-René Laennec as a pathological anatomist*). Медицински преглед (Београд) 1926 – 27., стр. 136 – 39.
6. Јоанновић Ђ. Почасни докторат д-ра Владана Ђорђевића (*Honorary PhD thesis of Vladan Djordjević, MD*). Српски архив за целокупно лекарство 1927., 211-3.
7. Јоанновић Ђ. О патологији исхране (*About the pathology of nutrition*). Српски архив 1927; 22: 801 – 12.
8. Yoannovitch G. (Joannović Djordje): *L'institut de pathologie générale et d'anatomie pathologique à Belgrade. Methods and problems of medical education (Eighteenth series). The Rockefeller Foundation. New York, N.Y., U.S.A., 1930: pp. 139-51.*
9. Joannovics G. Über die Wirkung des intravenös eingeführten Radiothorium. Verh.d. Deutsch. patholog. Gesellschaft, 1930: 25.
10. Joannovics G. Dr. Vladan Georgevitch. Wiener klin. Wochenschrift 1930:42: 1296-7.
11. Јоанновић Ђ. О животу и раду др Владана Ђорђевића (*About the life and work of Vladan Djordjević, MD*). Српски архив за целокупно лекарство 1931., 2: 155 – 63.

## TWO PIONEER PAPERS BY Đ. JOANNOVIĆ WRITTEN IN VIENNA AND BELGRADE IN 1920 ESTABLISHING WORLDWIDE LEARNING ABOUT AUTOAGGRESSION IN MEDICINE

In the last third of the 19th century, medicine was dominated by the dogma “The human organism never creates substances against itself”. The dogma was particularly advocated by the Nobel laureate Paul Erlich (1854-1915) (40), an immunologist. By analogy with vaccination, he wanted to induce immunity against cancer by injecting weakened cancer cells into the patient. He also researched autoaggression, but rejected the possibility that the body’s immune system attacked healthy tissues of the human body. He called it “Horror antitoxicum” = “fear of antitoxin”. Silverstein (44) spoke of need for recognition: autoimmunity versus “Horror antitoxicum” (4, 13).

William B. Coley is considered the be the “father of tumor immunotherapy”: in 1893, he used bacteria and bacterial lysates in the treatment of tumors. Ehrlich’s student Ernest Witebsky (43) demonstrated that chronic thyroiditis was caused by autoimmunization. Pfeiffer and Merrill (42) confirmed that autoantibodies played a role in the pathogenesis of diffuse glomerulonephritis.

Đ. J. noted that soldiers with head surgeries and brain injuries from firearms sometimes had severe headaches and died. At their autopsies, numerous foci of softened brain tissue (encephalomalacia) were discovered, both near and far from the healed brain injuries.

He also investigated this experimentally in three groups of white rats. In the first group, he traumatized rats’ heads and brains with frequent blows to the head. Rats in the second and third group were injected parenterally at the beginning of the traumatization and whole time respectively with rat brain tissue emulsion. He obtained the same necropsy findings in all the groups of white rats. Based on these observations in humans and animals, he phenomenally concluded the following:

“The same elements of the brain, which as a result of trauma are the source of decay products, are later susceptible to the activity of these decay products”.

Today it is clear that decay products of the brain stimulate our immune system to create autoantibodies against them, but also against such substances (antigens) in healthy brain cells. This then leads to new foci of brain softening (28, 29).

Đ. J. tried to apply this newly discovered original etio-pathogenetic concept to the therapy of certain diseases – superficial carcinoma of the skin in humans and tuberculous granulomas in guinea pigs. He injected disintegrated cancerous or granulomatous tissue (the products of their “dissolution”) or digested Koch bacilli under the skin of the same people or guinea pigs.

In tuberculous granulomas, he observed an increase in phagocytosis of Koch bacilli in granuloma cells, which then facilitates repairing processes.

Đ. J. even had his own drug “Joannin” (38) - the old tuberculin for treating tuberculosis.

Also, he treated dermatoses: Trichophyton tonsurans with its “flakes” as well as psoriasis with its squamas (40, 41, 43). He wrote two important original papers where he described research in humans and animals:

1. Joannovics G. *Zur Wirkung fermentativ gewontern Spaltungsprodukte aus Geweben und Bakterien. Wiener klin. Wochenschrift 1920.; XXXIII (30): 649-52. “On the influence of decomposition products obtained from tissues and bacteria by fermentation”.* (Figure 5).
2. Joannović Dj. (in the original it is written incorrectly: Jovanović). *New views on the origin and treatment of certain diseases. Experimental studies. Serbian archive for all medicine, November and December 1920; XXII (11-12); 445 – 55* (Figure 6). The papers were printed in Serbian with an error in the author’s name, i.e., instead of Đ. Joannović it was written Đ. Jovanović (which, by the way, often happens, as proofreaders change the surname believing the original one is a mistake, as it is a rare surname; this is why they must be warned not to do that). Also, the title of the paper is general and unattractive, so it did not arouse the attention of readers. The authors of this paper about Đ. J. knew that these papers by Đ. Joannović existed but, due to the above-mentioned circumstances, it was difficult to find them while browsing the volumes of the Serbian Archives.

These two cited papers on autoaggression are the most important scientific discoveries of Đ. Joannović. Because of them, he is one of the pioneers of the world study of autoaggression, together with Noel Fissenger, M. Massugi (41) and others.

Noel Fissenger stated that a snake could have autoantibodies against its own venom after a self-bite. Also, he stated that animals and humans could produce autoantibodies against their own sperm. In both cases, however, these are products that are normally excreted from the body. For him, liver cirrhosis is also an autoaggressive disease.

M. Massugi (41) believed that autoaggression was involved in the pathogenesis of glomerulonephritis and liver diseases.

Today we have many other proofs that autoaggression and autoimmune diseases exist. We know of apoptosis. In case of autoaggression, the autoimmune bodies created on decay products (“debris”) in the body act on diseased tissue as well as on healthy tissue that has antigens as damaged tissue.

We treat their sources of decomposition with products of tissue decay, i.e., damaged tissue but damaging healthy tissue as well. It is like the Latin proverb “Clavus clavo eicere” says (“One nail drives out another”) (V. Kanjuh).

Levental (28, 29) described Đ. J.’s process of autoaggression as follows: “Đ. Joannović discovered the phenomenon of sensitivity of tissues and cells to their own

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1. Originalartikel: 1. Aus dem Institute für allgemeine und experimentelle Pathologie in Wien (Vorstand: Hofrat Professor Dr. R. Paltauf) und dem pathologisch-anatomischen Institute der Allgemeinen Poliklinik in Wien (Vorstand: Professor Dr. G. Joannovic). Zur Wirkung fermentativ gewonnener Spaltungsprodukte aus Geweben und Bakterien. Von Professor Doktor G. Joannovic. S. 649.
2. Aus der Universitätsklinik für Dermatologie und Syphilidologie in Wien. (Vorstand: Hofrat Prof. Dr. G. Riehl.) Ueber die therapeutische Wirksamkeit eines durch Verdauung von Triebphytonkulturen gewonnenen Präparates (Joannovic). Von Dr. Herbert Fuchs. S. 653.
3. Zur Wirkung fermentativ gewonnener Spaltungsprodukte auf Karzinome. Von Primarius Dr. G. Scherber, Wien. S. 654.
4. Aus dem Hygienischen Institut der deutschen Universität in Prag. Ueber die Bedingungen der Agglutininbildung durch Fleckfiebervirus. Von E. Weil und A. Felix. S. 655.
5. Aus der chirurgischen Universitätsklinik in Wien. (Vorstand: Hofrat Prof. Dr. Julius Hochenegg.) Ueber eine Modifikation der Schloßerschen Operationsmethode für eine häufige Form der Phimose. Von Dr. Franz Kazda. S. 657.
- II. Referate: Die Oedemkrankheit. Von Dr. Siegmund Pollag. — Wiener Archiv für innere Medizin. Unter Mitwirkung zahlreicher Mitarbeiter geleitet von W. Falta und K. F. Wenkebach. — Beiträge zur Schilddrüsenfrage. Von Dr. med. Otto Bayard. Ref.: J. Bauer.
- III. Aus verschiedenen Zeitschriften.
- IV. Vermischte Nachrichten.
- V. Verhandlungen ärztlicher Gesellschaften und Kongreßberichte.

**Aus dem Institute für allgemeine und experimentelle Pathologie in Wien (Vorstand: Hofrat Prof. Dr. R. Paltauf) und dem pathologisch-anatomischen Institute der Allgemeinen Poliklinik in Wien (Vorstand: Professor-Doktor G. Joannovic).**

### Zur Wirkung fermentativ gewonnener Spaltungsprodukte aus Geweben und Bakterien.\*)

Von Prof. Dr. G. Joannovic.

Während des Krieges hatte ich Gelegenheit, wiederholt Fälle von Kopfschüssen zu obduzieren, welche ein eigenförmliches, nicht ohne weiteres zu deutendes pathologisch-anatomisches Bild darboten. Es handelte sich um Schußverletzungen des Schädels mit Läsion des Gehirns, deren Träger nach sachgemäßer, chirurgischer Behandlung geheilt in die Heimat entlassen wurden, nach Wochen, Monaten, mitunter auch nach Ablauf von Jahresfrist, unter heftigsten Kopfschmerzen erkrankt in die Krankenanstalt zurückkehrten. Die rapide Zunahme der zerebralen Krankheitserscheinungen drängte zu einem neuerlichen operativen Eingriff. Nach Eröffnung des Schädels fandete man vergeblich nach einem Abszeß, der sich auch bei der Obduktion nicht fand. Die Sektion des Gehirns deckte dagegen multiple, zum Teil auch ausgelehntere Erweichungsherde auf, die nicht allein in der nächsten Umgebung der Schußverletzung, sondern auch weit entfernt davon gelegen waren. Für diesen Befund fehlt bisher eine ausreichende Erklärung.

Ich suchte mir eine solche in der Weise zurecht zu legen, daß durch die Resorption von zertrümmertem Hirngewebe im Organismus Substanzen gebildet werden, welche zytotoxisch oder fermentativ abbauend auf lädiertes Hirngewebe schädigend einwirken. Solche von klinischen Symptomen kaum begleitete Läsionen des Gehirns können zweifellos nebar und entfernt von der groben traumatischen ganz regelmäßig vor und sind jenen gleich zu stellen, wie sie der Gehirnerschütterung zukommen. An diesen durch die Commotio geschädigten Anteilen des Zentral-

\*) Vortrag, gehalten in der Ges. d. Aerzte in Wien am 25. Juni 1920. — Die Arbeit wurde mit Unterstützung der österreichischen Gesell-

nervensystems greifen die in Rede stehenden Substanzen an. Der Wirkung solcher spezifischer Reaktionsprodukte wären demnach die geschädelerten multiplen Späterweichungsherde des Gehirns zuzuschreiben, die sich auf dem Boden ganz geringfügiger Kompressionsläsionen entwickeln würden. Es galt nun die Richtigkeit dieser Deutung durch das Tierexperiment zu prüfen.

Gehirnerschütterungen lassen sich beim Tiere durch Verhämmerung des Kopfes unschwer erzeugen. Kombiniert man diesen Versuch mit einer einmaligen oder wiederholten Injektion von Gehirnbrei, so lassen sich im Tierversuche willkürlich jene Verhältnisse schaffen, welche nach der entwickelten Auffassung beim Menschen zu multipler Erweichung des Gehirns führen sollen. Als Versuchstiere dienten mir Ratten, mit denen in Gruppen zu zwölf folgende Serienexperimente unternommen wurden:

1. Wiederholte Verhämmerung des Schädels ohne Injektion von Gehirnbreiemulsion.

2. Wiederholte Verhämmerung des Schädels, kombiniert mit einer einmaligen, intraperitonealen Injektion von Gehirnbreiemulsion zugleich mit der ersten Verhämmerung, und

3. wiederholte Verhämmerung des Schädels und wiederholte Injektion von Gehirnbrei.

Die Verhämmerung des Kopfes wurde durch leichtes Beklopfen des Schädels mit dem Stiele einer Aneurysmanadel durchgeführt (150 Schläge in 75 Sekunden). Zur intraperitonealen Injektion gelangte je 1 cm<sup>3</sup> einer frisch bereiteten Emulsion von frischem Rattengehirn in 5 cm<sup>3</sup> physiologischer Kochsalzlösung. Die Verhämmerung des Schädels erfolgte in Intervallen von einer Woche.

Die ersten Krankheitserscheinungen zeigten die Tiere aus der letzten Versuchsreihe, bei welcher also die experimentelle Gehirnerschütterung und die Injektion von Gehirnbrei jede Woche wiederholt wurden. Schon nach wenigen Verhämmerungen wurden die Ratten ruhiger, apathisch, mitunter auch reizbarer; unter allmählich zunehmender, allgemeiner Abmagerung stellten sich dann zum Teil tonische, zum Teil klonische Krampfzufälle vorübergehender Natur in einzelnen Muskeln und Muskelgruppen ein, die an Intensität und Extensität zunahmten, um schließlich in all-

Figure 5. Paper by Djordje Joannović about autoaggression in medicine from 1920 in Vienna in Journal Wiener klin. Wochenschrift.

decomposition products. These products, combined with other noxes, significantly increase and accelerate destruction processes of the altered tissue. If we translate the part of the sentence "combined with other noxes" into the language of modern immunology, then, in fact, we are talking about the creation of autoantibodies against the decay products of tissues ("scraps"), which act on both diseased and healthy tissue.

It is surprising that little is known about the papers of Đ. J. on autoaggression, both in native Serbia and abroad especially!?

## THE TRAGIC END OF Đ. JOANNOVIĆ ON JANUARY 28, 1932

After the assassination of Croatian deputies in the Assembly, ethnic, religious and armed local riots in the country, King Aleksandar I Karadorđević, decided to take all power into his own hands. He established his monarchist dictatorship on January 6, 1929, in the Kingdom of Serbs, Croats and Slovenes. Slobodan Jovanović and others dissuaded him from that idea in vain. The king announced that "from now on, there is no mediator between me and

# СРПСКИ АРХИВ

ЗА ЦЕЛОКУПНО ЛЕКАРСТВО

ОРГАН СРПСКОГ ЛЕКАРСКОГ ДРУШТВА

УРЕЂУЈУ:

Д-Р ЈОВАН ДАНИЋ и Д-Р ВОЈИСЛАВ МИХАИЛОВИЋ

ГОД. XXII.

НОВЕМБАР и ДЕЦЕМБАР 1920.

СВ. 11. и 12.

## НОВИ ПОГЛЕДИ НА ПОСТАНАК И ЛЕЧЕЊЕ ИЗВЕСНИХ БОЛЕСТИ

Експерименталне студије од професора Д-р Ђорђа Јовановића.

Дозволите ми, да Вас упознам са радовима, којим сам се последњих година бавио. Чини ми се, да су питања, којима ћемо овом приликом имати посла, исто тако важна за теорију различних болести као и за практично лекарство.

Моја истраживања почела су, студијом неких повреда главе са нарочитим патолошким налазом. Ови случајеви тицали су се војника са повредама главе и мозга ватреним оружјем, који су се после стручне хируршке терапије вратили као излечени кући. После дужег бављења у домовини, после више недеља, месеци, па чак и после годину дана и више вратили су се понова у болницу, тужећи се на несносне болове у глави. Ови симптоми у кратко тако су се погоршали, да је нова операција постала неопходна. Извршена је поново трепанација али у мозгу није ни при самој операцији ни при аутопсији нађен никакав апсцес. При секцији мозга утврђена су мултипла огњишта размекшања мозга, како у близини, тако и у даљем одстојању од повреде мозга. Оваки особити патолошки налаз не може се за сад тачно објаснити. По мом мишљењу нарав ове лезије могла би се овако схватити.

Из резорпције повређеног мозганог ткања стварају се у организму супстанције, које као токсини или као ферменти на повређено ткање мозга дејствују, мозак даље мењају, рашчине. Лезије мозга без клиничких симптома од значаја су нам давно познате; њих има не само у близини повреда мозга, него и удаљено од њих. Оне су једнаке оним повредама, које припадају потресу мозга. На ове комозијом повређене делове централног живчаног система дејствују те супстанције, о којима је реч, тако да од безначајне повреде, произведене комозијом, постају већа или мања огњишта енцефаломалације.

30

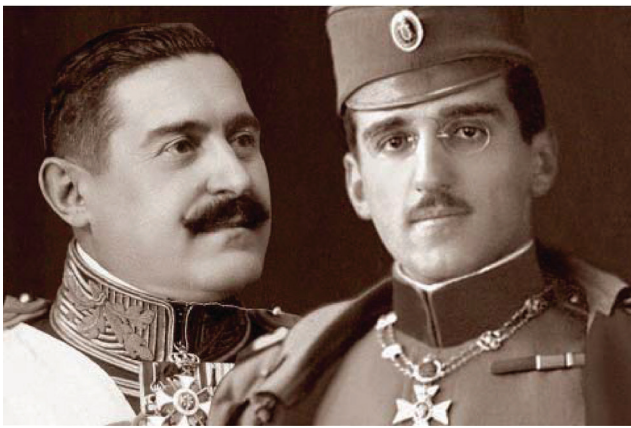
Figure 6. The paper by Djordje Joannović on autoaggression in medicine from 1920 in the Journal Serbian Archives. The title of the paper is general and nonattractive and the surname Joannović was changed to Jovanović, so it was hard to detect.

my people". He had to find a firm personality to be the executor of his dictatorship, and he found it in general Petar Živković, whom he appointed the president of the Ministerial Council (Figure 7).

Živković was the captain, who in 1903 unlocked the door of the Court and let Apis and other conspirators in. They murdered Aleksandar Obrenović and Queen Draga and threw their corpses from the balcony into the courtyard. Borislav Mihajlović-Mihiz, a literary critic cynically said: "We had it, we threw it away". Živković supported the movement of Draža Mihailović.

During World War II in exile in London, Živković supported the movement of Draža Mihailović and the Yugoslav Army in homeland. Borislav Mihajlović Mihiz, a literary critic cynically said: "We had it, we threw it away". Nevertheless, he was a little jealous of Draža, believing that the refugee Government glorified him too much he immediately promoted him to the rank of general, proclaimed him the commander of the Yugoslav army in the Fatherland and the minister of the army and navy).

He never married and was accused of homosexuality, but this was rejected at the trial. He was guilty, among



**Figure 7.** General Petar Živković, President of the Council of Ministers, the executor of the dictatorship of the January 6, 1929 and King Alexander I Karadjordjević.

other things, for murdering 39 communists. The international public condemned it with an Appeal against “white terror” on December 1, 1929. Albert Einstein was also a signatory of the Appeal.

He died in Paris in 1947, still in exile. After World War II (1946), he was sentenced by the new authorities to death in absentia with the group of Draža Mihajlović.

In 1932, students of the Faculty of Medicine in Belgrade, leftists and rebels, organized the annual St.Sava student Ball.

They said that the patron of the Ball, King Aleksandar, was welcome, but not his radical right-wing president of the Council of Ministers general Petar Živković. He was furious and called Đ. Joannović to his cabinet. He allegedly told him: “You old fool, how can you not calm down your rebellious students?” and, even worse, he slapped him. All red with humiliation, Đ. Joannović ran out of the cabinet and went to his room at the Institute of Pathology where he lived. The lights in his room were on all night. The bed remained untouched, as he didn’t sleep that night. On the morning of January 28, 1932, he was found hanging from the window handle, the loop was a cord for pulling the curtain. He sat down in an armchair and pushed it away. It was found hanging against the wall on the floor. At that moment he was 61 years old and at the peak of his scientific creativity.

### SUICIDE OR MAYBE EVEN MURDER?

Đ. Joannović’s death occurred in the night following the incident and humiliation experienced in Petar Živković’s cabinet. It was certainly a big emotional blow, a disappointment, and shock for Đ. J. Like old Serbs who used to die for their honor, he committed suicide.

Investigating the case, the author of this text heard from the late Prof. Marija Višnjić Frajnd, Đ. J.’s associate, that “a lot of ash was found in his fireplace in the morning”. This means that he burned some of his documentation (what? and why?) and it strongly suggests suicide (1-3).

However, Dr M. Kovačev, Đ. J.’s cousin (1-3), a gynecologist and obstetrician in Novi Sad, presents certain indications in his books, which, according to him, point to murder (10, 11, 23, 24):

- one evening before Đ. J.’s death, the suicide of a famous scientist Pirke and his wife in Vienna was discussed. Đ. Joannović said that he could not imagine a cultured and famous scientist could do such a thing; therefore, he expressed his negative attitude towards suicide;
- a few days before his death, his friends visited him, and he had a long pleasant conversation with them, which by no means predicted a tragedy;
- suicides usually leave a “farewell letter”, in which they explain why they decided to take the fateful step. No farewell letter was found in this case;
- Đ. J. told his brother Simeon: “No matter where and no matter how I die, you should know that I am here”, and pointing with his hand to the right pocket of his jacket, he also said: “I have put a letter here in which you will find everything of interest.” That letter was never found; this indicates that someone threatened him for something;
- his brother Simeon and the Council of the Faculty of Medicine demanded an autopsy, but it was not done;
- the police report on the investigation of the circumstances of the death has been lost;
- there is no evidence that the pollution test (ejection of suspended seeds) and the expertise of changes on the loop of the cord due to suspension were attempted;
- Đ. J. was not politically committed, but he loved all his students, both Ornas (nationalist students) and communists. He was on good terms with King Alexander. The injured General Petar Živković’s vanity who was probably satisfied by humiliating and slapping Đ. J., so it is hard to doubt that on the same night he faked his suicide and then covered everything up;
- at the time, Dr G. Stanulov worked at the Institute of Pathology and later became a professor of internal medicine at the Faculty of Medicine in Novi Sad. He said to the author of the text that the eventual murderer might be a “cadaver master” (a worker who arranges corpses after autopsy) who was primitive, rebellious and caused trouble, so that Đ. J. was inevitably often in conflict with him. However, that primitive man certainly did not know the technique of sophisticated suicide performed by Đ. J. It is known to forensic medicine, but laymen understand hanging as the situation in which a body should hang. On the other hand, Đ. J. was a tall, big and strong man and he would certainly have defended himself against an attempt of assassination;
- from Belgrade, two telegrams were sent by the Council of the Faculty of Medicine to his brother Simeon in Beodra about the tragic event, but he did not receive them; allegedly, the Post Office in Beodra was





**Figure 8.** Djordje Joannović on his deathbed in 1932 after suicide or murder. (Figure courtesy of Dr Nada Kovačev Šljapić, profesor of pathology at the Faculty of Medicine in Novi Sad, Đ. Joannović's cousin).

ordered not to send telegrams from Belgrade to the addressees;

- the housekeeper, who brought Đ. J. tea in the morning and who saw him hanged, alerted the rest of the staff of the Institute. The corpse was immediately transferred to another room, and in front of his room where the tragedy happened, a gendarme was constantly standing, not allowing anyone to enter the room;
- when accompanying the coffin from Belgrade to Beodra, the crown of the Court was not seen, but the representative of the Court was present;
- after Joannović's death, it was gossiped that his successor Ksenofon Šahović (K. Š.) had something to do with his death (but there is no evidence) and that he had "stolen" Đ. J.'s scientific papers (which is also not true because the author of this paper knows papers of both Đ. J. and K. Š. well, and they have absolutely no similarities).

#### **FUNERAL FAREWELL OF Đ JOANNOVIĆ AT THE RAILWAY STATION IN BELGRADE ON THE WAY TO BEODRA (1932) COMMEMORATION, POSTHUMOUS ACKNOWLEDGMENTS AND HONOURS PATHOLOGISTS' ETERNAL MEMORY OF Đ. JOANNOVIĆ**

Never before had Belgrade seen such a large and sad procession (**Figure 8**). The Serbian Patriarch Varnava approved a funeral service for Đ. Joannović, although the Serbian Orthodox Church opposed it due to suicide (out of reverence for the great scientist or he did not believe it was suicide). A procession of 2,000 students paraded past the bier, as they wished to show that they were not guilty of Đ. Joannović's death, as it was rumored. Mustafa Golubić and the communists organized protests against the Government because of this mysterious death (50, 54-65).

After his death, numerous commemorations and articles about Đ.J. followed, including obituaries and In memoriam 54-65.

In the dean's chain of the Faculty of Medicine in Belgrade there is also a medallion with the image of Đorđe Joannović.

Today, the Institute of Pathology of the Faculty of Medicine bears his name: "Prof. Đorđe Joannović", and there is a bust of him in the hall of the Institute.

As an illustration of pathologists' eternal memory of this man, we will quote nine lectures that were held at different time intervals.

## NINE LECTURES ON Đ. JOANNOVIĆ, WHICH SHOW PATHOLOGISTS' ETERNAL MEMORY OF HIM

1. Levntal Z. Joannović Đorđe. *Forerunner of the idea of autoaggression in the pathogenesis of the diseases. Comunicazione presenta al XXI Congresso di Storia della Medicina, Siena, 22-28. Settembre 1968, Arti Graficke E. Cassidente, Roma, 1970.*
2. Kanjuh V. *60 years since the death of Serbian Royal Academy correspondent member Djordje Joannović. Today's view of his life and scientific work. XI meeting of the Department of Medical Sciences SASA. Belgrade, October 28, 1992.*
3. Kanjuh V. *60 years since the death of Djordje Joannović, founder of the Institute of Pathology at the Faculty of Medicine in Belgrade. Institute of Pathology. Belgrade, November 2, 1992.*
4. Kanjuh V. *Djordje Joannović as the founder of pathology in Serbia. Memorial lecture held at the 6th Congress of Pathologists of Yugoslavia. Zlatibor, June 17, 1994.*
5. Kanjuh V. *Djordje Joannović's contribution to medical science. Scientific gathering dedicated to the work and personality of Djordje Joannović (on the occasion of the 70th anniversary of his death). Organizer: Prof. Dr. Teodor Kovač (Novi Sad). Academy of Medical Sciences SMS. Belgrade, December 17, 2002.*
6. Kanjuh V. *70 years since the death of Djordje Joannović. I meeting of the Department of Medical Sciences of the SASA. Belgrade, January 29, 2003.*
7. Kanjuh V. *Djordje Joannović's contribution to medical science and book promotion: M. Kovačev "From a medical perspective. Life, work and fate of professor Djordje Joannović", vol. 4, 2nd ed. Editors: M. Kovačev and V. Kanjuh. Ed. Printing house "Futura" Petrovaradin. Novi Sad, 2004. Lecture at the SASA Branch in Novi Sad, March 19, 2004.*
8. Kanjuh V, Radojević Škodrić S. *Dr Djordje Joannović - founder of the Institute of Pathology. Lecture at the 46th symposium "Aspirations and innovations in medicine" Med.fak. Univ. in Bgd. Dec. 13 2017 as part of the Mini Symposium "Celebration of 95 years of the Institute of Pathology Dr. Đorđe Joannović".*
9. Kanjuh V. *Corresponding member of the Serbian Royal Academy Djordje Joannović, one of the pioneers of study-*

*ing autoaggression in medicine. X meeting of Dept. Med. Science of SASA Dec. 27, 2017.*

V.Kanjuh, as the president of the Yugoslav (Serbian) Society of Pathologists, introduced a permanent Memorial Lecture dedicated to Đ.J.

The General Hospital in Zrenjanin bears his name and has a bust of him in its park.

The primary school in Novo Miloševo also bears his name. The house where his brother Simeon lived, as well as the grave of Đ. J. are in relatively good condition.

The Cancer Society of Serbia issued a postage stamp with his image (6,14).

At the Celebration of 80 years of the fight against cancer in Yugoslavia and Serbia, Đ. J. was the first to receive the Gold Plaque of the Yugoslav Society for the Study and Treatment of Cancer and the Serbian Society for the Fight against Cancer on December 10, 2007 "For a great contribution to the work of the Society and the development of oncology in Serbia". The President of the Society Prof. Slobodan Čikarić presented the Plaque to V. Konjuh for safekeeping.

There are encyclopedic references about Đ. J. written in Zagreb's Yugoslav Medical Encyclopedia (28) as well as in Stanojević's National Encyclopedia in Serbia (58). In the upcoming seventh book of the Serbian Encyclopedia (letter J), V. Konjuh prepared a text on Đ. J.

Đ.Joannović is the holder of 14 domestic and foreign awards.

## CONCLUSION ABOUT THE LIFE, WORK AND SIGNIFICANCE OF DJ. JOANNOVIĆ

Đ. Joannović was a full-time professor of pathology at the Faculty of Medicine of the University of Vienna - a city that at the time was one of the world's medical capitals. He was, therefore, at the time a Serb with the highest university medical title of all the Serbs in the world. Out of noble patriotism, ignoring that he could run an institute of pathology in Europe or in the USA, he came to Belgrade to help Serbia and the Serbian people in 1920.

He participated in the triumvirate for the establishment of the Faculty of Medicine in 1920 and in 1926 he opened the newly built Institute of Pathology, which was significant on a world scale. He was the dean four times and a vice-dean three times. He is the author of numerous papers in the field of experimental oncology and pathological morphology and one of the pioneers of the world's study of autoaggression in medicine.

With his tragic death (suicide or murder) Serbia lost the best and most deserving Serbian medical teacher and scientist in the first third of the 20th century, who was 61 years old and in full scientific creativity when he died. Đ.J. Joannović. is the most tragic figure in the 100-year-long tradition of the Faculty of Medicine in Belgrade.

“We lost the wing that lifted us up”, M. Ivković (53) wrote in the text “Instead of a Preface” for the Đ. Joannović’s Memorial book.

We, Serbs, are proud of our scientific greats: Nikola Tesla, Ruđer Bošković, Milutin Milanković, Mihajlo Pupin... We can safely and with a clear conscience, add one more Banatian to the list - Djordje Joannović.

He came to help us - and what did we do to him!

At the celebration of the 95th anniversary of the Institute of Pathology “Prof. Đorđe Joannović”, academician V. Kanjuh and prof. S. Radojević Škodrić held a lecture – to the memory of Đ. J. The dean at the time, academician N. M. Lalić (24), a pioneer of cardio-diabetology in Serbia and Republic of Srpska, said of Đ. Joannović: “We hope

that such a cruel conflict between the Executive Political Authority and the Autonomy of the University will never happen again.” The current dean prof. L. Davidović, a world-recognized vascular surgeon, a foreign member of the Russian Academy of Sciences, gave a significant place to Đ. Joannović when organizing the celebration of the 100th anniversary of the Faculty of Medicine.

We, his successors in pathology of the third and fourth (current) generation, V. Kanjuh and S. Radojević Škodrić, and his successors as deans, N. M. Lalić and L. Davidović, owe him respect and eternal memory.

#### DIXIMUS ET SERVAVIMUS ANIMAS NOSTRAS WE SAID AND SAVED OUR SOULS

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## PROF. DR ĐORĐE JOANNOVIĆ, DOPISNI ČLAN SRPSKE KRALJEVSKE AKADEMIJE, DEKAN, PATOLOG I PRVI SRPSKI ONKOLOG, JEDAN OD SVETSKIH PIONIRA UČENJA O AUTOAGRESIJI, NAJTRAGIČNIJA LIČNOST U JEDNOVEKOVNOJ ISTORIJI MEDICINSKOG FAKULTETA (151 GODINA OD ROĐENJA I 90 GODINA OD SMRTI)

Vladimir Kanjuh<sup>1</sup>, Sanja Radojević Škodrić<sup>2,3</sup>, Lazar Davidović<sup>2,4</sup>, Nebojša M. Lalić<sup>1,2,5</sup>

### Sažetak

Najveća naučna dostignuća Đ. Joannovića, pored učešća u otkrivanju autoagresije u medicini, bila su u oblasti eksperimentalne onkologije i patološke morfologije tumora. Bio je prvi onkolog-naučnik u Srbiji.

Đ. Joanovićevo smrt dogodila se u noći nakon incidenta i poniženja doživljenog u kabinetu Petra Živkovića. Bio je to svakako veliki emotivni udarac, razočarenje, šok za Đj. Joanovića. Kao i stari Srbi koji su ginuli za svoju čast, izvršio je samoubistvo.

**Ključne reči:** Medicinski fakultet, Institut za patologiju, Đorđe Joannović, Univerzitet u Beogradu

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**REVIEW**

# The beginnings and the restoration of the Institute of Medical Physiology of the Faculty of Medicine University of Belgrade through the work and character of its restorer Professor Milutin Nešković

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The author has declared that no competing interests exist.

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With the passage of time and the lack of quality archival materials, both at the Institute and at the Faculty of Medicine and bearing in mind the “culture of memory”, the work on this text, which is a continuation of the work on the published monograph on the occasion of the 100th anniversary of the establishment of the Institute of Medical Physiology of the Faculty of Medicine of the University of Belgrade and the beginning of classes, was an extremely challenging undertaking. The texts previously published by fellow teachers in faculty publications on various anniversaries, as well as in the “Serbian Archive” journal, significantly helped the realization of this undertaking. The willingness and kindness in providing important historiographical material, documents and photographs, by the family members of Professor Richard A. Burian from the USA (Richard M. Burian, Jim Huntington), Milutin Nešković from France and Belgrade (Nenad and Nikola Nešković, respectively) and Božidar Nikolić (Emilija Nikolić Đorić) should be appreciated, and then by numerous colleagues from our country, including Vojislav Voki Kostić, son of the famous professors Aleksandar Đ. Kostić and Smilja Joksić-Kostić. I owe everyone a big thank you, because they made it possible to systematize these important data. However, I am aware that this will not be a complete text, which primarily dealt with the beginnings of work and the restoration of the Institute, and with an exceptional professor and patriot, Prof. Dr. Milutin Nešković, the restorer of the destroyed Institute after the end of the Second World War, whose personality and work, as well as the strength of character, can be a role model for future generations of teachers and associates.

**Keywords:** Faculty of Medicine, Institute of Medical Physiology, Milutin Nešković, Richard Burian, University of Belgrade

Institute of Medical Physiology “Richard Burian” of the Faculty of Medicine in Belgrade on 09.12.2022. marked the 100th anniversary of its founding with a festive symposium, during which a monograph was promoted and a lecture on the history of the institute was held (1,2).

### ESTABLISHMENT OF PHYSIOLOGY INSTITUTE. ABOUT PROFESSOR RICHARD BURIAN (1871–1954), ITS FOUNDER

According to the memorial published by the Faculty of Medicine in Belgrade in 1935, on the 15th anniversary of its work, the Physiology Institute (today the Institute of Medical Physiology) of the Faculty of Medicine was

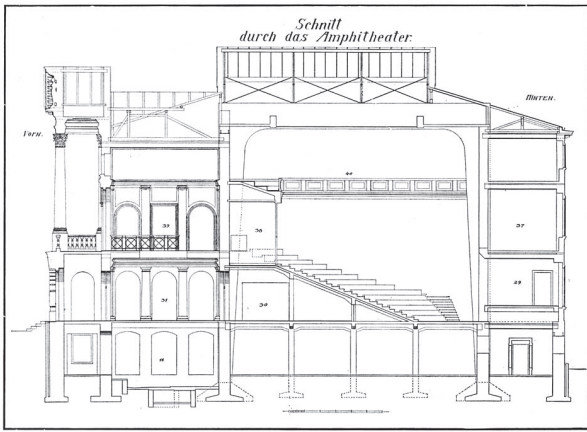
founded in 1921 (3). At the request and proposal of the first dean of the newly founded Faculty of Medicine in Belgrade, Professor Milan Jovanović Batut, at the session of the Council of the Faculty of Medicine on October 10 1920, Richard (Anton) Burian (in Serbian language the name is Rihard Burijan), born on 8th January 1871 in Vienna, former professor of the Faculty of Medicine in Leipzig, was elected full-time (contractual) Professor of Physiology, and this election made by a decree of His Majesty the King was soon confirmed (3).

According to Professors Milutin Nešković and Ilija Đuričić, Professor Richard Burian, as a founder, started his first lectures in the fall term of the school year 1922/23, which were experimental at the very beginning and thus required great efforts. Professor Burian gave



**Figure 1.** (left) Temporary accommodation of the Institute of Physiology from the Archives of the Institute of Histology and Embryology “Prof. Dr. Aleksandar Đ. Kostić”, and (bottom and right) the view of the new and later bombed building and of the Physiology-Histology Institute; digitized in the Audiovisual Archive and Digitization Center of SASA (courtesy of Prof. Nela Puškaš)





**Figure 2.** (left) Building plan for the construction of the Institute of Physiology (Richard Burian “Das Physiologische Institut der medizinischen Fakultät in Belgrad als Unterrichtsanstalt-New York: Rockefeller Foundation”, 1930.), and (right) the layout of the training room.

his first lectures in French and German, and to the third generation of students he did it in fluent Serbian (4). The temporary accommodation in the adapted building could not meet the needs of the Physiology Institute, both in teaching and in scientific work (Figure 1). In 1924, according to the conceptual design of Professor Burian and under his constant control, the construction of the Physiology-Histology Institute began - one wing for each institute, which was completed and decorated in 1926 with a modern amphitheater, exercise rooms, research laboratories and a vivarium, and activities in it began in 1927 (Figure 2). For the construction of vivarium, laboratories, the purchase of equipment and other contents, funds were provided from war reparations and loans, but to a large degree from the “Dr. Elsie Inglis” memorial fund from London as well (author’s note: With the funds of this fund, several hospitals were built in Serbia and named after a military doctor of British origin, who fought with the Serbian army in the First World War, and who was awarded the Order of the White Eagle by the Regent Prince Aleksandar Karađorđević for her many merits). Therefore, in gratitude for her support, the Physiology Institute named the laboratory for scientific research “Dr. Elsie Inglis”, and a memorial plaque was placed in the hall of the building in 1929. The existence of the laboratory under the name “Dr. Elsie Inglis” is proved by affiliations and acknowledgments in the published works of researchers Ilija Đuričić and Milutin Nešković. Professor Burian wanted, from the very beginning, to make our school and physiology keep pace with the corresponding universities in Europe. Under the auspices of the Rockefeller Foundation, as part of the “Methods and Problems of Medical Education” edition, Professor Rihard Burian published a paper in German entitled “Das Physiologische Institut der Medizinische Fakultät in Belgrad als Unterrichtsanstalt” in 1930, thus discussing at the international level the significance of the establishment of the Physiology Institute (5). It is worth mentioning that Prof. Richard Burian held the position of dean in 1923/24, 1926, 1933/34, and a vice dean in 1924/25, 1927/29,

1932/33. He selflessly helped the newly founded Faculty of Veterinary Medicine in the organizational and scientific aspects, so he was a member of the first Council of this faculty and the first vice-dean, and he was the dean in 1937/38. He and Prof. Dr. Aleksandar Đ. Kostić, in the role of supervisors, handed over the duty to the first dean of the Faculty of Veterinary Medicine, Prof. Dr. Živojin Đorđević. Prof. Burian also participated in the founding of the Faculty of Pharmacy (1939).

According to Burian’s first collaborators and successors, Professors Milutin Nešković and Ilija Đuričić (quote): “His rich research experience, extraordinary energy, idealism of a great scientist, day-and-night total dedication to work, school and science, tact and gentle consideration, readiness to advise and help, attracted a large number of excellent students-demonstrators to the Physiology Institute, who later grew into very successful doctors, teachers and scientists” (4) (Figure 3).



**Figure 3.** Professors Richard Burian and Aleksandar Đ. Kostić with colleagues in front of the building of the Physiology-Histology Institute. Seated (left to right): Branko Vlatković, Milutin Nešković, Aleksandar Kostić, Alida Hirsch (Prof. Burian’s wife), Ilija Đuričić, Richard Burian and Antonije Vuković; standing Nedeljko Ercegovic (between Burian and Đuričić), Božidar Nikolić (above Mrs. Burian), Aleksandra Volkanovska (next to Nikolić), Radmilo Anastasijević (between Kostić and Nešković), Aleksandar Sabovljević (in the 1930s, courtesy of Dr. Emilija Nikolić Đorić)

On the day of 14 December 1940 Prof. Richard Burian wrote a letter to the Dean of the Faculty of Medicine, in which he wrote that on January 8, 1941 he would turn 70 “and that according to legal regulations he should be retired” and which was sent to the Rectorate. Based on the attached documents, it could be seen that his work experience acquired before coming to Belgrade was also recognized. In the same year, the Council of the Faculty of Medicine elected Prof. Richard Burian as an honorary doctor of the Faculty of Medicine in Belgrade.

In the preface to the second edition of the *Physiology Practicum* (1941), professor Richard Burian says (quote): “Concluding this preface, glad that I have brought my teaching boat to a calm shore, I am even happier to state that the second edition of this book has been jointly published by Dr. Ilija Đuričić, Full Professor of the Faculty of Veterinary Medicine and my student and friend, and Dr. Milutin Nešković, Full Professor of the Faculty of Medicine, successor to my Chair. This cooperation is only a pale and modest reflection of the deeper community of understanding and activity that unites these two scientific workers. In this community I see the incarnation of my scientific activity” (6).

The year 1941 represented a tragic period in the history of the Institute. Although there was a clearly visible sign of the Red Cross on the roof of the building (underlined by the author), the Institute was bombed and destroyed on April 6, 1941 (author’s note: According to the available memoirs of Professor Burian’s daughter Maria Louisa, there was a conversation during an accidental meeting between her and a German officer in front of the destroyed Institute, where, when she asked why that had been done, he stated “that the building was not accidentally bombed”). Great material and spiritual assets were destroyed - buildings, schools, and a library richly equipped with books and journals. A lot of unpublished results of Professor Burian and his collaborators were lost forever – parts of the inventory, devices, a certain number of journals and books which Professor Burian enriched the library of the Physiology Institute with, as well as some documents. Everyone who was in that area took part in rescuing those things and Professor Nešković was one of them. This is how Professor Nešković was able to use the saved things – inventory and some of his studies – immediately after liberation. On the day of December 17<sup>th</sup>, 1941, after Professor Burian’s retirement, Professor Nešković takes over the duties of the director of the Physiology Institute. During the occupation, the Physiology Institute existed only nominally. The premises of the Institute were moved to the building of the Institute of Pathology, and only a few employees who remained in Belgrade worked there. Certain activities took place, as evidenced by the records from the “Administrative Protocol 1941-1945”.

Among many good works that Richard Burian left behind, an extraordinary humane event from the period

of the Second World War was recorded by the composer Vojislav Voki Kostić, the son of the famous medical professors Aleksandar Đ. Kostić and Smilja Kostić-Joksić, in the book entitled “Life with a deep pain in the soul” (quote): “In the evening hours of August 21, 1942 a young medical captain of the Wehrmacht visited our home (we concluded this by the markings on his uniform) and, without saying his name, he greeted us on behalf of Prof. Richard Burian, whose distant relative he was, and told us that he had asked him to intervene for Prof. A. Kostić, because he had found out that he was arrested. By the way, Prof. Burian was an anti-fascist, so he moved to the USA, where he died several years later. This was the last greeting to his good friend Professor A. Kostić” (7) (author’s note: On the night of July 20, 1942 Prof. A. Kostić was arrested by the Special Police. He was released after countless interrogations, after almost a month (August 15, 1942) with a ban on leaving Belgrade).

After the liberation of Belgrade, Professor Richard Burian, with the help of new authorities (author’s note: He was helped by his former student Aleksandar Sabovljević, an officer of the national liberation movement and a high-ranking official at the time) moved to the USA, to Iowa City, joined his son Hermann, a student of medicine educated in Belgrade and later a famous American professor of ophthalmology, where, according to the announcement of the American news agency Associated Press, “Richard A. Burian died on April 6, 1954 in Iowa City, and he was one of the world’s greatest physiologists and the founder of the Faculty of Medicine at the University of Belgrade”. As a pensioner, he often wrote to his associates from the USA and advised them how to rebuild the Institute (**Figure 4**). Instead of the commemoration that was never held, according to his contemporary Professor Aleksandar Đ. Kostić (8), its Physiology Institute made the decision to name the institution after its founder, in memory and respect for its first director, and to place a relief plaque with his name and image on a wing of the Histophysiology Institute building (1983). Also, busts to professors Aleksandar Đ. Kostić, Richard Burian and Milutin Nešković were placed and revealed in the hall of the Histophysiology Institute (2001). Professor Rihard Burian was earlier described in the edition of Serbian Academy of Sciences and Arts (SASA) under “Life and work of Serbian scientists” (9). On the 55th anniversary of his death, in 2008, a scientific meeting of the Serbian Physiological Society was organized in Belgrade, an essay was published in the section of Famous European Physiologists on the website of the Federation of European Physiological Societies (FEPS), and an editorial was published in the leading international journal *General Physiology and Biophysics* published by the Slovak Academy of Sciences (10).

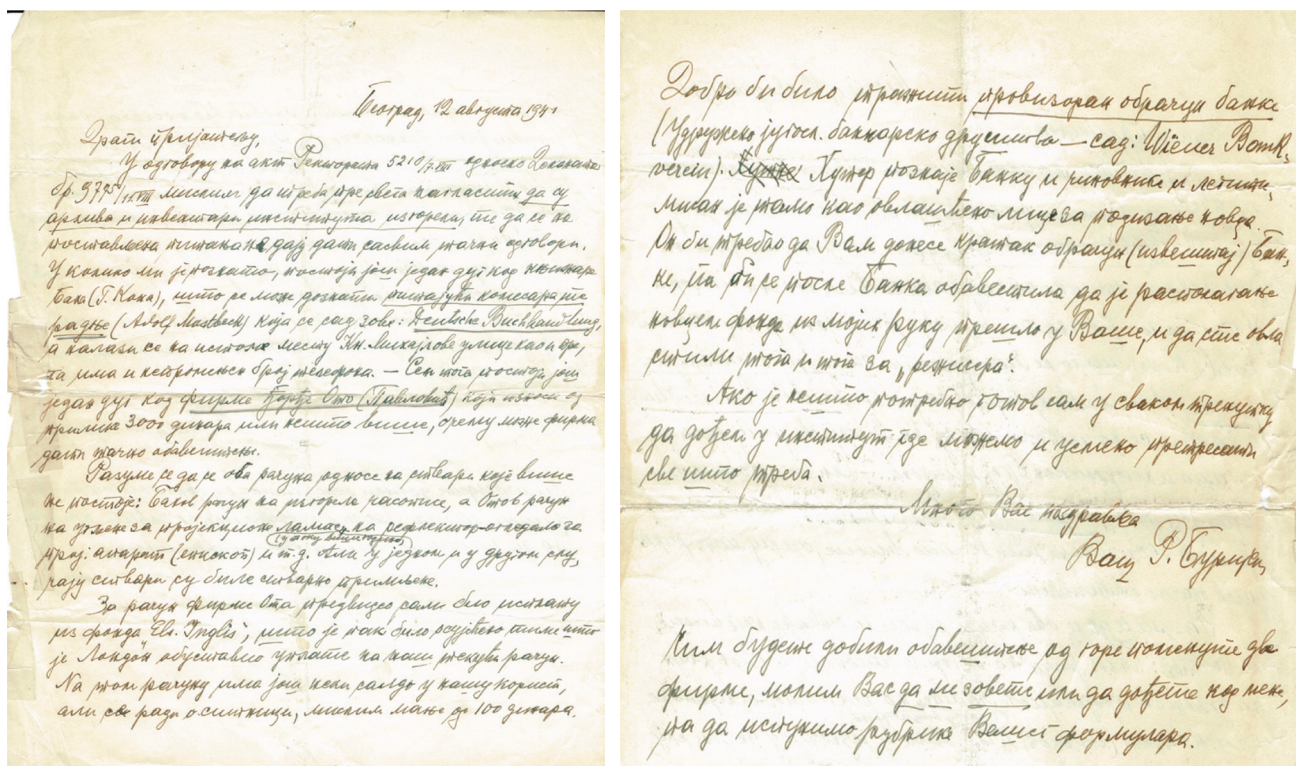


Figure 4. Letter from Prof. Burian, to the new director Prof. Nešković, with advice regarding activities at the Institute (1941) (copy of letter obtained thanks to the courtesy of Nenad and Nikola Nešković)

## ABOUT PROFESSOR MILUTIN NEŠKOVIĆ (1894-1980), THE RESTORER OF THE INSTITUTE OF PHYSIOLOGY AND THE FOUNDER OF THE INSTITUTE OF BIOCHEMISTRY

As a long-time associate and professor at the Institute of Medical Physiology of the Faculty of Medicine in Belgrade, I came across numerous written data from various sources about Professor Richard Burian, the founder of the Institute, including data from the unpublished family memoirs of his daughter, which I received with a courtesy and blessing of his family (grandson Richard M. Burian from Virginia and grandson Jim Huntington from California). I wrote about this in detail in the Institute's published monograph (1), as well as in an earlier internationally published editorial (10). Numerous written data are also available on one of the first professors of Physiology, the famous Professor Ilija Đuričić (11). As the first graduate student of the Faculty of Medicine in Belgrade, Dr. Ilija Đuričić was appointed an assistant on July 2, 1926 and as an assistant professor on November 28, 1929, and in 1936 he was elected as a Full Professor for the subjects of Physiology and Pathological Physiology at the newly established Veterinary Faculty in Belgrade. In the period 1938-1941, he was the dean of the Veterinary Faculty. Prof. Dr. Ilija Đuričić founded the Physiology Institute of the Veterinary Faculty, after war he was the founder and director of the SASA's Institute for the Study of Physiology of Work (1947-1954), the dean of the Veterinary Faculty (1945-1947, 1948/49), the rector of the University of Belgrade (1950/51, 1951/52, 1954/55), a vice-president

and the president of SASA (1960-1965), and one of the initiators of the founding of the Yugoslav Society of Physiology (November 23, 1956) and the Serbian Physiological Society, whose president he was later. He died suddenly in Belgrade on April 2, 1965.

However, for reasons unclear to me, there is far less written information about the versatile personality of extremely strong character, Professor Milutin Nešković (a patriot, a doctor, a professor, a scientist, a teacher, a social worker, a poet, a writer, a hunter, etc.), born on September 7, 1894 in Kragujevac, from father Veljko Nešković ("boss Veljko", a respected and wealthy merchant) and mother Bosiljka Todorović (originating from a merchant family) who gave birth to twelve children, of whom Milutin was the tenth in line. Milutin belonged to the generation that survived two world wars and changes in the social and ideological organization of the states in which he lived and created (Figure 5). Despite his sufferings, and perhaps owing to that, he preserved his inexhaustible life and creative energy, and in a philosophical sense, searching for meaning and origin, he initiated the artistic expression of his personality, and he often returned to his native land, to which he remained faithful until the end of his life. He was a restorer (so to say the "re-founder of the destroyed Institute"), according to the Institute's chronology, the second elected teacher and director, who participated in the construction of the new building after the Second World War, selected and educated younger staff, renewed teaching and scientific research work, and laid the foundations of the modern Institute, as we have known it in recent decades. According to the certif-

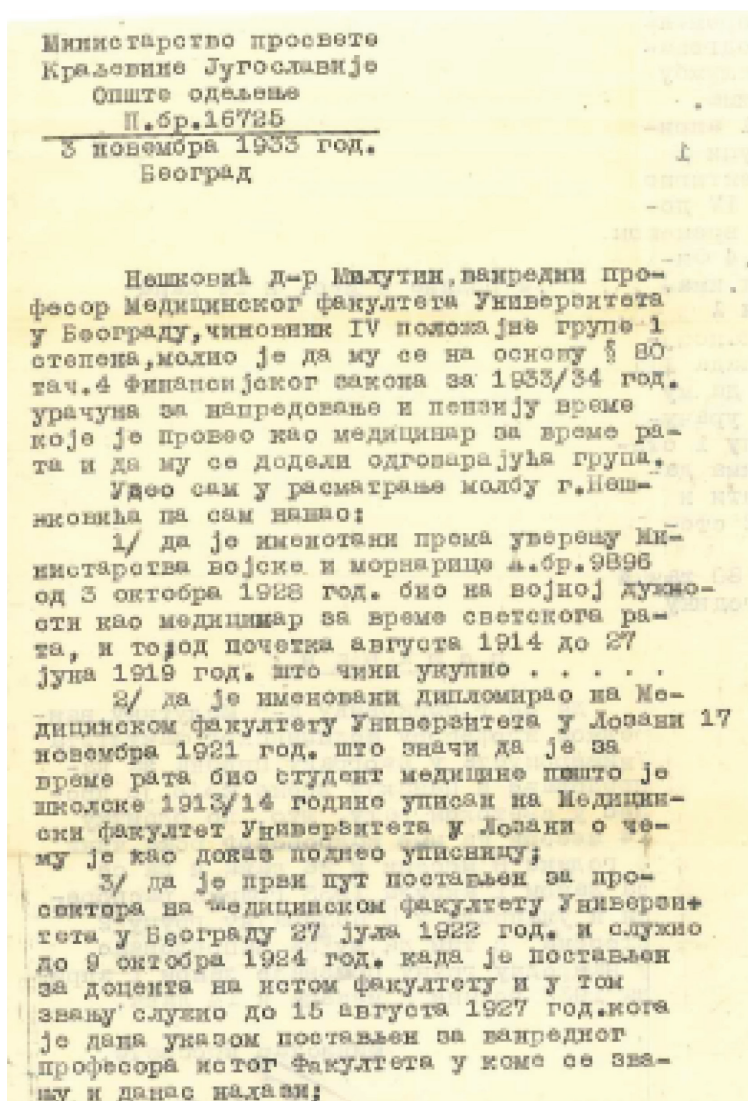


**Figure 5.** Photos of Professor Milutin Nešković from different periods of his life, in the top row left (in Lausanne, Switzerland, 1919), as well as during his duties as professor, the director of the Institute, and the dean of the Faculty of Medicine (photos obtained thanks to the courtesy of Nenad and Nikola Nešković )

icate of the Yugoslav Ministry of Army and Navy A. No. 9896 from October 3<sup>rd</sup> 1928, Milutin Nešković was on military duty as a medical worker during the First World War, from the beginning of August 1914 to June 27, 1919 (**Figure 6**). He enrolled in medicine in the academic year 1913/14, and graduated on November 17, 1921, at the Faculty of Medicine of the University of Lausanne. His father Veljko educated him with his personal funds.

He was an assistant and the head of practical classes under Professor Maurice Arthus at the Institute of Physiology of the Faculty of Medicine in Lausanne (**Figure 7**), and as soon as July 27, 1922 he was appointed as a prosector at the Faculty of Medicine of the University of Belgrade (**Figure 8**). He was elected assistant professor of Physiology on October 9, 1924, an associate professor on September 15, 1927 and as a full professor on July 6, 1940 at the same faculty (Note: The data partly differ from the data presented in the published monograph and

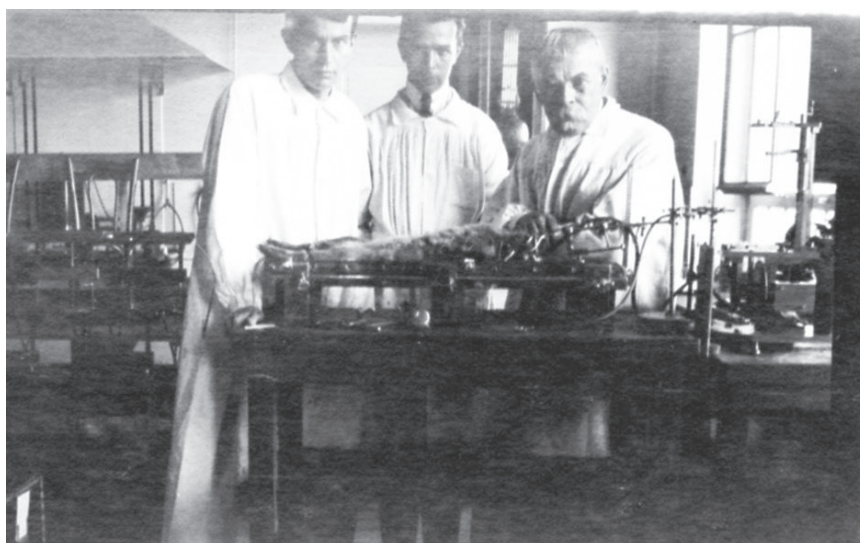
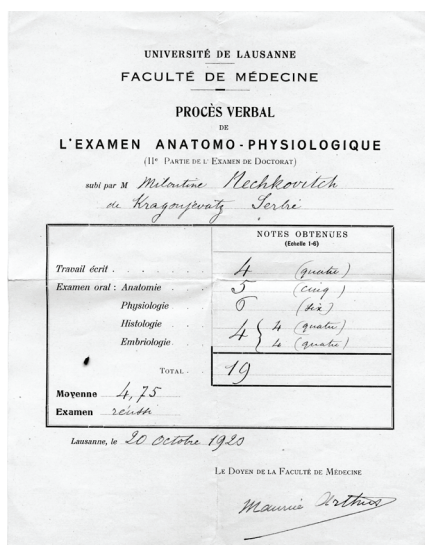
were taken from the decision of the Ministry of Education of the Kingdom of Yugoslavia - General department P. No. 16725, dated November 3<sup>rd</sup> 1933). His long-time associate and former student, Prof. Miodrag D. Cvetković, Full Professor of Biochemistry at the Faculty of Medicine of the University of Belgrade, in the book entitled "Professors of the Faculty of Medicine in Belgrade - from its foundation to the 1950s" (12), wrote about Professor Nešković (quote): "He was a very intelligent man and an extraordinarily strong personality. His thoughts and remarks in the introductory class in Physiology were a great incentive to study this fundamental subject at the Faculty of Medicine. In Kragujevac, where he was born, he finished elementary school and high school. He enrolled at the Faculty of Medicine in Lausanne (Switzerland) in 1913. After the outbreak of the First World War (1914), he returned to his homeland, where for a time he was engaged in the health service in Kragujevac. Then he moved



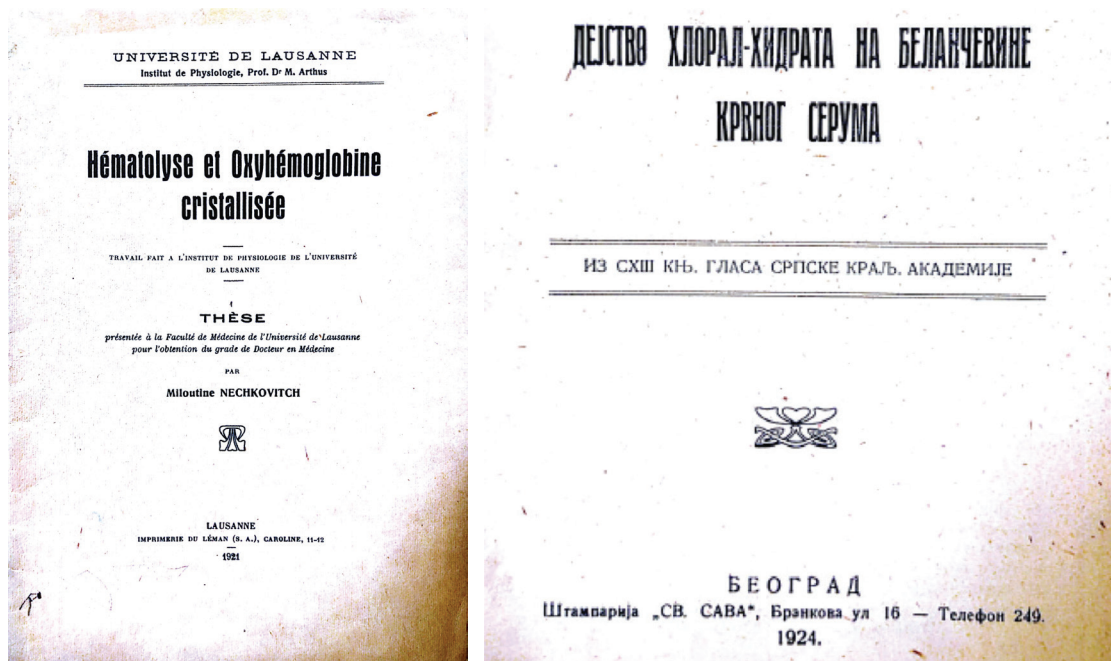
**Figure 6.** Milutin Nešković, a Serbian soldier-medic with his comrades in the First World War on the islands of Corfu and Vid (copy of the decision of the Ministry of Education and photos obtained thanks to the courtesy of Nenad and Nikola Nešković)

to Albania with the Serbian army and worked as a medical worker on Corfu island and Vid. He graduated from the Faculty of Medicine in Lausanne in 1921, after which he

worked as an assistant to Professor Arthus at the Institute of Physiology of the Faculty of Medicine in Lausanne. In 1922, he moved to Belgrade to the newly founded Facul-



**Figure 7. (left)** Certificate of passed exams for habilitation ("doctorate"), **(right)** Milutin Nešković during experimental work in the laboratory of Prof. Maurice Arthus, Lausanne, Switzerland, immediately after the end of the First World War (courtesy of Nenad and Nikola Nešković)



**Figure 8.** (left) Title page of habilitation thesis in French by Dr. Milutin Nešković (1921), (right) title page of PhD thesis by Dr. Milutin Nešković (courtesy of Nenad and Nikola Nešković)

ty of Medicine. Soon upon his arrival in Belgrade, he was chosen as an assistant at the Physiology Institute. He was appointed director of the Institute of Physiology in 1941. He remained in this position until his retirement in 1964. During the German occupation of our country, he was persecuted by the Gestapo and the Special Police.”

### IMPRISONMENT AT THE BANJICA CAMP

According to his grandson Nikola Nešković, this happened because he refused to sign the infamous “Appeal to the Serbian People” dated August 13, 1941 and for a time he was at the Banjica camp. Belgrade, as a university and cultural center, housed many prominent cultural and public workers, friends of books and science, who were under constant surveillance by the occupation authorities. In them, the fascists saw potential opponents, whose views and attitudes could represent an additional danger in the otherwise dire situation in Serbia that arose after the uprising. That is why the occupying military administration decided to eliminate that danger by arresting prominent public and cultural workers. On November 2, 1941, on behalf of the commanding general in occupied Serbia, Turner, the chief of the military staff, signed an order for an operational group of the German Police and security service, in cooperation with the Belgrade Special Police, to undertake an extensive action against intellectuals, “whose behavior in the past years was anti-German” and who were mostly “members of the lodge of freemasons and communists.” On the basis of this order, a massive arrest of intellectuals was carried out in Belgrade on November 4, 1941. They were brought to the Banjica camp and placed in special rooms, separated

from other detainees. Those were room 3, which was vacated for them, and rooms 35 and 36, which were ready and waiting for them. The treatment for arrested intellectuals and prominent citizens was somewhat more favorable and lenient. They had beds and bedding, which they received regularly from houses, a longer walk in the camp grounds, less abuse by the camp staff. The other detainees called this part of the camp where this group of intellectuals was housed “Masonic rooms”. Those were mostly professors and teaching staff of the University of Belgrade, several well-known professors from Belgrade secondary schools, former ministers, businessmen, writers and artists, lawyers, and doctors. There were 176 names on one list, and 192 names on the other list (three of whom were added later), therefore also those who were taken to the Banjica camp later following the same Turner’s decision. Among the renowned professors of the University of Belgrade, the group of arrested intellectuals included physiologists, biologists and pathologists: Dr. Ivan Đaja, Dr. Milutin Nešković, Dr. Siniša Stanković (arrested again in 1944 as an active participant in the national liberation movement) and Dr. Ksenofon Šahović (13). As they represented a concentrate of knowledge from various scientific disciplines, and they lived in more tolerable conditions, they initiated various lectures (the initiator of the lectures was Dr. Aleksandar Belić, the president of SASA and the president of the Kolarac Foundation), whereby one lecture was held in the morning around 10 a.m., and the second in the afternoon around 4 p.m. Various lectures influenced the hostages not to think about their unenviable position. Conversations after lectures helped to break monotony in prison. These lectures enriched knowledge and cheered the spirit. According to the preserved diary of Vladislav Pavlović, pre-war official

at the Ministry of Social Policy and Public Health, the list of topics included a lecture by Dr. Milutin Nešković, a university professor entitled “Man in continuous space”. By the beginning of January 1942, when Vladislav Pavlović was released from the camp, 36 lecturers spoke on 68 topics (14) (Figure 9).



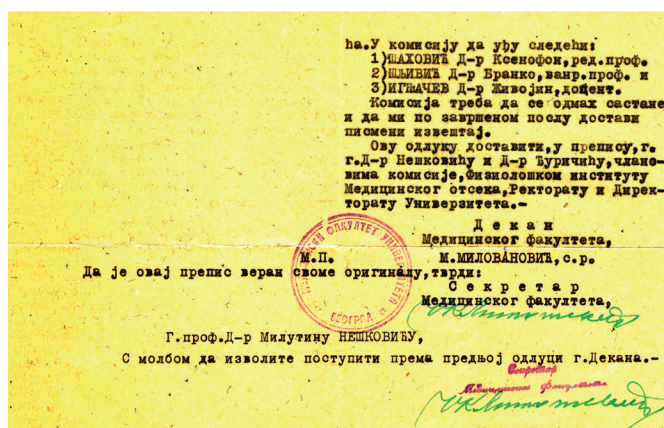
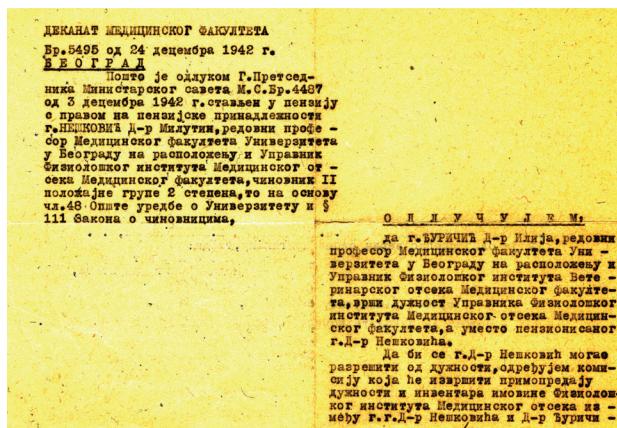
**Figure 9.** A drawing of a camp inmate Professor Milutin Nešković, made on kraft paper from a package for camp inmates, during his imprisonment at the Banjica camp (drawn by camp inmate Risto Stijović on December 4, 1941, later an academician of SASA, a famous Yugoslav and Montenegrin sculptor) (a copy of the drawing obtained thanks to the courtesy of Nenad and Nikola Nešković)

After leaving the Banjica camp, Professor Milutin Nešković soon assumed the position of the director of the Physiology Institute. A little later, the typhus epidemic (spotted fever), which broke out in that period, required the engagement of a larger number of medical workers. That is why the Dean's Office received a request from the Institute to hire Prof. Milutin Nešković, with a certain number of collaborators (Act of March 9, 1942, Administrative Protocol 45/42). A student Đordina Škerović

was in this group of collaborators, who stopped studying medicine during the war, but when she graduated from the faculty after the end of the Second World War, Professor Nešković immediately admitted her to the Institute, where she, after his retirement, as his devoted student and follower, managed the Institute from 1964-1985, when she retired.

## EARLY RETIREMENT AND REMOVAL FROM THE FACULTY

As he continued with showing disagreement and resistance during 1942, by the decision of the President of the Ministerial Council M.S. No. 4487 from December 3, 1942 he was suddenly retired, and the Dean of the Faculty of Medicine, and by decision No. 5495 from December 24, 24 1942 it was decided that Prof. M. Milovanović would replace Prof. Nešković, and as a new director Prof. Ilija Đuričić was appointed, who was also supposed to handle duties and inventory (Figure 10). As it seems, it did not go smoothly, as in a short period of time the duty of temporary director of the Institute was given to Prof. Ksenofon Šahović (December 31, 1942), and as soon as on January 31, 1943 Prof. Nešković was relieved of his duties not only as the director of the Physiology Institute, but also of his title of Full Professor (author's note: At the dean's request on 23 November 1942, the Institute sent the requested report on the scientific research work of Prof. Milutin Nešković). On February 4, 1943 the position of the director of the Institute was taken over by Prof. Ilija Đuričić, a professor of Physiology at the Faculty of Veterinary Medicine. Prof. Dr. Milutin Nešković refused to receive the pension that was given then during the entire war period. Even though the police returned his personal document on February 12, 1943 (Administrative Protocol 22/1943), Prof. Nešković was out of the University. In that period, Prof. Nešković spent a year as the head of the central lazarett for refugee children. However, after the liberation, by the decision of the Ministry of Education dated June 26, 1945, V No. 7570, Prof.



**Figure 10.** Copy of the document on the retirement and dismissal of Prof. Milutin Nešković and the appointment of Prof. Ilija Đuričić to the position of the director of the Institute during the Second World War was obtained thanks to the courtesy of Nenad and Nikola Nešković

Milutin Nešković was accepted to the Faculty of Medicine, and as soon as June 28, 1945, he was appointed to attend the ceremony of the Faculty of Medicine in Zagreb.

Immediately after returning to the Faculty of Medicine in Belgrade, Prof. Nešković worked on the reconstruction of the Institute of Physiology and the Faculty of Medicine, but also in other fields - he was the first post-war commissioner for public health in the city of Belgrade. In 1949, the reconstruction of the destroyed part of the building was completed, when the institute moved to new premises with a modern amphitheater, training rooms and equipment, a preparatory laboratory and an operating room. In the basement and on the first floor of the building there were scientific research laboratories, the office of the Institute and the library. In the preface to his work "Practical Teaching in Physiology" from 1950, Professor Nešković said (quote): "Earlier, I expressed the opinion (author's note: Practical Teaching in Physiology, second edition, 1941) that practical work in physiology has two main goals: to facilitate understanding and learning of facts presented in theoretical lectures and to educate medical students in a physiological way of reasoning (in the spirit of understanding) that a good doctor can only be one who thinks physiologically. Today, this opinion of mine, remaining essentially the same, has been given a fuller expression. The opinion that teaching in physiology, and especially practical teaching, should also fulfill this higher task: to nurture in future doctors with a physiological way of reasoning about the facts that will be played out in front of them, should be completed with a concrete statement: that the task of medical teaching (including physiology) is to build a new type of doctor, a medical practitioner, who thinks physiologically when faced with professional problems, and works in the social community as a socially aware individual" (15).

## LIFE AND CREATIVITY AFTER WORLD WAR II

Shortly after the end of the Second World War and the great efforts to restore work at the Faculty of Medicine in Belgrade and the Institute of Physiology, personnel and ideological problems arose in addition to material problems. Some professors were accused of "espionage work for foreign services" (D. Borić, Svetislav Stefanović, Milivoj Genčić), membership in freemasons, "Serbian chauvinism", getting rich through private practice, cooperation with Germans and chetniks (A. Kostić, S Barjaktarović, D. Borić, Aćim Marković and others), sabotage, immoral behavior (A. Kostić, among other things, was accused of dealing with "pornographic writings" and "weak criteria for student lovers") (Note: of Đorđe Stanković's private collection, UDBA reports for NRS by faculties, September 7, 1948). After the conflict with the Soviet Union in 1948, information about the attitude towards the conflict and the Resolution of the Informburo was

especially highlighted in the features, reports, and analyses. At the time, the supervision of the Communist Party and State Security over professors was even more intensified, as well as the activity of individuals who openly or anonymously provided party or state authorities with data on the behavior of professors during the war, their attitude towards the Informburo, etc. The competent authorities checked the submitted data in detail, interrogated the accused, and controlled the situation at the University in order to prevent the "potential danger from the information bureau, but also from the "reactionary" actions of individuals and groups (note: AS, MNK NRS, f. 17, Interrogation in a State Security of Milutin Nešković and Marko Anaf, teachers at the Faculty of Medicine). In addition, for personnel advancement, in addition to moral and political suitability, research papers were also required, which of course could not be in the appropriate number and quality, because the horrors of the war and the Nazi camps had just passed (16). In this sense, the request dated April 16, 1952 could also be interpreted. The dean Prof. Vladimir Spužić demanded from Prof. Milutin Nešković a "survey sheet asking for a list of doctors' research works in the post-war period".

Furthermore, Professor Miodrag Cvetković says: "Professor Milutin Nešković was the founder and the director of the Balneoclimatology Institute of the Faculty of Medicine in Belgrade, and the founder and director of the Biochemistry Institute of the Faculty of Medicine in Belgrade (quote from the records of Prof. Đordina Škerović-Mijušković: "It is a long time to teach at the Institute included the combined contents of physiology and biochemistry. Later, due to the constant development of biomedical science and an increase in the volume of materials from both subjects, there was a separation, that is, the formation of the Institute of Biochemistry of the Faculty of Medicine in 1959"). Professor Nešković wrote several textbooks and monographs in the field of physiology and biochemistry. He wrote the Physiology Practicum with Professor Ilija Đuričić, and then he wrote the Supplement to Physiology, Practical Teaching in Physiology, the monograph Ferments, etc. He published numerous research papers in the field of physiology and biochemistry, for which he received the 7<sup>th</sup> July Award in 1962, and in 1971 he received an honorary doctorate from the University of Belgrade (Note: According to his son Nenad Nešković, he was one of the first professors of physiology at the newly established Faculty of Medicine in Tunisia over the period 1965-1967, and at that time he lived with his wife in Carthage.). He is the holder of domestic and foreign decorations, among others he is the holder of the Royal Order of the Yugoslav Crown in 1936 and the Legion of Honor, which the French President awarded him in 1958" (Figure 11). In the post-war period, Prof. Nešković was a vice dean in 1954/55 and the dean twice, in 1955/56 and 1956/57. He is one of the founders and the president of the Yugoslav Society of Physiologists (later





**Figure 11.** Order of the Legion of Honor awarded to Prof. Milutin Nešković by the President of the Republic of France (courtesy of Nenad and Nikola Nešković)

Yugoslav Physiological Society), and in 1961, he was the founder and the president of the section for Serbia of the Yugoslav Society of Physiologists (Society of Physiologists of the Republic of Serbia, later Serbian Physiological Society). For many years, the department was a nursery of staff not only in the clinics (teaching bases) of our school, but also in numerous faculties of the former Yugoslavia (Figure 12, Figure 13). For several years, Professor Milutin Nešković taught Physiology at the Faculty of Medicine in Skopje and Biochemistry at the Faculty of Medicine in Niš, he participated and assisted at the newly founded medical faculties in Novi Sad and Sarajevo. According to the records of Prof. Julijana Vojvodić (quote): “During the dean’s term in 1956/57, Professor Nešković, on the initiative of the Faculty of Medicine’s Student As-

sociation, allowed converting several rooms into reading rooms for students in the facilities of the Faculty of Medicine. As a sign of respect and appreciation, the Faculty Board presented Professor Nešković with a hunting gun after the dean’s term expired.”

According to the memories of his grandson Nikola Nešković, grandfather Milutin was interested in everything - books, poetry, paintings, movies; he went to the cinema, hung out with fellow artists, wrote poems and essays. Professor Trajanović, the builder of the incredible bridge on the Đurđevića Tara, used to come to his place on Slava (St. Michael the Archangel). His radio was always on. When his grandson Nikola, who worked for many years at Radio Belgrade, edited and hosted the most popular rock and roll radio show “Friend of the Stars”, which the whole country listened to at the time, his grandfather’s question was: “Do you think only young people listen to this?” He went to football matches too. On one occasion, when his grandson Nikola told him that he had had lunch with Moša Marjanović (because he used to hang out with his daughter) (author’s note: Blagoje Marjanović Moša, famous Yugoslav football player), his grandfather Milutin told him to say hello to Moša, even though he personally preferred Tirke (author’s note: The famous football player Aleksandar Tirnanić Tirke). Tirke and Dr. Mihailo Andrejević Andrejka (author’s note: Serbian doctor, football player and prominent football worker) were regular guests of his Slava. Grandson Nikola remembers that his grandfather Milutin took him to the match between veterans of Serbia and Croatia in 1954 at the Yugoslav Army stadium, and he also told him that he was present at the old Belgrade fair, when in 1937 televi-



**Figure 12.** The staff of Prof. Dr. Milutin Nešković, the director of the Institute of Physiology. In the first row, from left to right, seated: Miodrag Cvetković, Mihailo Mojović, Đordina Škerović, Milutin Nešković, Radmila Šegović, Dragoljub Petković, Mileva Ivić and Veselinka Šušić. In the second row, first from the left, Julijana Vojvodić; in the middle, Đorđe Popović Erak in a dark suit; in the same row, first on the right, Dragica Matejević Stranjanac (behind Mileva Ivić) (photographed by Dr. Nenad Nešković in 1961)

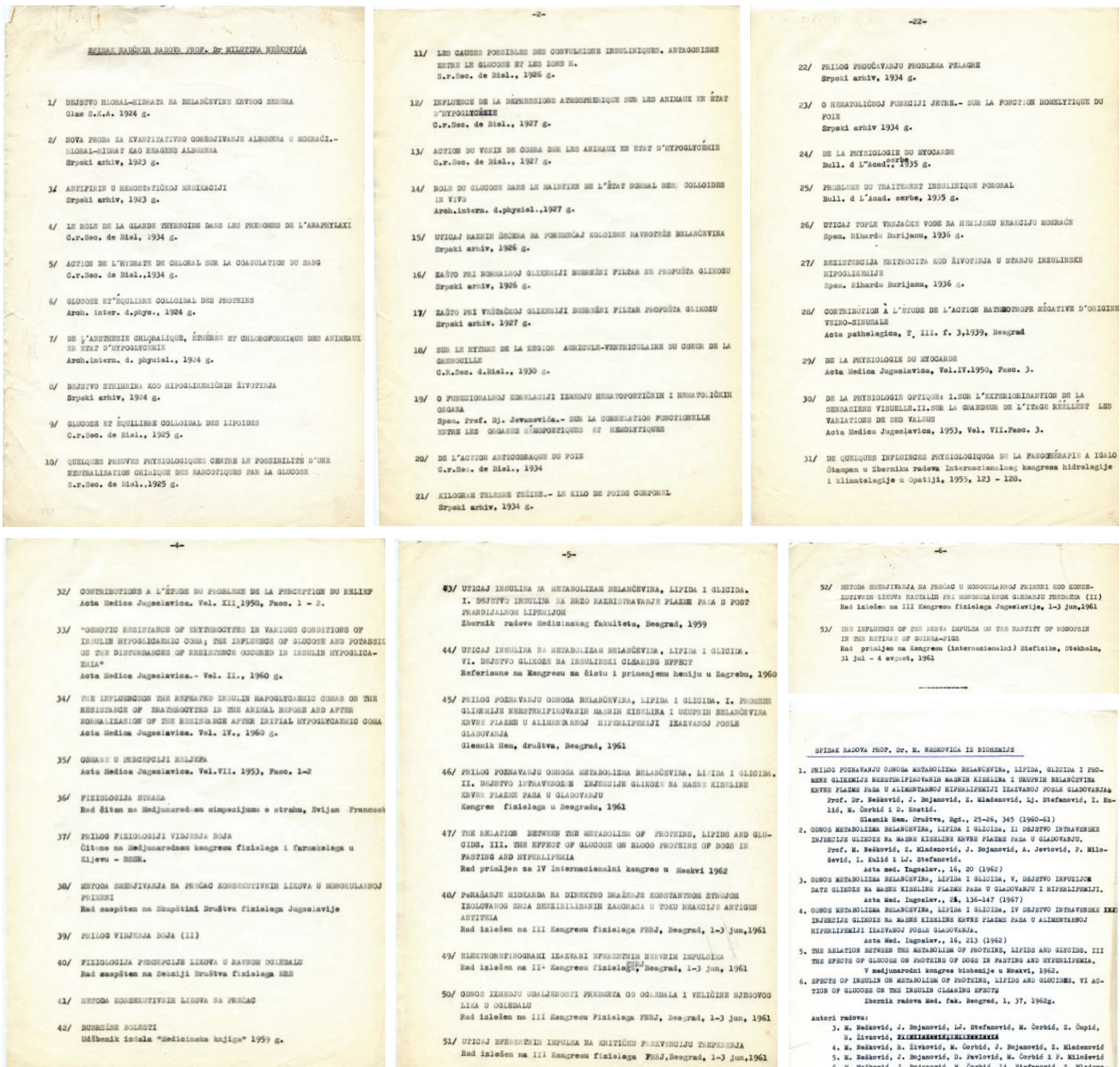


Figure 13. The list of publications by Professor Milutin Nešković in the scientific fields of physiology and biochemistry (in Serbian)

sion was presented for the first time in southern Europe.

Professor Dr. Milutin Nešković, one of the newly founded Faculty of Medicine, died on August 13, 1980, in Belgrade. He was buried in the Alley of Meritorious Citizens in Belgrade. On this occasion, the newspaper “Politika” published the article entitled “In Memoriam Prof. Milutin Nešković” on August 15, 1980. He was married and had two sons: Prof. Predrag Nešković, a professor of Microbiology at the Faculty of Dentistry, and Prof. Nenad Nešković, a former assistant at the Biochemistry Institute of the Faculty of Medicine in Belgrade, later a professor of Biochemistry, who lives in Strasbourg, France. Grandson Nikola Nešković, who helped me tremendously in the preparation of this text, is the son of Professor Predrag Nešković.

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- Đuričić I, Nešković M. Fiziološki praktikum (sa predgovorom Dr Riharda Burijana prof. Univ.). Izd. Izdavačko i knjižarsko preduzeće Geca Kon A.D., Beograd, 1941. COBISS.SR-ID – 101285376
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# POČECI RADA I OBNOVA INSTITUTA ZA MEDICINSKU FIZIOLOGIJU MEDICINSKOG FAKULTETA UNIVERZITETA U BEOGRADU KROZ STVARALAŠTVO I KARAKTER OBNOVITELJA PROFESORA MILUTINA NEŠKOVIĆA

Dragan Djurić<sup>1</sup>

## Sažetak

Sa protokom vremena i u nedostatku kvalitetne arhivske građe, kako na Institutu, tako i na Medicinskom fakultetu, a imajući u vidu „kulturu sećanja“, rad na ovom tekstu koji predstavlja nastavak rada na publikovanoj monografiji povodom obeležavanja 100 godina od osnivanja Instituta za medicinsku fiziologiju Medicinskog fakulteta Univerziteta u Beogradu i započinjanja nastave, bio je izuzetno izazovan poduhvat. Tekstovi koje su kolege nastavnici ranije objavili u izdanjima fakulteta povodom raznih jubileja, ali i u časopisu „Srpski arhiv“, značajno su pomogli realizaciji ovog poduhvata. Posebno treba istaći spremnost i ljubavnost u pružanju značajnog istoriografskog materijala, dokumenata i fotografija, članova porodica profesora Riharda Burijana iz SAD (Jim

Huntington, Richard M. Burian), Milutina Neškovića iz Francuske i Beograda (Nenad i Nikola Nešković) i Božidara Nikolića (Emilija Nikolić Đorić), a zatim i mnogobrojnih kolega iz naše zemlje, uključujući i Vojislava Vokija Kostića, sina čuvenih profesora Aleksandra Đ. Kostića i Smilje Joksić-Kostić. Svima dugujem veliku zahvalnost, jer su omogućili da se ovi važni podaci sistematizuju. Ipak, svestan sam da ovo neće biti potpun tekst, koji se pre svega bavio počecima rada i obnovom porušenog Instituta, kao i jednim izuzetnim profesorom i patriotom, prof. dr Milutinom Neškovićem, obnoviteljem porušenog Instituta posle završetka Drugog svetskog rata, čiji lik i delo, kao i čvrstina karaktera, mogu biti uzor budućim generacijama nastavnika i saradnika.

**Cljučne reči:** Institut za medicinsku fiziologiju, Medicinski fakultet, Milutin Nešković, Rihard Burijan, Univerzitet u Beogradu

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**REVIEW**

# The Institute of Histology and Embryology in the most modern building of the Faculty of Medicine in Belgrade between two worlds wars

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**Summary**

The Institute of Histology and Embryology was founded in 1921, but it was moved into its own building a few years later, in 1927. The project of the building was done by the architect Svetozar Jovanović, and the pedimental sculpture in the gable of the building was done by the academic sculptor Živojin Lukić. The building housed two institutes: the Institute of Physiology and the Institute of Histology. Each of the institutes owned one wing, and they shared the central part of the building, which also contained an amphitheater. The building was equipped with the most modern technical devices and provided excellent conditions for scientific work and teaching. In addition, within the Institute of Histology there were the Photography Department, the Terminology Department, the central catalog of the books and journals of the Faculty of Medicine, and a museum was planned as well. The largest part of the building was destroyed in the German bombing on April 6, 1941. After liberation, according to the project of the architect Milan Sekulić, the reconstruction of the central part and the construction of new wings of the building were carried out.

**Keywords:** Faculty of Medicine in Belgrade, Institute of Histology and Embryology, Aleksandar Đ. Kostić

## ESTABLISHMENT, THE FIRST PROFESSOR OF HISTOLOGY

The Institute of Histology and Embryology “Prof. dr Aleksandar Đ. Kostić” was founded on November 21, 1921. On that day, Dr. Aleksandar Kostić was appointed a part-time lecturer of Normal Histology, by the minister of education. At that time, Kostić was a young doctor from Belgrade who had completed his studies of medicine in France and who was working as an assistant to Prof. Pol Bouin at the Faculty of Medicine in Strasbourg (1,2).

Shortly thereafter, he began working on the first collection of microscope specimens for his future students in Belgrade. Prof. Bouin, his professor, mentor, and friend, was a huge help and support in his work. It is interesting to mention that Prof. Kostić once wrote how Prof. Bue made it possible to get “human material” in a “rather exceptional way”. He took human tissue from the body of a person convicted to death by guillotine because of having robbed the post office (3). “Human material” was extremely valuable then, as it is today, due to the fact that some structural characteristics in humans cannot be seen in the material obtained from laboratory animals. By the end of December 1921, a collection of between 2000 and 3000 microscope specimens was completed. It was the first and very important asset of the Institute of Histology. In January 1922, Kostić returned to Belgrade with his wife and colleague Dr. Smilja Kostić Joksić (1,2), who became the first teaching assistant at the Institute of Histology and Embryology (1,2,4). In 1924, she was hired as an assistant at the newly opened Pediatric Hospital, where she later advanced to the title of associate professor.

## THE FIRST PREMISES OF THE INSTITUTE

In January 1922, the Institute was primarily accommodated in two rooms on the ground floor of the administration building of the Main Military Hospital (today, the administration building of the University Clinical Center of Serbia). Furniture was borrowed from the Danube Hospital Company whereas microscopes were taken from the Institute of Physiology and the Institute of Pathology. The first caretaker, Dimitrije Veličković, was employed on March 1<sup>st</sup> 1922 and student Momčilo Milojević was hired as the first demonstrator. In less than two months, everything was ready for classes to begin (1,5,6).

On March 6, 1922, Prof. Kostić held the introductory lecture for his colleagues, and the next day for students as well. That is why March 7 is considered the day when histology began to be taught at the Faculty of Medicine in Belgrade. (6). The Institute’s inventory grew over time, first with a blackboard and then with a table for demonstration microscopes. The 35 Zeiss microscopes ordered while Kostić had still been in Strasbourg finally arrived. In spite of all the efforts, enthusiasm and teaching equip-

ment, classes took place in extremely unsuitable conditions, and because of this, as soon as November the same year, the Institute was moved to the new building of the University, to the premises intended for the Physics Institute of the Faculty of Philosophy. Apart from improved teaching conditions, there were also favorable conditions for establishing a laboratory for the preparation of microscope specimens (7). During the time spent at University building, Kostić wrote and prepared the first book on practical laboratory work „Osnovi histološke tehnike” (“The basics of the histological technique”), published in 1923. It was his first printed textbook, which had two more editions: 1948 and 1953. The second book he prepared for the press was „Rečnik histoloških izraza” (“Dictionary of histological terms”), published in 1924 (1). The first exam in histology was held at the end of the winter semester, and the chair of the exam committee was Prof. Đorđe Joannović, the dean of the Faculty of Medicine at the time (7,8).

In January 1924, the building of the Nursing School of the Red Cross Society became the Institute’s new home. The entire third floor, as well as the attic of the School, were available to the staff and working conditions in the school building were much better (7,8).

For the first time, there was enough space at the Institute for organizing a library. In addition to the library, in 1924, Prof. Kostić also organized the work of the Photography Department. „Mikrofotografski atlas normalne histologije” (“Microphotographic Atlas of Normal Histology”), which was published the very next year, in 1925, was the first successful result of this department. In addition, that same year Aleksandar Šafranski, a photographer, started working at the Photography department. He was a Russian military and aviation photographer who came into the Yugoslav Air Force in August 1922. Prof. Kostić also founded the Belgrade Photo Club in 1928, and photographer Aleksandar Šafranski was one of its prominent members (6).

The Institute stayed in the building of the Nursing School of the Red Cross Society until February 1927, when it was moved to its own building (6,7).

## PROJECTS AND CONSTRUCTION OF THE INSTITUTE’S BUILDING

In 1921, the properties at the corner of Resavska and Višegradska Streets were purchased for the Faculty, so the first condition for constructing a building for two institutes (Institute of Physiology and Institute of Histology) was fulfilled and Prof. Richard Burian, the founder of the Institute of Physiology, started working on the preparation of the building’s project in early 1921. Six plans for that project have been preserved in the Archives of Yugoslavia, but it is unknown who drew them. The complex resembled the letter C and it included a central building with

an amphitheater and two wings. As the left wing, it was planned to use the existing building of the Department for patients with tuberculosis, built in 1912 according to the project of the first Serbin woman architect Jelisaveta Načić. In 1920, the Department was given to Institute of Physiology by the Minister of National Health. The second wing, intended for the Institute of Histology, as well as the central building, were to be built and connected to the existing object. The building was designed in an academic style, with the application of certain details characteristic of romanticism in architecture (6,9).

Although that project was rejected, the fundamental idea – constructing a building in the shape of the letter C and incorporating the existing structure as one wing – was used to develop a new project that was given to architect Svetozar Jovanović at the end of the year. Jovanović completed the project in January 1922, but it took more than two years for all the administrative work to be finished (determination and approval of funds from all instances, announcement of tenders, and selection of contractors). Svetozar Jovanović was chosen as the supervising architect, “because he is familiar with the site and the current structure”. Namely, Jovanović had been previously engaged in the project of reconstruction of the building of the Department for patients with tuberculosis, into which the Institute of Physiology temporarily moved in 1922. In the process of constructing the new building, Jovanović’s associate was Anatolij Hmara (Анатолий Ильич Хмара), employed as an architect-engineer in the Construction Department of the Municipality of Belgrade (6,9,10).

The construction of the building began on July 14, 1924, and it was scheduled to be finished on September 1, 1925. However, as is often the case, the deadline had to be extended for several reasons. As soon as the summer of 1924, it became clear that the building of the Department for patients with tuberculosis would not be possible to use because, despite the reconstruction, it was destabilized, with cracked walls and a tendency to fall down. At the conference of professors of the Faculty of Medicine held on September 7, 1924, a decision was made to demolish the largest part of that Department and build a new building in its place. Professors Burijan and Kostić agreed on the new organizational plan for the institutes. The right wing, which could have been completed earlier, would belong to the Institute of Physiology, and the left wing (on the site of the demolished building) was intended for the Institute of Histology. By the way, the construction was delayed due to unexpected work and waiting for funding that had not been originally planned. According to some data, the contract estimates were not complete and accurate; the construction was started too soon, without enough preparation, so changes were made during construction - “demolition, rebuilding and additions at the request of the professors because they wanted to introduce all the latest modern designs into the insti-

tute so that it would correspond to the requirements of science” (9,11).

A clearer picture is given by the document in which these works are listed with the necessary explanations: since it was clay soil, it was necessary to make stronger foundations, especially since the Faculty wanted to have the possibility to add another floor in the future; the gallery in the amphitheater, which had not been originally planned, was built for two reasons: to increase the number of seats and to lower the amphitheater’s height to improve the acoustics; the amphitheater’s seats, which were initially planned in straight rows, were arranged in the shape of an arch so that students could better see experiments and projections; an additional concrete booth was built in the amphitheater for the projection apparatus donated by the Rockefeller Foundation; the carpentry in the entire building was painted white, and one part was enameled “due to the need for absolute cleanliness”; the windows were adapted to the needs of microscopy (their height was adjusted to the height of the tables) and supplied with roller blinds; the floors were “adapted to the purpose” (four types of floor coverings were used in the building - concrete, terrazzo, xylolite for laboratories and parquet); the basement premises were expanded to house the gas installation and the department for burning waste and carcasses of experimental animals; around the building there was a communication for freight cars, and between the two wings there was a concrete pool for frogs. Among the unexpected costs was the amphitheater’s glass-iron roof, which, despite having been planned from the start, “fell out of the contract by mistake.” Additional funds were once again approved, and the total cost of building and equipping the building was 14,968,541.37 dinars, which was more than twice as much as planned. Based on the available documentation, it can be concluded that professors Burijan and Kostić, who worked closely with the architect Jovanović, paid attention to every detail during the arrangement and furnishing of the premises (6,9).

Professor Kostić documented the construction process of the central building and the wing intended for the Institute of Histology with a series of photographs that are kept in the Institute’s archives. Today, they are valuable testimonies of the construction process, the technical capabilities used during construction and the dynamics of the works.

The building was completed on December 29, 1927. It was a monumental building in the academic style, which was dominant in the architecture of public buildings at the time. The central part had a prominent entrance with Corinthian columns and a pediment decorated with a sculptural composition made by the academic sculptor Živojin Lukić. In the middle was the figure of Hygia, and on each side of it there were three figures. A standing female figure stood to Hygia’s right, and next to it there was a kneeling male figure with a child clinging to his body.

A standing male figure with his back turned stood to Hygia's left, and a seated female figure with a child in her lap sat next to it. Adult figures were linked together by vessels that they added to each other. The wings of the building were decorated with balustrades and cornices. Although the space in the back of the building served no public purpose, the facades on all four sides were treated equally. Compared to the building of the Institute of Pathology, completed in 1926, which was also designed by Jovanović, this building had a more luxurious external appearance. Owing to the carefully planned organization of space and excellent equipment, the institutes were provided with the most modern conditions for both scientific work and teaching (6,9,12).

### ORGANIZATION OF COMMON SPACE IN THE NEWLY BUILT BUILDING OF THE INSTITUTE OF HISTOLOGY AND PHYSIOLOGY

As it was said, the institutes had one wing each, but each one had some space in the basement, in the central building, on the ground floor, and on the first floor. The directors of the institute, Burić and Kostić, each had a large, luxurious apartment in their own wing, and the building was also home to ushers/cleaners, laboratory assistants, custodians, and photographers. In the central building, there were rooms with various facilities, e.g. battery room, a room for an internal telephone switchboard, a water distilling department, a gas central, a laundry room, an ironing room, a room for wood, ventilation, and air heating plants. On the second floor, which existed only in the central part of the building, there was a corridor for the gallery of the amphitheater and the apartment of the caretaker of the building. In accordance with the regulations of the time, there was a fire extinguishing installation in the building (7,8).

According to Professor Kostić, the amphitheater was the largest in Belgrade and the most modern in Yugoslavia at the time. There were 312 seats in semicircular rows, and another 200 listeners could be standing in the gallery, at the level of the second floor. Such a large capacity was planned with the idea that in addition to teaching, it will be utilized for public lectures, gatherings, and film screenings. The width of the amphitheater is 20 m, and the height above the presentation desk is 13 m. The project did not include windows, but a specifically designed ceiling with a glass skylight measuring 9 x 7.5 m and a horizontal blackout curtain that was driven by an electric motor. At the level of the ceiling, there were also openings of the ventilation system, which, if necessary, conducted heated air. The installations and the curtain mechanism have been preserved to this day, but have not been used for decades. The presentation desk, which is still in use, has impressive dimensions, so there is enough space on it to carry out experiments. Behind the presentation desk

there were three glass panels driven by electric motors, then a paraffined screen separating the projection chamber from the amphitheater, and finally, an airtight projection screen for vivisection projections (5,6,9).

The projection chamber was equipped with an epidiascope for microprojections and a galvanometer for demonstrating bio- and thermoelectric phenomena. The vivisection chamber, which no longer exists, was on the upper platform of the amphitheater. It had the shape of a semicircular tower, four meters wide and three meters high, and it was equipped with a Primard epidiascope (*H. Primard, Paris*), specially designed for the projection of surgical procedures. The assembly and partial modification of the device were carried out by workers from the Mechanical Department of the Institute of Physiology (5,7).

### ORGANIZATION OF THE WORKSPACE AND WORKING CONDITIONS AT THE INSTITUTE OF HISTOLOGY

In the basement of the building, under the amphitheatre, there was a department for keeping and working with animals, i.e. a vivarium. Exceptional attention was paid to this area during the design and furnishing of the building. The vivarium was organized into several rooms: one was used for keeping and breeding animals, another for experimental animals, and the third for operations. The cages were built into reinforced concrete walls, with iron bars, and at the same time they could be cleaned and disinfected very easily. The capacity of the vivarium was for more than 1500 small animals. All animals were systematically marked with special plates on their ears. In addition to this labelling, there was also more detailed data for each experimental animal (1,5,8).

In the basement of the histology wing of the building, there were rooms for storing reagents, various equipment, and glassware, a workshop with all the necessary tools and a laundry room. In that part of the building, there were also two rooms for employees (5,8).

On the ground floor, in the central part of the building, directly next to the amphitheater, there were two large laboratories measuring 11 x 5 m. A corridor led to them, with cupboards containing instruments and laboratory glassware. The laboratories were designed for laboratory assistants, students, and doctors. They were divided into four compartments each by oak walls for isolation and undisturbed work. There was a spot for washing clothing next to the laboratories, as well as eight huge sinks that students utilized after workouts (5,8).

The greatest space on the ground floor of the side wing was occupied by a large student practice room spanning 21 x 9 m, with 90 workplaces. The long tables were oriented toward the windows, and each consecutive table was raised by 20 cm in respect to the one before it, allowing light to reach all microscopes. The conceptual solu-



tion for making the tables was given by Prof. Kostić. Each workplace was equipped with a microscope and a lamp, and two neighboring workplaces each shared a sink and a battery for staining the preparations. From the initial 35 microscopes that the Institute had had before moving to the new building, the number of 90 microscopes was reached due to war reparations. The student practice room was named Paul Buen, in honor of a recognized histologist, teacher and a great friend of Prof. Kostić. After the introductory classes, slides were projected “par transparence” from the chamber located next to the practice room. The darkening of such a large room with a large number of windows was ensured by simultaneously lowering the curtains using an electric motor. In addition to slide projections during introductory classes, learning was facilitated by a large number of posters presenting microphotographs of histological preparations, which covered the walls of the practice room, but also almost all other rooms at the Institute. By the way, the total number of histological preparations for the needs of regular exercises has increased over time to the number of several thousand. In the extension of the practice room, there was a laboratory for the research work of assistants (5,6,8).

Opposite the practice room there were Terminology Seminar, director’s office and laboratory, tissue culture laboratory, office, library and reading room. Immediately after moving in, impressive wood furniture was custom-made for the library, with floor-to-ceiling shelves and stairs that could be moved along the shelves. By 1935, the library included over 4.000 books, journals, and offprints largely in German and French. At the Institute there was also the central catalog of books and journals from all of the Faculty of Medicine’s institutions. In addition to the library, there was a reading room for students with a small library of histology textbooks in different languages, where exams were held during the exam periods (1,7,8).

## PHOTOGRAPHY DEPARTMENT

The Photography Department was located on the first floor of the central building, next to the amphitheater, and it consisted of six rooms and three darkrooms.

At the very entrance to the Department, there was a large corridor where an *Ascania* microcinematography camera with an accelerating device was and it allowed 200 shots per second (5,6).

On the opposite side of the corridor there was a studio, completely adapted to taking photos in both daylight and artificial light. Sufficient daylight was provided by a large window with opaque glass and blue mobile curtains, while artificial light was provided by strong reflectors (5,12).

Another important room in the Department was a room for chromophotography i.e. for making color photographs,

positives and slides. Color positives were made according to the *Jos-pe* system, and today at the Institute there are 43 color slides that have been saved. They are unique and very rare color slides not only in our country but in the world as well. Another room equipped with a large *Leitz Uma* microphotographic camera was in the Photography Department for making photomicrographs (5,9,13).

Next to two dark modern chambers was a room for magnifying photos equipped with a *Furor II* camera. The equipment for copying cinematographic films was also installed there, as well as the device for developing and drying films. Next to the room for magnifying photos there was a room for washing negatives and positives, and there were strings with clips for drying positives (5,6,13).

Kostić was well aware of the importance of the photography department, and that’s why he insisted on its modern equipment. He established cooperation with colleagues from almost fifty institutions. It is very important to emphasize that the first microphotographs not only in Belgrade, but in Yugoslavia, were made at this Department. In addition to photography, the Department enabled many University teachers to learn photography and it was a model for many later established photography laboratories at the University in organizing space and equipment (7,9).

In addition to the Photography Department, a laboratory for embryology and teratology was located on the first floor of the wing, and next to it, a room measuring 15 x 8 m was intended for the museum. By 1935, a large number of macroscopic preparations, embryos and fetuses, were collected and prepared, but the museum was not established. The museum room was given to the Institute of Chemistry for use. On the same floor there was the office of Prof. Kostić and the apartment of the Kostić family (5,7,9).

The modern building of the two institutes was the pride of the Faculty of Medicine when it was completed (**Figure 1**), but in order for it to remain so, greater investments were occasionally required in addition to routine upkeep. The last extensive reconstruction was undertaken to repair the roof due to problems with leakage. The works, which lasted for almost a month, were completed on April 5, 1941. The next day, on April 6, during the German bombing of Belgrade, the building was hit, although it had a prominent Red Cross sign on the roof. Both of its wings were almost completely destroyed, while the central part was significantly damaged (6,9).

## REBUILDING AND RECONSTRUCTION

After the liberation, a decision was made to rebuild both wings of the building and reconstruct its central part. The project was entrusted to the well-known architect Milan Sekulić. The works, which began on July 22, 1946 and completed at the end of 1948, were carried out by the



**Figure 1.** Building of the Institute of Physiology and Histology in 1927 (Archive of the Institute of Histology and Embryology "Prof. dr Aleksandar Đ. Kostić", digitalized in SASA Audiovisual Archives and Digitalization Center)



**Figure 2.** Construction and reconstruction of the building of the Institute of Physiology and Histology (Archives of Yugoslavia, Committee for the Protection of Public Health / Φ-31 / United Yugoslav Relief Fund of America, Extracts from Field Trip Report of Phillip E. Nelbach, Executive Director, May 13, 1948)

Construction Company *Neimar*, under the supervision of architect Đ. Grosović. The management of the Faculty wanted to get more space in the building in order to accommodate several institutes, and therefore the central part was expanded, wings of larger dimensions than the

previous ones were built, and the whole building got another floor (6,9). It was an impressive construction in the spirit of the modern architecture of that era. The building still houses the Institute of Histology and Embryology, which today bears the name of its founder (**Figure 2**).

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## INSTITUT ZA HISTOLOGIJU I EMBRIOLOGIJU U NAJMODERNIJOJ ZGRADI MEDICINSKOG FAKULTETA U BEOGRADU IZMEĐU DVA SVETSKA RATA

Nela Puškaš<sup>1</sup>

### Sažetak

Institut za histologiju i embriologiju je osnovan 1921. godine, ali se tek nekoliko godina kasnije, 1927. godine, uselio u svoju namenski projektovanu zgradu. Projekat je izradio arhitekta Svetozar Jovanović, a figuralnu kompoziciju u zabatu zgrade akademski vajar Živojin Lukić. U zgradi su bila smeštena dva instituta: Institut za fiziologiju i Institut za histologiju. Svaki od instituta je imao po jedno krilo, a delili su centralni deo zgrade u kome je bio i amfiteatar. Zgrada je bila opremljena najsavremenijim

tehničkim uređajima i pružala je odlične uslove za naučni rad i nastavu. Osim toga, u okviru Instituta za histologiju su organizovani Fotografsko odeljenje, Terminološki seminar, centralni katalog knjiga i časopisa Medicinskog fakulteta, a bio je planiran i muzej. Najveći deo zgrade stradao je u nemačkom bombardovanju 6. aprila 1941. godine. Posle oslobođenja, izvršena je rekonstrukcija centralnog dela i izgradnja novih krila zgrade prema projektu arhitekta Milana Sekulovića.

**Ključne reči:** Medicinski fakultet u Beogradu, Institut za histologiju i embriologiju, Aleksandar Đ. Kostić

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**REVIEW**



# A century of pulmonology in Serbia

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## Summary

The year 2022 marked 100 years of modern Serbian pulmonology and 90 years of the Clinic of Pulmonology, University Clinical Center of Serbia. This paper presents a concise history of the development of the Clinic, which includes the establishment of the clinic, its organizational and educational development, as well as its most prominent directors who made it all possible. Also, the current activities at the clinic and the current state of the employees are described. The aim of the paper is to show the development of the Clinic for Pulmonology, and thus to acknowledge its predecessors and contemporaries.

**Keywords:** pulmonology, history, Serbia

Professor Aleksandar Radosavljević is considered the founder of the Clinic for Pulmonology. Dr Radosavljević was born in 1877 in Budapest, and he finished primary and secondary school in Belgrade and Sremski Karlovci. He completed his medical studies in Vienna, as a student of Nobel laureate Julius Wagner. After graduating from Medical school, with the money he received from his uncle for graduation, doctor Radosavljević bought his first microscope, and in the analysis of his own sputum, he discovered *M.tuberculosis*. Therefore, he decided to further specialize in the field of internal medicine in Vienna and Graz, where he was also treated for his tuberculosis. The doctor spent the First World War as a physician in the Supreme Command of the Serbian Army, and then as the personal physician of Duke Radomir Putnik. During the withdrawal of the Serbian army through Albania and his stay in Corfu, Professor Radosavljević collaborated with the doctors of the Italian and French armies, and received recognition from the states of Italy and France. Upon the end of the First World War, on February 15, 1922 Dr Aleksandar Radosavljević was elected as an associate professor at the Faculty of Medicine in Belgrade, in the field of internal medicine, with a special focus on “diseases of the respiratory tract”. This day is considered the beginning of modern Serbian pulmonology. The following year, the III internal clinic was founded, headed by Professor Radosavljević, with a total of 30 beds, a laboratory and an X-ray room. Initially, the main pulmonary pathology was tuberculosis of the lungs, and due to the increasing number of patients, in 1926 the clinic was moved to the building of the General State Hospital, in the I and II internal departments. Simultaneously with the development of the clinic, Professor Radosavljević, together with his colleagues, participated in the founding of the Serbian Physiological Society as part of the Serbian Medical Society (1928) and the Yugoslav Physiological Society (1933), as well as in writing the paper “Lung Diseases”. In 1932, the clinic moved to a newly built building where it is still located. In the new building, the clinic was renamed into Hospital for Chest Patients and was a part of the General State Hospital in Belgrade, and as such, it had 145 wards distributed in 3 departments: chest internal, chest surgical and chest children’s department. The first manager of this hospital was Dr Ljubiša Ilić, under whose leadership the hospital became the best equipped hospital for the treatment of tuberculosis in the country. Also, in the same period, the first thoracic surgical interventions in Serbia were performed in the hospital. In 1947, the hospital merged with the Department of phthysiology of the III internal clinic and a large anti-tuberculosis center was founded and named the Phthysiology Clinic, headed by Professor Jevrem Nedeljković. Professor Nedeljković, student and assistant of Professor Radosavljević, formed the first specialized laboratory for the tuberculosis bacillus in Belgrade and introduced new

methods of treating tuberculosis using artificial pneumothorax. With successful implementation of systematic vaccination and radiography, on February 9, 1952 a decree was passed on the formation of the Institute for Tuberculosis of the National Republic of Serbia, headed by Assistant Professor Milić Grujić. Under the leadership of assistant professor Grujić, the institute was adapted, the number of beds increased from 180 to 305, the number of employees rose to 180, of which 33 were doctors. The institute also got a library, and new diagnostic and therapeutic methods began to be applied, and new departments were opened. With the further development of the Institute, in 1957 the Institute had one professor, four assistant professors, five teaching assistants, seven specialist phthysiologists, eighteen residents and one resident in bacteriology; due to further training needs, professional literature was obtained from other parts of Yugoslavia, France, England, the United States of America, Switzerland, Sweden, Germany, Italy, the Soviet Union and China. The education of doctors in the field of phthysiology, as well as nurses, X-ray technicians, laboratory assistants and medical assistants for the needs of the BSG service was also carried out. In addition to the education of staff and colleagues from other institutions, the number of beds in the Institute increased to 320, and new outpatient clinics, operating rooms, X-ray, spirometry, bronchoscopy and other offices were opened. Special importance was given to children suffering from tuberculosis, so visits by writers and singers were organized, and a school for children with two full-time teachers was open in 1955. In view of successful suppression of tuberculosis and the increase in the incidence and prevalence of other lung pathologies, in 1971 the Institute became the Institute for Tuberculosis and Lung Diseases of the Socialist Republic of Serbia, and in 1975 the Executive Council appointed Professor Manojlo Budisavljević as the Director of the Institute. In 1976, the Institute changed its name to the Institute for Lung Diseases and Tuberculosis of the SRS, and at that time it had 520 beds, 405 employees, of which 43 were doctors. In addition to clinical and surgical departments, the Institute also had an epidemiological and pathoanatomical service, as well as a specialized laboratory. Because of all the contributions made by the Institute, in 1977 this institution was awarded the Order of Merit for the People with a gold star by the then President of the Republic, Josip Broz Tito. In addition to the improvement of the Institute, Professor Budisavljević also participated in the establishment of the Clinical Center of the Faculty of Medicine in Belgrade in 1982, and the Institute itself became one of the 26 basic organizations of joint work. Due to development in the field of diagnostics, in 1987 the polyclinic of the Clinical Center was opened, where part of the Institute’s diagnostics also moved. The next significant step in the Institute’s development is the annexation of the Clinic for Pulmonology,



**Image 1.** Aleksandar Radosavljević (taken from SANU)

which was developed as a part of the Internal B Clinic, and professor Milivoje Stevanović was appointed as its director. In systematization, a significant shift was made by uniting the internist and pneumophthisiology services into a single pulmonology service; the unification lead to the formation of a unique teaching base of pulmonology

at the Department of Internal Medicine. Reconstruction of the Institute building was also carried out, an intensive pulmonary care unit, a day hospital for chemotherapy for patients with lung cancer and a service for physical therapy and rehabilitation of lung patients were established. In the further development of the Institute, in 2010, the Institute for Lung Diseases and Tuberculosis was divided into two special organizational units: the Clinic for Pulmonology and the Clinic for Thoracic Surgery. During the SARS CoV-2 pandemic, the Clinic for Pulmonology actively participated in the treatment of patients, both at the clinic itself and as support to other centers in Serbia. Due to its contribution to the development of the pulmonology school in Serbia and the centenary of its existence, in February 2022, the Clinic for Pulmonology was awarded the Order of Merit of the third degree, and the Director of the Clinic, assistant Mihailo Stjepanović, received a Gold Medal for outstanding merits and contribution to the implementation of activities to prevent the spread of the disease COVID-19.

Today, the Clinic for Pulmonology is a reference institution for tuberculosis and it participates in the creation and improvement of guidelines for prevention, diagnosis, treatment and rehabilitation in the field of tuberculosis. The Clinic itself consists of an inpatient and a polyclinic-diagnostic center and is a center for carrying out scientific research and teaching activities. As part of its work, the Clinic cooperates with other pulmonology centers in the country and the world. The institution consists of the polyclinic service, the department for the reception and treatment of urgent pulmonary conditions, specialist



**Image 2.** The staff of the Clinic for Pulmonology of the University Clinical Center of Serbia on the occasion of the 90th anniversary of the Clinic

clinics, the department for functional lung diagnostics, the department for bronchoscopy and invasive diagnostics (which also includes an outpatient clinic for interventional pulmonology), the department for cardiac monitoring of pulmonary patients, day hospitals for malignant lung and pleural diseases, eight inpatient wards, units for intensive pulmonary treatment and units for semi-intensive pulmonary care. As part of the work, cabinets for mechanical ventilation and other respiratory support, the cabinet for prevention and smoking cessation, the echosonography cabinet, the cabinet for scientific research work and the outpatient clinic for the diagnosis of sleep breathing disorders were created. Further work with children led to the development of highly specialized clinics that deal with pulmonary hypertension, severe asthma, interstitial lung diseases and post-COVID clinic. Scientific research works concern theoretical and practical teaching as part of propaedeutics and internal medicine at integrated academic studies, as well as teaching as part of specialization in internal medicine and general medicine, and subspecialty teaching in pulmonology; prepa-

ration of doctoral theses was also carried out at the clinic. Clinic teachers are holders of scientific research projects, the results of which have been published in international journals; the teaching staff of the clinic participated in writing numerous chapters in several textbooks and monographs, the last of which, "Selected chapters in pulmonology" was approved as a textbook for postgraduate teaching. One century of Serbian pulmonology was also marked by a large pulmonology congress lasting 3 days, with over 70 lecturers from the country and abroad and with 350 participants. Today, the Clinic for Pulmonology is the largest and most modern pulmonary institution in Serbia and a source of pride for doctors and patients. 66 doctors participate in the work of the clinic, of which 42 are specialist doctors and 24 are residents. 14 doctors participate in classes at the medical faculty, of which 3 are full professors, one associate professor, 3 assistant professors and 7 teaching assistants. We are thankful to our teachers and to our colleagues for everything they have done for the development of pulmonology.

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## JEDAN VEK PULMOLOŠKE ŠKOLE U SRBIJI

Mihailo I Stjepanović<sup>1,2</sup>

### Sažetak

Godine 2022. obeleženo je 100 godina moderne srpske pulmologije i 90 godina Klinike za pulmologiju Univerzitetskog kliničkog centra Srbije. Ovaj rad predstavlja sažet istorijat razvoja Klinike, u kojem je obuhvaćeno osnivanje klinike, organizacioni i edukativni razvoj, kao

i najznamenitiji direktori koji su to omogućili. Takođe, opisane su i aktuelne delatnosti klinike i trenutno stanje zaposlenih. Cilj rada je prikazati razvoj Klinike za pulmologiju, i time odati priznanje prethodnicama i savremenima.

**Ključne reči:** pulmologija, Srbija, istorijat

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**REVIEW**

# Writing phd thesis in English: importance, challenges, and thesis originality

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In line with the ORPHEUS guidelines, to encourage international recognition of PhD theses, the Faculty of Medicine University of Belgrade (FMUB) promotes writing PhD theses in English. FMUB also requests and encourages PhD candidates to publish their results in international journals before thesis submission so as to increase their visibility in the scientific community. In addition to specific topics in medicine, PhD education needs to cover topics of general interest to researchers, in particular copyright and originality issues in scientific research. By adopting the concepts and terms of copyright, PhD candidates learn the importance of intellectual property and avoid plagiarism. As writing a PhD thesis in English may increase textual overlap between the thesis and the candidate's own published papers (in English) originating from the thesis, there may be some dilemmas in practice as to whether such textual overlap should be considered self-plagiarism or not. In line with the regulations at the top universities in the field of medicine, FMUB has adopted the conclusion that textual overlap between the thesis and the thesis-based publications of the candidate does not represent self-plagiarism, provided that certain conditions are met. Namely, regardless of the language of the dissertation, the key aspects of academic integrity in writing a PhD thesis should be honesty and transparency, namely, transparently linking the thesis-based publications with the final thesis; honestly and appropriately referencing the statements or any other content taken from the candidate's own previous work (unrelated to thesis) or other people's work; and transparently acknowledging the contribution from coauthors and team members in the thesis. These recommendations will improve transparency of thesis writing, protect PhD candidates and their supervisors, enhance internationalization of PhD programs, and further promote academic honesty in medical research and publishing

**Keywords:** PhD studies, doctoral thesis, originality, English

## INTRODUCTION

PhD studies are completed by writing and defending a PhD thesis, which is an outcome of several-year-long research. A traditional PhD thesis provides an opportunity for detailed presentation of the performed investigations and the methodological approaches that have been used, together with extensive review of literature and discussion of the results (1). Thesis writing is a skill that all PhD candidates should acquire during their PhD studies so that they could present their research findings in an optimal way (2).

According to the ORPHEUS recommendations, “the PhD thesis should be the basis for evaluating if the PhD candidate has acquired the skills to carry out independent, original, and scientifically significant research and to critically evaluate work done by others (BR6.1)” (3). The standard that should be achieved in biomedicine and health sciences is to publish the equivalent of at least three *in extenso* papers resulting from the PhD project in internationally recognized, peer-reviewed journals, in which the PhD candidate should be the first author, although fewer papers may also be accepted if published in highly rated journals. Apart from this, to encourage international recognition of PhD theses, the ORPHEUS promotes writing theses in English, unless local regulations require otherwise.

## THE IMPORTANCE OF PUBLISHING JOURNAL ARTICLES BASED ON THE THESIS

It is a well-known fact that unpublished findings from a PhD thesis are a lost opportunity for both the candidate and the scientific community because research findings reported in thesis are less likely to be cited in academic journals, especially if the thesis is not written in English (4). This is an important reason why both candidates and supervisors would like to publish the results before the PhD thesis is submitted and defended. Hence, timely dissemination of scientific results is one of the key reasons for publishing the findings from a thesis. A greater number of publications in high-ranking journals has implications for the development of the future career of PhD candidates, as it contributes to their recognition in the scientific community. It has been shown that without publications and presentations at conferences, PhD candidates cannot hope to achieve professional visibility necessary for the development of their academic careers (5). Additionally, publishing thesis-based results in international journals further provides opportunities for collaboration with other researchers, and preparation and application of joint projects, and increases the chance of receiving grants. The European Commission documents also emphasize the need for research excellence and interdisciplinarity and advocate international networking, underlining that PhD education makes a valuable contribution to the European

knowledge society that will be able to compete with other economies of the future (6, 7).

It is very important to keep in mind that for those PhD candidates for whom English is not the first language, writing a thesis in English can be an overwhelming task per se and, consequently, a source of anxiety (8). Additionally, this task is both quantitatively and qualitatively different from their previous experience in academic writing. Particularly sensitive are those for whom English is a second language as they must fight simultaneously in several domains, all of which have been identified as important influencing factors of academic writing at an advanced level (9). Supervisors have a crucial role in providing support to PhD candidates to overcome these obstacles (10).

## EDUCATING PHD CANDIDATES ABOUT THE SYSTEM OF SCIENTIFIC COMMUNICATION

In addition to a particular curriculum of doctoral studies, education of PhD candidates must cover the whole system of scientific information that includes topics of general interest for researchers. Specifically, search of scientific resources (commercial as well as noncommercial), journal categorization, open science, citation managers, and copyright are the topics that create a whole system of scientific communication, applicable for all research areas of PhD candidates' expertise.

The scope of systematic education of PhD candidates was given through a survey conducted in 2021 by the EUA Council for Doctoral Education, which was a follow-up of the large-scale EUA-CDE study “Doctoral education in Europe today: approaches and institutional structures,” realized in 2017–2018 (11). One of the key conclusions of this survey is that, besides the fact that doctoral education must deal with a multitude of priorities, the research ethics, integrity and quality of supervision “continue to be the two main elements of doctoral education” (11). Likewise, the top three mandatory training topics for PhD candidates offered by most institutions are research ethics and integrity, research methodology, and dissertation writing (12).

## Establishing the education of PhD candidates at the national level in Serbia

Planned and continuous education of PhD candidates in Serbia was primarily established through the activities of the Consortium for Joint Acquisition (Serbian, *Konzorcijum biblioteka Srbije za objedinjenu nabavku [Kobson]*), which was founded in 2001. During mid-2000s, the Consortium started educating PhD scholarship holders with the support of the Ministry of Education and Science of the Republic of Serbia. The program offered one day of intensive education about online services and resources. The other topics covered were copyright, plagiarism,

open access, and Creative Commons Licenses as the key stones for academic integrity.

From 2015, the University Library “Svetozar Marković,” the central library of the University of Belgrade and the biggest scientific library in the country, started programs on the form of doctoral dissertations, necessary elements of the documents, requirements of the university related to digital depositing of the dissertations, and finally—since all dissertations must be in open access—Creative Commons Licenses. Since that time, education on copyright for PhD candidates has become a regular program of education organized by the Department for Scientific Information and Education of the University Library “Svetozar Marković.” The program has been further developed, enriched with new topics (originality check by online services such as *iThenticate*), and oriented towards comprehensive introduction of the concept of copyright (13). It has been used by the various faculties of the University of Belgrade, including the Faculty of Medicine and the Faculty of Law.

In 2022, the University Library established the Center for Supporting PhD Studies, with the mission to regularly (i.e., monthly) organize and conduct various educational programs intended for PhD candidates that would be performed by librarians but also by invited lecturers, professors, researchers, and publishers (14). Copyright and ethical issues in scientific research are among the important pillars of this program (15).

### The content of the copyright education

Copyright education programs are organized with the idea that only by adopting the elementary concepts and key terms of copyright will PhD candidates be able to understand properly the importance of intellectual property and give correct answers to the question why copyright infringement is such a huge problem. More importantly, only by understanding what copyright really means can PhD candidates realize that the true research is in strong opposition to plagiarism.

In particular, the program explains the meaning of the term “work.” Namely, the work (article, book, etc.) is an original creation, which means that its author, no matter how much he or she relied on previous works through cited references, must put his/her own original, unique contribution to this new, previously nonexistent creation. The work is under copyright from the moment of its formation, which means that it can exist independently from its creator. Of note, “copyright protection does not extend to ideas, procedures, methods of operation, or mathematical concepts as such” (16), which is why the primary research data are a most sensitive issue related to open science: not being explicitly under copyright, they can easily become subject of large dispute. Finally, the program must underline that copyright is related to the whole work, but also to every part of the work and finally the title of the work.

The program also indicates the rights that are guaranteed for the author as the copyright holder. The basic right of the author is attribution, that is, the author is entitled to be recognized as the author of a particular work. If the work is used by someone else without attribution to the original author, it means that the work is plagiarized. Research activity is completely incompatible with plagiarism: having an intention to give original scientific contribution, the researcher needs to demarcate his/her contribution from the previous works that he/she has cited in the paper.

The Code of Professional Ethics of the University of Belgrade (17)—the basic document for regulation of ethical issues at the University—defines plagiarism not only as direct usage of other author’s text, but also as paraphrasing of someone else’s text and usage of other people’s ideas and concepts. That is how The Code extends the term plagiarism from the form of the work to its content, enabling better and more sophisticated approach to plagiarism assessment. The explanation of such basics is also necessary for understanding the real meaning and purpose of Creative Commons Licenses as models of contracts between a copyright holder and unknown user of the copyrighted work; the work available in open access is not “free for plagiarism,” but quite the opposite.

## CONTENT OVERLAP BETWEEN A THESIS AND PREVIOUSLY PUBLISHED TEXT: LOCAL AND INTERNATIONAL REGULATIONS AND GUIDELINES

### Procedure for checking the originality of PhD theses at the University of Belgrade

According to the “Ordinance of the Procedure for Checking Originality of Doctoral Dissertations to be Defended at the University of Belgrade” (Serbian, *Pravilnik o postupku proveriti originalnosti doktorskih disertacija koje se brane na Univerzitetu u Beogradu*; in the following text “Ordinance”) (18), each submitted doctoral thesis is checked by *iThenticate* software for the extent and type of textual overlap between the thesis and all texts available to the software. The software-generated report is presented to the thesis supervisor, who is invited to evaluate the thesis originality and write a report with the verdict as to whether the thesis is original (in which case the procedure can be continued) or if the originality of the thesis is disputable (in which case the procedure is interrupted until the thesis is revised as necessary). The members of the thesis evaluation committee (three or five university professors or senior scientists from the appropriate field) are also informed about the software analysis results and the supervisor’s verdict before they compile the thesis assessment report, which is then forwarded to the Professional Body for Medical Sciences (Serbian, *Veće naučnih oblasti medicinskih nauka*) of the University of Belgrade for final approval of the thesis.

## Textual overlap between the thesis written in English and thesis-based articles published in English: Is it self-plagiarism or not?

Writing a thesis in English may bring about some challenges during *iThenticate* analysis, especially regarding the textual overlap between the thesis and the candidate's own published papers (in English) that originated from the thesis. In this context, there may be some dilemmas in practice as to whether such textual overlap is to be considered self-plagiarism or not. In addition, there may be some dilemmas about the numerical "threshold" of originality/plagiarism in all theses, regardless of the language they are written in.

It should be emphasized that there are three different types of content overlap in a thesis: (1) overlap with the candidate's own publications based on the work on the thesis (thesis-based publications); (2) overlap with the candidate's own publications that are not directly related to work on the thesis; (3) overlap with other authors' publications. These three types of overlap are essentially different and should not be treated equally during the assessment of thesis originality.

The Faculty of Medicine University of Belgrade (FMUB) has adopted the conclusion that textual overlap between the thesis and the thesis-based publications of the candidate does not represent self-plagiarism. Namely, the main requirement that each PhD candidate at FMUB has to fulfil before submitting the PhD thesis is to publish at least two articles based on the thesis (in English) in journals indexed in *Journal Citation Report*, with the Impact Factor of each journal being higher than 1 (19). These papers are the direct results of the thesis, and thus, the content overlap between the thesis-based papers and the final thesis is understandable and necessary. This conclusion of the Scientific Council of FMUB is in accordance with the "Ordinance," which clearly acknowledges that textual overlap may be necessary "as a consequence of previously published results of the candidate's work on the thesis" (18).

In contrast, regarding the overlap between the thesis and the candidate's own publications that are not directly related to work on the thesis, FMUB has adopted the conclusion that this should be treated similarly to textual overlap between the thesis and other authors' publications. Occasionally, some university professors bring about the question of numerical "threshold" of thesis originality, that is, the percentage of textual overlap that is acceptable. However, the "Ordinance" (18) does not define any numerical "threshold" of originality or lack thereof, and clearly states that "information about the amount of textual overlap is not sufficient" to decide whether the thesis is original or not. According to the "Ordinance," the purpose of originality assessment is to "determine whether and to what extent the dissertation is original, that is, whether it represents the result of the candidate's

own work, and whether and to what extent the academic standards of citing and referencing were adhered to" (18). Indeed, software analysis is just a useful tool to help the supervisor and the assessment committee in performing a thorough assessment of thesis originality. Originality and plagiarism are not just the matter of text but also content, ideas, illustrations, and their source; hence, the same percentage of textual overlap may be interpreted completely differently in different theses depending on the wider context. Software does not evaluate illustrations and ideas, which should also be considered carefully to profoundly determine the degree of thesis originality.

## Writing a thesis in Serbian: Is it a way to avoid textual overlap with the published papers?

Most candidates at FMUB write their PhD thesis in Serbian but have to publish the minimum required number of papers in *Journal Citation Report*-indexed journals in English. However, *iThenticate* typically does not recognize Serbian translation of their thesis-based papers previously published in English, so the textual overlap detected by the software is usually low and there is rarely a dilemma as to whether their theses are original. However, it is important to understand that the use of a Serbian translation of an article is no different from using the original article in English as regards possible plagiarism; thus, if a thesis includes a Serbian translation of a published article, it is necessary to indicate this clearly. Indeed, it is important to understand that the issues of originality and plagiarism are not exclusively a matter of form and language, and mere paraphrasing (17, 20) or translation (21) does not necessarily avoid plagiarism when it exists even though the software may not detect it. Therefore, it is important to educate PhD candidates about the foundations of academic integrity and teach them how to read literature and how to write and cite references appropriately.

## International regulations about the reuse of one's own publications in the thesis

As mentioned above, there are sometimes conflicting views at our university as to whether it is acceptable to reuse parts of the text from the candidate's own publications that have originated from the thesis in the finally submitted thesis. Nevertheless, FMUB has adopted a clear conclusion, which is based on the positive "Ordinance" (18). Before reaching this conclusion, we also considered the current regulations and guidelines at the top universities from the Shanghai ranking list in the field of clinical medicine (22-36). It is quite consistent between these universities from diverse countries (e.g., the United States, the United Kingdom, the Netherlands, Germany, Canada, Australia) that the reuse of content from the candidate's own papers based on the thesis in the final thesis is not

the matter of self-plagiarism. Hence, these universities allow PhD candidates to reuse parts of their previously published related content in the thesis; however, they emphasize that the main issues with such reuse include the issue of journal publisher's copyright (22-35) and the issue of coauthor contributions (37). As described in guidelines of some of these universities, most publishers allow such reuse but require acknowledging in the thesis that the initial article was published by the publisher and providing the full reference (27, 29, 32). As for the contribution issue, it is normal that the candidates have multiple coauthors on the thesis-based papers because modern research in medicine is conducted in research teams and is often multidisciplinary; however, candidates can use parts of these publications in their theses, provided that they are the first authors and that they clearly acknowledge in the thesis that their contribution was more than 50% (33, 37); it is also important to describe the specific contributions of the candidate and each of the coauthors (26). Furthermore, there are requirements at some universities that the coauthors provide a written statement of consent (33).

## CONCLUSIONS

In accordance with the ORPHEUS guidelines, FMUB strongly recommends writing a PhD thesis in English. Regardless of the language of the dissertation, it is obvious that the key aspects of academic integrity in writing a PhD thesis should be honesty and transparency: transparently linking the thesis-based publications with the final thesis, regardless of the language in which the thesis is written; honestly and appropriately referencing the statements or any other content taken from the candidate's own previous work (unrelated to thesis) or other people's

work; and transparently acknowledging the contribution from coauthors and team members in the thesis.

Therefore, considering the current international regulations and guidelines, the Scientific Council of FMUB in principle allows content overlap between the candidate's thesis and the thesis-based publications; nevertheless, FMUB requires that the candidate confirms that the publishers of journals in which the thesis-based articles were printed allow the reuse of content from these papers in the author's own thesis and cite these publications in line with academic rules of referencing and according to the publishers' requirements. Moreover, the candidates need to clearly acknowledge in the text of the thesis all their coauthors and specify their exact contributions to the thesis research. The same requirements have to be met by the candidates who write their thesis in Serbian and those who write it in English. We particularly recommend following the extensive and detailed instructions from the universities KU Leuven and Charite on increasing transparency in PhD theses (20, 25). We believe that such recommendations will improve transparency of thesis writing, protect PhD candidates and their supervisors, enhance internationalization of PhD programs, and further promote academic honesty in medical research and publishing.

## Conflict of interests:

None to declare.

## Author contributions:

PM, DS, and TP conceived and wrote the paper, revised it for important intellectual content, and approved the final submission.

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## PISANJE DOKTORSKE DISERTACIJE NA ENGLESKOM JEZIKU: ZNAČAJ, IZAZOVI I ORIGINALNOST DISERTACIJE

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### Sažetak

U skladu sa smernicama ORPHEUS-a, Medicinski fakultet Univerziteta u Beogradu (FMUB) promovise pisanje doktorskih disertacija na engleskom jeziku. FMUB takođe zahteva i ohrabruje studente doktorskih studija da objave svoje rezultate u međunarodnim časopisima pre podnošenja same disertacije radi veće vidljivosti rezultata u naučnoj zajednici. Pored specifičnih tema u odgovarajućoj oblasti medicine, doktorske studije treba da pokriju i teme od opšteg interesa za istraživače, a posebno pitanja autorskih prava i originalnosti naučnog rada. Usvajanjem osnovnih koncepata pojma autorskih prava, studenti doktorskih studija se uče značaju zaštite intelektualne svojine i izbegavaju plagijarizam. Kako pisanje doktorske disertacije na engleskom jeziku često povećava stepen preklapanja teksta između same disertacije i objavljenih radova kandidata (na engleskom) koji potiču iz disertacije, u praksi se nekada može javiti dilema da li takvo preklapanje teksta treba smatrati autoplagijarizmom ili ne. U

skladu sa propisima vrhunskih univerziteta u oblasti medicine, FMUB je usvojio zaključak da preklapanje sadržaja između disertacije i publikacija proisteklih iz disertacije kandidata ne predstavlja autoplagijarizam, pod određenim, precizno definisanim, uslovima. Naime, bez obzira na jezik kojim je pisana doktorska disertacija, ključni aspekti akademskog integriteta treba da budu iskrenost i transparentnost: transparentno povezivanje publikacija proizašlih iz disertacije sa samom disertacijom; pravilno citiranje sadržaja preuzetog iz prethodnog rada kandidata (koji nije u vezi sa disertacijom) ili rada drugih autora; i transparentno uvažavanje doprinosa koautora i članova tima u radu. Ove preporuke će poboljšati transparentnost pisanja doktorskih disertacija, zaštititi kandidate i njihove mentore, poboljšati internacionalizaciju doktorskih programa i dalje promovisati akademsko poštenje u medicinskim istraživanjima i objavljivanju rezultata.

**Ključne reči:** doktorske studije, doktorska disertacija, originalnost, engleski jezik

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**REVIEW**

# Cardiac cephalalgia

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The authors have declared that no competing interests exist

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**Summary**

Cardiac cephalalgia has a small incidence, but unrecognized it can prolong the time to diagnose a life-threatening condition such as acute coronary event. According to its clinical presentation, it can refer to a migraine. Even in the absence of clinically and laboratory evident signs, the diagnosis of cardiac migraine should be kept in mind because sometimes it is the only symptom of a threatening coronary event. The choice of treatment depends on a correctly established diagnosis. A reckless inclusion of vasoconstrictors as a standard therapeutic modality of migraine in a patient with a cardiac cephalalgia could worsen ischemia and endanger the patient's life. By solving an acute coronary event conservatively, with percutaneous coronary interventions or coronary "bypass," cardiac cephalalgia is eliminated as well.

**Keywords:** Migraine, cardiac cephalalgia, ischemia, coronary

## INTRODUCTION

Headaches belong to the most common diseases affecting the human species. In 2016, it was estimated that almost 3 billion people suffered from some form of a headache (1). Headaches are divided into primary and secondary headaches according to their cause. Cardiac cephalalgia belongs to the group of secondary (symptomatic) headaches.

Cardiac cephalalgia (“heart headache or anginal headache”) was first described by Lipton et al. in 1997 as a secondary headache phenomenon that occurred in conditions of cardiac ischemia (2). It is defined as a headache whose characteristics are similar to those of a migraine, which is usually, but not always, initiated by exertion, which occurs during an episode of myocardial ischemia, and which is relieved by nitroglycerin therapy (3). The choice of therapeutic measures in treating this condition must be carefully made because using vasoconstrictors (e.g., triptans), and specific antimigraine drugs, could worsen myocardial ischemia and be fatal.

## EPIDEMIOLOGY

The frequency of cardiovascular diseases and ischemic heart disease, as comorbidities, in patients with primary headaches is higher than in general population (7% vs. 2.6%) (4). In contrast, a headache can sometimes be a predictor of cardiovascular disease or the first clinical presentation of angina pectoris and acute myocardial ischemia. In ischemic heart disease, the most common localization of angina is in the middle of the chest, with propagation to the arm, back, neck, jaw, or epigastrium. The occurrence of a headache as the main or the only symptom of ischemic heart disease is infrequent. Based on previous data from literature, in 5.2%-6% of patients, a headache is an accompanying symptom of acute myocardial ischemia. In only 3.5%, the head was the only place of pain (5-6) during the coronary event, although the headache was not the only symptom of the disease (6). Despite the current data on the prevalence of cardiac cephalalgia, its characteristics and pathophysiology are still insufficiently known.

## PATHOPHYSIOLOGY OF CARDIAC CEPHALALGIA

Four hypotheses could explain the mechanism of its origin (7-9).

According to the first hypothesis, pain with predominance of a headache is transmitted in 50% to 60% of patients by sympathetic fibers, in 10% to 20% of patients by parasympathetic fibers, and through both types of fibers in 30% to 40% of patients. This phenomenon could be due to the convergence of afferent autonomic visceral fi-

bers, which carry nociceptive stimuli from the heart via dorsal roots from C8 to TH5, and somatic sensory fibers, which innervate the chest and the arms, on typical neurons of the posterior horns of the spinal cord, sympathetic ganglions, or thalamus. The pain manifested in the lower jaw is a consequence of the convergence of autonomic fibers and trigeminal somatic fibers in the nucleus of the trigeminus. In occipital headaches, the convergence of fibers occurs in the typical neurons of the posterior horns in the upper part of the cervical spinal cord. Parasympathetic sensory impulses traveling via the vagus converge with somatic sensory impulses in the thalamus. Based on this convergence theory, afferent somatic and visceral fibers converge on the same neurons. When visceral afferent impulses stimulate neurons, information in the higher centers of the central nervous system is transmitted to the corresponding somatic regions (2, 10-11). The concentration of cardiac afferent autonomic fibers varies for each part of the heart. A large concentration of sympathetic fibers is thought to be located in the anterior part of the left ventricle.

In contrast, parasympathetic fibers are concentrated and innervate the inferior and posterior walls of the left ventricle. Since perfusion of the anterior wall of the left ventricle is achieved through the anterior left descending artery, and the posterior and lower walls of the ventricle are perfused through the right coronary and circumflex arteries, the dominant activation of the fibers depends on the artery responsible for myocardial ischemia. Therefore the localization of cardiac cephalalgia depends on the part of the heart affected by ischemia (12-13).

The second hypothesis is based on a sudden reduction in cardiac output during ischemia. Consequently, pressure increases in the left ventricle and then in the right atrium as well, and there is a decrease in the venous drainage of blood from the head and an increase in intracranial pressure (2). Due to the distension of the head and neck blood vessels, the nociceptive stimulation of intracranial structures (blood vessels, brain cells) increases.

According to the third hypothesis, pain is caused by the release of neurochemical mediators due to tissue ischemia. Mediators such as serotonin, bradykinin, histamine, substance P, and atrial natriuretic peptide have a solid vasodilatory effect on the arteries in the brain (2,11).


The fourth theory assumes that the headache could be present due to the simultaneous presence of vasospasm on the coronary and small intracranial arteries due to sympathetic activation by myocardial ischemia (14-16).

## CLASSIFICATION OF CARDIAC CEPHALALGIA

Cardiac cephalalgia was introduced in the second edition of the International Classification of Headache Disorders (ICHD-2) as a secondary headache related to homeostasis disorders (3). As soon as 2004, based on a review of



**Table 1.** ICHD-3 diagnostic criteria for cardiac cephalgia

10.6 Cardiac cephalgia
A. Any headache that meets criterion C
B. Confirmed acute myocardial ischemia
C. Evidence of cause confirmed by at least two of the following:
1. The headache developed in close relation with the onset of acute myocardial ischemia
2. One or both of the following:
a. Headache significantly worsened concurrently with worsening ischemia
b. The headache significantly eased or disappeared at the same time as ischemia receded
3. A headache has at least two of the four characteristics:
a. Moderate to severe intensity
b. Accompanied by nausea
c. Isn't accompanied by photophobia or phonophobia
d. Worsens with exertion
4. Headache resolves with nitroglycerin use
D. Not better explained by another ICHD-3 diagnosis


literature, the criteria were revised. According to the criteria from the latest classification, ICHD-3, cardiac cephalgia is described as a migraine-like condition that is usually (but not always) triggered by exertion and occurs during an episode of myocardial ischemia (3). **Table 1.** shows the most recent criteria for this type of headache.

## CLINICAL PRESENTATION

Risk factors for cardiovascular disease such as advanced age, hypertension, hyperlipidemia, diabetes, smoking, and positive family history of vascular disease are commonly present in patients with cardiac cephalgia. Many patients with cardiac cephalgia may not have these risk factors (17).

Cardiac cephalgia can vary considerably in its clinical presentation. It often resembles other forms of primary or secondary headaches in terms of their characteristics and triggering factors (e.g., exertion). The presentation of the disease can vary by location, time, primary symptoms, and the presence of risk factors for a cardiac event.

Concerning localization, it can be bifrontal, bitemporal, or occipital. Depending on the onset, it can be acute, subacute, or intermittent. The nature of the pain ranges from pulsations, stabbing pain, throbbing pain, dull pain, shooting pain, or explosion-like pain. Headaches of this type can also be associated with signs from the autonomic nervous system: nausea, vomiting, redness or paleness of the face/skin, and sweating. The duration of the headache can vary from a few minutes to several hours, and its severity can range from moderate to severe. Mostly, the majority of hospitalized patients registered a severe form of headache.

With myocardial ischemia, a headache may or may not be accompanied by chest pain. In most cases, patients

also had chest pain (17-18), but cases of patients whose headache was the only symptom of angina pectoris or a coronary event have also been described (19-21).

## DIAGNOSIS

A headache with accompanying symptoms of myocardial ischemia is a typical manifestation of cardiac cephalgia. In addition to a positive medical history and data on previous headaches and accompanying ischemia, an electrocardiogram (ECG) should be performed at rest and during exertion, and cardiac enzymes: Creatinine Phosphokinase - Muscle/Brain (CPK-MB), myoglobin and troponin may be helpful.

The problem in establishing the correct diagnosis is usually the absence of typical chest pain. However, a common cardiac cephalgia that worsens with exertion and resolves with administered nitroglycerin should raise suspicion about this diagnosis. Not all forms of cardiac cephalgia worsen at exertion, so other factors, including new or unusual headaches, age over 50 years, and vascular risk factors: current or previous smoking, hypertension, hyperlipidemia, diabetes, and positive family history, should be considered. The presence of any of the above-mentioned factors requires an urgent neurological examination that includes additional diagnostics in the form of magnetic resonance imaging, imaging of cerebral arteries, EKG, nitroglycerin test, and consultation with a cardiologist. Lumbar puncture and cerebrospinal fluid (CSF) analysis could help rule out subarachnoid hemorrhage or meningitis/encephalitis as the most common differential diagnoses. Continuous monitoring of cardiac function, exercise tolerance test, and dobutamine stress echocardiography could be considered with a cardiologist in order to determine the changes that occur during an episode of cardiac cephalgia (22).

In patients in whom all findings, including ECG, laboratory tests, neurological findings, neuroimaging, and findings of CSF and electroencephalogram, are negative, the resolution of ST depression can be determined by a stress test (18). Sometimes, in order to establish a diagnosis, it is necessary to suspect cardiac cephalgia, even when there are no other symptoms or signs of angina pectoris or myocardial infarction in addition to the headache. Coronary angiography was an essential diagnostic tool when the ECG and stress test did not show signs of myocardial ischemia.

In a review of previous literature, which included 59 patients with cardiac cephalgia, the majority of patients were men (62.7%), middle-aged or older (over 50 years, 79.7%). In the most significant number of cases, pain occurred during some kind of effort, while in 27.1%, it occurred at rest. In 39% of patients, pain affected the occipital region, mainly on both sides. On the ECG, 39% of patients had ST elevation, and 15.2% had ST depression.

In 25% of patients whose cardiac enzymes were measured in the laboratory, an increase in enzymes was present in 21%. The underlying clinical condition in 50.8% of patients was acute myocardial infarction, in 47.5% it was angina, and in 1.7% it was cardiomyopathy. Coronary occlusion or severe stenosis were present in almost all patients with (8).

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of cardiac cephalgia includes a wide range of diagnoses. It includes primary headache syndromes, such as migraine and tension headaches, and secondary headache syndromes, especially those related to effort.

Due to the high risk for the patient, it is essential to rule out the existence of subarachnoid hemorrhage (SAH), which is clinically manifested by the occurrence of a “thunderbolt-thunderclap” headache that may resemble the occipital localization of cardiac cephalgia. Pain may be the only symptom of SAH. The intensity of this headache is disabling and unbearable. The diagnosis is based on brain computerized tomography (CT) of the brain and lumbar puncture that proves the presence of blood in the cerebrospinal fluid when a further urgent care by a neurosurgeon is necessary.

Establishing a diagnosis is much more difficult if a headache appears to be the only symptom of ischemia. In such situations, suspicion of acute myocardial ischemia is established based on data on the patient’s age. Older age is highly indicative of a secondary origin of headaches.

Data on risk factors for vascular diseases as well as the occurrence of headaches in conditions of stress and exertion, additionally help in establishing the diagnosis. In the case of new-onset headaches in patients over 50, it is recommended to perform an ECG and check cardiac enzymes.

It is essential to differentiate between cardiogenic headaches and the occurrence of migraine headaches. Migraine headaches usually appear between the second and third decade of life, more often in women, and the first headaches can also appear during the first menstrual cycle. Migraine headaches can also be accompanied by mood swings, tremors, and increased appetite. The intensity of the headache, which usually starts in the morning, increases and reaches its maximum during the day. Both types of headaches may be accompanied by signs of the autonomic nervous system in the form of nausea and may worsen at exertion but also at rest. The correct diagnosis affects the choice of therapy. Vasoconstrictor drugs used in migraine therapy (triptans or ergotamine derivatives) are contraindicated in cardiac cephalgia. Although these drugs exert their primary effect (antag-

onists of 5-HT<sub>1B-1D</sub> receptors) on meningeal arteries, perivascular sheaths of trigeminal endings, and the central nervous system, their minimal vasoconstrictive effect was also observed on coronary vessels (23-24).

When there are no other symptoms of ischemia, the differential diagnosis should be thought of as headaches related to effort, and primary headache associated with sexual activity and cough headache. The common feature of these headaches is the sudden onset of pain strictly related to a specific effort. The pain is usually bilateral, of high intensity, pulsating, and can last from a few minutes to 24 hours. These headaches must rule out secondary causes with appropriate diagnostic procedures.

A headache can also occur after the administration of nitroglycerin, usually in the form of a migraine attack due to the vasodilator effect of nitrates. The pain develops within 10 minutes of drug administration, being primarily bilateral, with stabbing worsened at exertion, and it resolves one hour after drug administration. Late forms of this headache may occur in people who are otherwise prone to headaches. They also occur after nitro preparations but disappear after 72 hours (3). In the differential diagnosis of these patients, it is crucial to assess the time of drug administration and the time when symptoms appear.

Extra cephalic presentations of migraine headaches should also be suspected in the differential diagnosis. They appear in uncontrolled pain syndromes, including migraines (25). Extra cephalic manifestations of migraine have been described in literature, but chest pain in the form of allodynia as part of migraine is rare. In a study involving 33 patients, Roland showed that chest pain occurred immediately after a migraine. Visual analog scale (VAS) median headache intensity was 8/10, and the most common localization was the left hemicrania. The median duration of migraine was about 26 hours. The majority, about 76% of patients, described chest discomfort as pain. The median VAS of chest pain was 7/10. Chest pain did not change at exertion, but it increased at palpation (26).

Chest pain and headache can occur as part of many other conditions. According to the Anxiety and Depression Association of America (ADAA), chest pain and headaches can occur with panic attacks as part of anxiety. In a panic attack, chest pain resembles angina pain and is usually accompanied by other signs such as tachycardia, shortness of breath, weakness, sweating, and tremors. In autoimmune diseases such as systemic lupus, other organs and tissues, such as the heart and blood vessels, are affected. Therefore, these patients may have symptoms of chest pain and headache that resemble cardiogenic shock. As a part of other diseases and conditions such as fibromyalgia, carbon monoxide poisoning, sarcoidosis, peptic ulcer, pneumonia, and tuberculosis, a similar clinical presentation of headache may occur, which has cardiogenic characteristics and can be accompanied by chest pain.

## MANAGEMENT OF PATIENTS WITH CARDIAC CEPHALALGIA

Very often, this form of headache is misdiagnosed as a migraine. According to data from literature, these patients can have undiagnosed cardiac cephalgia for years before acute myocardial infarction occurs (19). Triptans should be avoided in patients with myocardial infarction, cerebrovascular insult, uncontrolled hypertension, or diabetes. Tricyclic antidepressants, selective serotonin reuptake inhibitors, and selective serotonin-norepinephrine reuptake inhibitors can increase blood pressure and should be used with caution. Nitroglycerin causes vasodilation and worsens migraine, and with its use, headaches can be expected in patients who commonly suffer from migraine headaches.

In carrying out the necessary therapy, the cooperation of neurologists and cardiologists is essential. In addition to the standard therapy for patients with a coronary event, nitro-derivatives relieve symptoms. However, performing recanalization of the affected coronary artery or arteries is of crucial importance for these patients. In line with that, percutaneous coronary intervention or coronary bypass is crucial in solving headaches. With a successful intervention, myocardial ischemia is resolved, and pain symptoms subside. A recurrent headache may indicate coronary artery restenosis (27-28).

## CONCLUSION

The present review summarizes the current knowledge on cardiac cephalgia and emphasizes the importance of recognizing headaches as a symptom of certain, sometimes very serious and life threatening, conditions. Headaches as a part of the clinical presentation of cardiovascular disorders are not unusual, but their occurrence as the only symptom of cardiovascular events is rare. Keeping cardiac cephalgia diagnosis in mind, even without laboratory and clinically evident signs, is necessary because it can be the only manifestation of serious ischemic events. It is essential to differentiate cardiac cephalgia from migraine because introducing vasoconstriction drugs, as a standard therapeutic modality for migraine, can be life-threatening in the setting of a coronary event.

## Conflict of interests:

The authors have declared that there are no competing interests.

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## KARDIOGENA GLAVOBOLJA

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### Sažetak

Kardiogena glavobolja je retka po svojoj učestalosti, ali neprepoznata može da produži vreme dijagnostikovanja životno ugrožavajućeg stanja kao što je akutni koronarni događaj. Po svojoj kliničkoj prezentaciji može upućivati na migrensku glavobolju. Čak i u odsustvu klinički i laboratorijski evidentnih znakova, dijagnozu kardiogene migrene bi trebalo imati na umu jer je nekada ona jedini simptom pretećeg koronarnog događaja. Izbor lečenja

zavisí od pravilno postavljene dijagnoze, a nesmotreno uključivanje vazokonstriktora kao standardnog terapijskog modaliteta migrene, kod pacijenta sa kardiogenom glavoboljom bi moglo pogoršati ishemijsku i životno ugroziti pacijenta. Rešavanjem akutnog koronarnog događaja konzervativnim putem, perkutanom koronarnom intervencijama ili koronarnim "by-pass"-om otklanja se i kardiogena glavobolja.

**Ključne reči:** Migrena, kardiogena glavobolja, sekundarna glavobolja, akutna srčana ishemija

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**REVIEW**

# History of gestational diabetes mellitus

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## Summary

The goal of this paper is to present the chronological development of knowledge about diabetes mellitus from the time of Hippocrates, through Langerhans and White, how it was discovered that inadequate pancreatic function was the cause of diabetes mellitus, and that the kidney was just an organ that became weaker due to unregulated pancreatic function. Studying gestational diabetes mellitus leads to a better control of diabetes in pregnancy, better perinatal outcome with fewer peripartal and perinatal complications. In the second part of the paper, there is a review of literature available on the Web of Science, containing the number of papers published over the years, as well as areas and countries they had been published in.

**Keywords:** gestational diabetes mellitus; diabetes in pregnancy; literature review

## INTRODUCTION

It was estimated that the number of patients with diabetes would increase from 135 million in 1995 to 300 million in 2025 (1). However, the World Health Organization announced that in 2009, 300 million people worldwide were already suffering from diabetes. There were 422 million people with diabetes worldwide in 2022, most of whom lived in low- and middle-income countries, and diabetes is responsible for 1.5 million fatalities every year (2).

If we go back through human history to the time of Ancient Greece, diabetes mellitus was an issue of great attention even then. Ancient records cite symptoms such as increased fluid intake and frequent urination as evidence of diabetes. The first official record of the disease was found in an Egyptian tomb near the city of Thebes in 1862, written on papyrus (3).

Hippocrates, a Greek physician who lived from 460 BC to 370 BC, was one of the first to suggest that the disease was due to environmental factors such as diet and lifestyle. He believed that physical health could be maintained through proper diet, exercise, fresh air, and personal hygiene. He was also the first to categorize diseases into acute, chronic, endemic, and epidemic. During Hippocrates' time, medicine was still a developing science, and physicians were only able to evaluate a patient's condition and make predictions based on case histories (4).

Hippocrates described diabetes as "producing fluids much and often" while Aristotle termed it "wasting of the body" (5). The term "diabetes" traces back to Demetrius of Apameia (1st or 2nd century BC) and is derived from the Ionic word meaning "to pass or run through" as in a siphon, later becoming the Latin word for "siphon" (6). The sweetness of diabetic urine was first described in ancient Indian texts, and later by Avicenna (980–1037) (7) and Morgagni (1635–1683). In 1674, Thomas Willis (1621–1675) recognized this sweet taste (lat. *quasi melle*) as a sign of diabetes, distinct from other causes of polyuria, and suggested that it was due to sugar in the blood. This was later confirmed by Matthew Dobson (1732–1784), who showed that sweetness originated from sugar in the blood, which passed unchanged into the urine (6).

Willis' careful examination of the symptoms of the disease resulted in naming it "diabetes mellitus". It took more than a hundred years for his argument to be supported by the demonstration of sugar in the blood and urine of diabetics by Robert Wyatt in 1774 and subsequently by more thorough studies of Matthew Dobson (1732–1784) (8). After that, diabetes has become a dietary disorder where there is an excessive buildup of sugar in the bloodstream, leading to its excretion in urine. This initiated a new strategy for managing diabetes through diet, focusing on the digestive organs as the cause of the disease, with a particular emphasis on the absorption of sugary substances in the stomach (6).

At the time of Tiberius, Celsus, a Greek writer, wrote about a condition in which greater amounts of urine were excreted in comparison with the amount of fluid ingested, although painlessly. This concept was echoed by many authors in the Middle Ages (5).

Areteus of Cappadocia provided the earliest known accurate clinical description of diabetes, referring to it as an infrequent condition characterized by "melting down of the flesh and limbs into urine", as well as intense thirst, copious urination, and shortened, uncomfortable life. He believed that it could be caused by other diseases negatively impacting the kidneys and bladder (9).

Cawley was the first to suggest a relationship between the pancreas and diabetes. In 1889, Oscar Minkowski (1858–1931) and Joseph Mering (1849–1908) verified the initial clinical observations by demonstrating that when the pancreas was removed from dogs they developed diabetes, which could be reversed by implanting pancreatic fragments beneath the skin (8–12).

A significant progress was achieved by finding out that the pancreas was the target organ in diabetics. In 1869, Paul Langerhans (1849–1888) identified the distinct morphological characteristics of pancreatic islands, which were subsequently named after him, and this led to a deeper understanding of the specific role of the pancreas (8,10,13).

In 1909, Eugene L. Opie observed that the islands of Langerhans in diabetics had hyaline degeneration, which was later corroborated by a series of experiments. This prompted Edward Sharpey-Schafer in 1916 to postulate that the islands of Langerhans produced a hormone that regulated glucose levels, which he named insulin. Frederick Banting (1891–1941) and Charles Best (1892–1978) isolated this hormone in 1922. It was determined that diabetes was an endocrine disorder, rather than a kidney disease as had been previously thought. However, it was yet to be seen how diabetes caused kidney disease (6).

Paulescu published most comprehensive papers in significant journals describing all the physiological functions and pharmacodynamic characteristics of the new hormone he isolated and named "Pancreine". These papers marked the first-time diabetes not only as a disorder of carbohydrate metabolism, but as a disorder of the entire energy metabolism of the human body, including lipid and protein metabolism. In 1916, he began conducting experiments using a pancreatic extract that he obtained using his own method, and then injecting it intravenously into diabetic dogs which led to the disappearance of diabetic symptoms (14).

Leonard Thompson, a fourteen-year-old boy, was the first person to receive the pancreatic extract. On 21st January 1922, he was hospitalized at Toronto General Hospital in critical condition, when he was injected with pancreatic extracts. His blood glucose was approximately 32 mmol at the time, and after the injection, his glucose levels dropped to about 5.5 mmol. Afterwards sterile

abscess appeared, so the extract was stopped. However, when a higher potency extract was administered between 23rd and 25th January 1922, his glucose levels returned to normal, and his urinalysis was much better (15). Banting and four colleagues wrote a report on the clinical use of insulin in diabetics. For this discovery, Frederic Banting and MacLeod received the Nobel Prize for Medicine in 1923 (16).

First reports of diabetes during pregnancy appeared in the 19th century. In 1824, Heinrich Gottlieb Benne- witz wrote about a pregnant woman who experienced polydipsia, polyuria, and fatigue. This was her fifth pregnancy, and it ended with the birth of a baby that weighed over 6 kg, who unfortunately died during labor. There was a large amount of sugar present in her urine (17). In 1846, Lever reported a similar case (18).

### Gestational diabetes mellitus

Research into gestational diabetes mellitus started in the 1940s. In 1954, the term “meta gestational diabetes” appeared, highlighting the fleeting nature of the condition. In 1964, O’Sullivan and Mahan suggested diagnostic criteria for gestational diabetes. In 1979, gestational diabetes was officially identified as a unique type of diabetes and characterized as “Carbohydrate intolerance of variable severity observed during pregnancy” for the first time (19).

Before the invention of insulin in 1922, it had already been known that women suffering from diabetes were often infertile. These women were believed to suffer from infertility due to amenorrhea, atrophy of the uterus and Graafian follicles, and malnutrition (20,21). After insulin was introduced in 1923, pregnancy rate among women with a short history of diabetes skyrocketed, rising by seven times. However, women who had been having diabetes for a long time still had low pregnancy rates or were unable to conceive for many years (22).

In 1882 in London, Duncan reported that out of 16 pregnant women and 22 pregnancies, high rates of maternal and perinatal mortality were recorded, with more than 60% of mothers and 47% of newborns not surviving. He drew several conclusions from his observations and findings about pregnancies, including the fact that diabetes may evolve during the course of pregnancy, may only appear during pregnancy, may cease after pregnancy and recur or develop after parturition, may not develop in pregnancy after it has been cured, woman may conceive when suffering from diabetes, diabetes may not affect the healthy progress of pregnancy and delivery, and pregnancy may be frequently interrupted by fetal death (23).

In 1909, Professor Williams of Baltimore reported 66 cases of diabetes in pregnant women from literature, 55 of which had diabetes before conception, nine developed diabetes during pregnancy, and the onset was unclear in two cases. The mortality rate at delivery was 27%, with

an additional 23% dying within two years after delivery. The perinatal mortality rate ranged from 27% to 53% (24). His manuscript primarily discussed how to interpret and use glycosuria as a diagnostic tool for diabetes during pregnancy, since it was the basis for diagnosing the condition at the time. He showed that if a female’s urine had 1-3 g/L of sugar, it was likely to be normal, but a greater amount pointed to diabetes, particularly during early pregnancy or in the presence of symptoms. This could have been the first instance of a diabetes screening program being conducted during pregnancy (24).

The source of glycosuria was not identified. It was suggested that the cause could be either alimentary, due to increased absorption of carbohydrates, or toxemic, due to liver abnormalities. In 1898, Brocard discovered pregnant women had lower tolerance for sugar than non-pregnant women, as evidenced by the presence of glycosuria two hours after ingesting 50g of glucose, which was found in 50% of pregnant women compared to just 11% of non-pregnant women (25).

Reports from the 1920s to 1930s suggested that still-born infants of mothers with diabetes had pancreatic abnormalities, mainly an enlargement of Langerhans’ islands. This was believed to occur due to glucose transfer from the mother to the fetus and inadequate maternal glucose control. There was a potential for newborns to experience deadly hypoglycemia within a few days of birth (20,26).

Many authors conducted reports on the efficacy of insulin after its discovery and use in pregnancy. In 1926, Lambie in Edinburgh noted that when diabetes developed during pregnancy, it occurred mainly in the fifth or sixth month, and rarely before the fourth or after the eighth month of gestation. He also proposed that the ketogenic-antiketogenic balance be determined using the 50 g oral glucose challenge test (OGCT) (27). In 1933, Skipper made a thorough review of literature regarding the use of insulin during pregnancy and discovered that it led to a marked decrease in maternal mortality and a slight improvement in fetal and newborn survival rates (28). He concluded that insulin use had led to a decrease in maternal mortality; women with diabetes often have glucose intolerance in the later stages of pregnancy; hypoglycemia is common postpartum and can cause severe problems, such as coma; if correctly treated, diabetes during pregnancy should not be harmful; ketonuria is common in untreated women; poor metabolic control, excessive growth of fetus, and congenital abnormalities are the leading causes of fetal death; therefore, any woman with glycosuria should be tested for diabetes, as it can emerge during pregnancy; monitoring glycosuria closely is essential; cesarean section may be necessary when the fetus is macrosomic; and breastfeeding should be encouraged, while sterilization should be considered for women with unstable diabetes, depending on the number of children they already have (28). His conclusions

are still being used today, albeit with some modifications and adaptations.

In 1945, Miller first recorded the presence of obstetric complications in the prediabetic period (29). During the 1950s the idea of gestational diabetes mellitus (GDM) was established, along with the identification of certain risk factors that can lead to the development of abnormal carbohydrate metabolism during pregnancy (30–33). Soon, it was proposed that screening programs be implemented for the early detection of diabetes in pregnancy.

In 1949, Dr. Priscilla White proposed the “White’s Classification” which became a standard for classifying diabetes and pregnancy. It was repeatedly modified to distinguish between patients who had gestational diabetes mellitus and those with pre-existing diabetes. The classification was enhanced by the addition of an alphabetic list that considered the onset of diabetes, how long the diabetes had been present, and if any complications were present due to diabetes (34).

### First steps in screening for gestational diabetes mellitus

Hoet first noted the heightened obstetrical risks associated with GDM in 1954. During the 1960s, GDM screening was performed solely by obtaining a patient’s history (35). In 1957, Wilkerson and Remein (31) proposed that a 3-hour oral glucose tolerance test (OGTT) should be given to patients with risk factors for diabetes, such as family history of diabetes, gestational glycosuria, and having an overdeveloped infant at birth, following Hoet’s study (35) and the observation of a large group of women by Dr. John B. O’Sullivan (22). They suggested that women with no known risk factors should have their blood glucose measured one hour after consuming a 50g glucose load. If the value is 130 mg or more, they should undergo a 3-hour OGTT (31).

The best way to screen and diagnose gestational diabetes mellitus was much debated. OGTT criteria for non-pregnant individuals suggested that approximately one-third of pregnant women would be diagnosed with diabetes. O’Sullivan and statistician Claire Mahan conducted 100-g OGTTs on 752 mainly pregnant women in the second and third trimesters and determined standard deviation upper limits for glucose values obtained from this test (36). The maximum values in the 2nd and 3rd hour were higher in pregnant individuals than those found in non-pregnant individuals, which is indicative of impaired glucose tolerance during pregnancy. The O’Sullivan and Mahan criteria were originally devised to predict type 2 diabetes in future, however, in the next few decades, they became an established method for detecting diabetes during pregnancy (36). O’Sullivan and Mahan proposed that fasting values should be 6,1 mmol/L, 1-hour values should be 9,4 mmol/L, 2-hour values should be 6,7 mmol/L and 3-hour values should be 6,1

mmol/L. If two or more of these values were abnormal, it would indicate an abnormal test result (36).

The findings of Pedersen and Priscilla White’s studies highlighting the importance of maternal glucose levels in the results of pregnancies for diabetic women have prompted a shift in the focus of diagnosing and treating these women earlier on. It is not only about a future risk of developing diabetes mellitus type 2, but also about the prevention of negative outcomes for the mother and the fetus in the current pregnancy (34,37).

### Gestational diabetes mellitus in literature

Bibliometric analysis geared towards a review of literature productivity and an observation of trends in gestational diabetes mellitus is presented in this section of the paper. The data are collected from the Web of Science platform (all sources), using the following search configuration:

$$TI = (gestational\ diabetes\ mellitus) OR TI = (diabetes\ in\ pregnancy)$$

*Indexes = SCI-EXPANDED, SSCI, AHCI, CPCI-S, CPCI-SSH, ESCI*

*Timespan = All years*

Data are collected for 10,207 scientific papers.

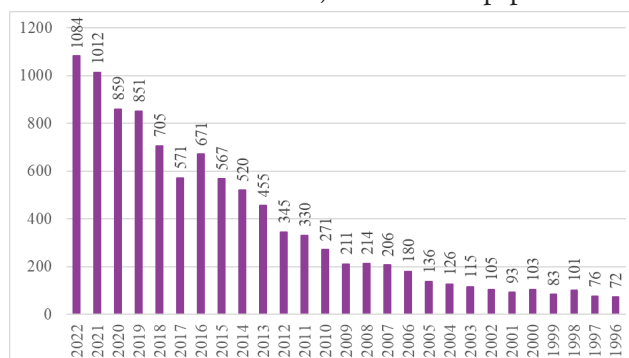


Figure 1. Number of published papers 1996-2022

The number of published papers with key words gestational diabetes mellitus or diabetes in pregnancy rose from 72 in 1996 to 1084 in 2022. A constant growth of the number of papers published with gestational diabetes or diabetes in pregnancy in title is evident.

Table 1 below shows 25 most popular research areas related to gestational diabetes mellitus. The highest number of papers comes from Endocrinology Metabolism research area (3981 papers), followed by Obstetrics Gynecology (2688 papers).

Those 10,207 papers were published in 1,378 journals. Table 2 presents 25 journals with the highest number of papers published in the observed period. The top contributor is DIABETES with 573 papers published, followed by DIABETOLOGIA and AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY.



**Table 1.** Most popular research area related to gestational diabetes mellitus

Research Areas	Number of papers	% of 10,207
Endocrinology Metabolism	3981	39.003
Obstetrics Gynecology	2688	26.335
General Internal Medicine	1015	9.944
Public Environmental Occupational Health	462	4.526
Reproductive Biology	429	4.203
Research Experimental Medicine	398	3.899
Nutrition Dietetics	381	3.733
Biochemistry Molecular Biology	327	3.204
Pediatrics	289	2.831
Pharmacology Pharmacy	217	2.126
Science Technology Other Topics	199	1.95
Environmental Sciences Ecology	171	1.675
Cell Biology	160	1.568
Cardiovascular System Cardiology	157	1.538
Developmental Biology	141	1.381
Nursing	113	1.107
Genetics Heredity	109	1.068
Medical Laboratory Technology	104	1.019
Health Care Sciences Services	99	0.97
Immunology	91	0.892
Physiology	86	0.843
Life Sciences Biomedicine Other Topics	67	0.656
Chemistry	65	0.637
Biotechnology Applied Microbiology	57	0.558
Neurosciences Neurology	50	0.49

**Table 2.** Most popular journals related to gestational diabetes mellitus

Publication Titles	Number of papers	% of 10,207
Diabetes	573	5.614
Diabetologia	515	5.046
American Journal of Obstetrics and Gynecology	426	4.174
Diabetes Care	389	3.811
Diabetic Medicine	280	2.743
Diabetes Research and Clinical Practice	232	2.273
Journal of Maternal-Fetal and Neonatal medicine	178	1.744
BMC Pregnancy and Childbirth	163	1.597
Obstetrics and Gynecology	154	1.509
Reproductive Sciences	147	1.44
BJOG: An International Journal of Obstetrics and Gynecology	139	1.362
Gynecological Endocrinology	139	1.362
Placenta	123	1.205
PLOS One	114	1.117
Frontiers in Endocrinology	113	1.107
Australian New Zealand Journal of Obstetrics and Gynecology	83	0.813
Acta Diabetologica	81	0.794
Acta Obstetrica et Gynecologica Scandinavica	76	0.745
Nutrients	75	0.735
Journal of Clinical Endocrinology Metabolism	71	0.696
Irish Journal of Medical Science	70	0.686
Journal of Obstetrics and Gynecology Research	68	0.666
Diabetes Technology Therapeutics	67	0.656
Journal of Diabetes Research	64	0.627
European Journal of Obstetrics, Gynecology and Reproductive Biology	62	0.607

**Table 3.** Top authors' affiliating countries

Countries/regions	Number of papers	% Of 10,207
USA	1969	19.291
People's R. of China	1754	17.184
Australia	730	7.152
England	699	6.848
Canada	468	4.585
India	361	3.537
Spain	345	3.38
Turkey	332	3.253
Italy	327	3.204
Denmark	278	2.724
Ireland	262	2.567
Iran	260	2.547
Poland	257	2.518
Israel	232	2.273
Brazil	227	2.224
Austria	225	2.204
Germany	222	2.175
Sweden	218	2.136
Netherlands	160	1.568
South Korea	153	1.499
France	150	1.47
Greece	146	1.43
Japan	145	1.421
Finland	132	1.293
Switzerland	122	1.195

**Table 3** presents top authors' affiliating countries. The USA and China are dominant in the field, followed by Australia, England, and Canada.

## CONCLUSION

The number of people with diabetes mellitus has slowly been increasing due to a longer life expectancy and faster detection of the disease. Modern treatments help to reduce the frequency of complications for those who already suffer from diabetes. Diabetes in pregnancy brings to light a new population, and the babies born from these pregnancies are a part of this group.

The high prevalence of diabetes around the globe is likely a result of changes in the modern lifestyle. This is a contemporary disease that is caused by an abundance of unhealthy food, lack of physical exercise, and obesity, just like Hippocrates suggested a long time ago.

Diabetes is mainly found in urban and industrialized areas, where individuals have access to unhealthy food and lack of physical activity, in addition to experiencing psychological effects of living in a city, such as chronic stress. All these factors combine to create an environment that leads to the development of diabetes.

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## ISTORIJA GESTACIJSKOG DIJABETES MELITUSA

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## Sažetak

Cilj ovog rada je da prikaže hronološki razvoj saznanja o dijabetes melitusu od vremena Hipokrata, preko Langerhansa i Vajtove, zatim kako se došlo do saznanja da je neadekvatna funkcija pankreasa uzrok nastanka dijabetes melitusa, a da je bubreg samo organ koji slabi usled neregulirane funkcije pankreasa. Izučavanjem gestacijskog dijabetes melitusa dolazi do bolje kontrole dijabe-

tesa u trudnoći, boljeg perinatalnog ishoda sa manjim brojem peripartalnih i perinatalnih komplikacija. U drugom delu rada dat je osvrt na celokupnu literaturu dostupnu na Web of Science-u, u smislu broja radova koji su objavljeni tokom godina, u kojim oblastima i u kojim zemljama.

**Ključne reči:** gestacijski dijabetes melitus; dijabetes u trudnoći; pregled literature

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## ORIGINAL ARTICLE

# Magnetic resonance angiography in children with arterial hypertension – a single-center experience

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**Competing interests:**

The authors have declared that no competing interests exist

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**Summary**

**Introduction:** Renal blood vessel (RBV) stenosis is the cause of secondary arterial hypertension (AH) in 10% of children. Digital subtraction angiography (DSA) is the gold standard in diagnosing RBV stenosis. Many authors suggest MR angiography (MRA), a non-invasive method without radiation, as an adequate diagnostic method. Our aim was to analyze the experience of our center in using MRA in children with AH. **Method:** This retrospective study included 148 patients hospitalized at the University Children's Hospital in Belgrade, due to AH. After initial examination, patients underwent DSA and/or MRA.

**Results:** According to the current guidelines, DSA was performed in patients with highly suspected RBV stenosis, and the diagnosis was confirmed in 13/29 (45%). Diagnostic MRA was done in 116/119 (97.5%) patients, and control MRA was done after therapeutic revascularization in 3/119 (2.5%). In 4/116 (3.5%) patients, the findings indicated RBV stenosis, and in 44/116 (38%) it indicated some other abnormality of the kidney parenchyma and the urinary tract or RBV varieties. After MRA, DSA was performed in 7/116 (6%) patients (4 with RBV stenosis on MRA and 3 with clinical suspicion of RBV stenosis), but all findings were normal.

**Conclusion:** According to the results, it is justified to perform a diagnostic MRA before DSA in children with highly suspected RBV stenosis, in order to avoid DSA which is an invasive procedure with radiation, in some patients with normal findings. Also, over time, we would have a clearer view of the sensitivity and specificity of MRA as a diagnostic method in RBV stenosis in children.

**Keywords:** Renal blood vessel stenosis, arterial hypertension, MR angiography, digital subtraction angiography, children

## INTRODUCTION

In children up to 16 years of age, the definition of arterial hypertension (AH) is arbitrary and implies systolic and/or diastolic blood pressure  $\geq$  95<sup>th</sup> percentile for sex, age and body height, and in adolescents over 16 year of age, it is an absolute value of blood pressure  $\geq$  140/90 mmHg, in three separate measurements (1). The prevalence of AH in children is between 2 and 4% (2). Stenosis of the renal blood vessel is the cause of secondary AH in about 10% of children and adolescents (3-6), and it is extremely important to establish the diagnosis considering therapeutic possibilities and treatment (5, 7). The causes of renovascular hypertension (RVH) in children are significantly different compared to the adult population (Table 1), in which atherosclerosis is the major cause in 75-80% of cases (5). In India and South Africa, Takayasu arteritis is the most common cause of RVH in children, while in the rest of the world it is fibromuscular dysplasia (8). Clinical symptoms, signs and laboratory findings that may raise suspicion of RVH (7) are shown in Table 2. Digital subtraction angiography (DSA), an invasive imaging method that requires radiation, is still the gold standard in diagnosing RVH in children (9). On the other hand, among the non-invasive imaging methods, Doppler ultrasound, renal scintigraphy, CT angiography (CTA) and magnetic resonance angiography (MRA) are also available. These methods are considered, by numerous authors, as possible adequate screening methods for the diagnosis of renal blood vessel stenosis (RBV stenosis) (7, 10-13). MRA has its advantages. In addition to being a non-invasive method and requiring no radiation, it enables a detailed analysis of the kidney parenchyma. The disadvantage is that it requires sedation or anesthesia in small children, and

**Table 1.** Causes of renovascular hypertension in children.

Genetics / Syndromes
Neurofibromatosis type 1
Alagille syndrome
Williams syndrome
Acquired conditions
Takayasu arteritis
Kawasaki vasculitis
Polyarteritis nodosa
Idiopathic renal artery stenosis
Fibromuscular dysplasia (histopathologic diagnosis)
Mid aortic syndrome
Congenital
Acquired
External renal artery compression
Neuroblastoma
Wilms tumor
Other
Radiation
Trauma
Transplant renal artery stenosis

**Table 2.** Signs, symptoms and laboratory findings associated with renovascular hypertension.

Extremely high blood pressure symptoms and secondary complications
Headache, convulsions, facial paralysis, stroke
Left ventricular hypertrophy, heart failure
Hypertension poorly controlled with two or more antihypertensive drugs
Conditions with high risk of renovascular hypertension
Neurofibromatosis type 1
Williams syndrome
Signs and symptoms of vasculitis
Malaise
High temperature
Weight loss
Weak pulses
Skin rash
Arthralgia
Auscultatory abdominal murmur
Previous vascular insults
Renal artery thrombosis
Umbilical artery catheterization
Previous trauma or radiation
Kidney transplant
Auscultatory bruits above renal arteries
Clomerular filtration rate drop after introducing ACE inhibitors or Angiotensin receptor blockers (ARBs)
Increase of Plasma rennin activity (PRA) or mild hypokalemia

the gadolinium-based contrast agent, is contraindicated in children with GFR<30 ml/min/1.73 m<sup>2</sup> (in most cases, gadolinium-based contrast agent should not be used in children with GFR<60 ml/min/1.73 m<sup>2</sup>) due to the risk of systemic fibrosis (14). There are few studies available in literature that investigated the sensitivity and specificity of MRA in children with RVH. The aim of this study was to analyze our center experience of using MRA in children with AH.

## PATIENTS AND METHODS

For the purposes of this retrospective study, medical data of 148 patients, hospitalized due to hypertension at the University Children's Hospital in Belgrade between January 2014 and October 2022 were obtained and processed. After establishing the diagnosis of AH, according to accepted recommendations (1), a general and targeted clinical examination and laboratory workup of importance for secondary causes of AH, and renal Doppler ultrasound, were performed, all according to the protocol for examining children with AH (7).

In patients with highly suspected RVH, DSA was performed. After giving detailed information and obtaining a written consent, DSA was performed by puncturing the femoral artery using the Seldinger technique. All procedures were done under medical sedation and local anes-

thetia, with antibiotic prophylaxis for bacterial endocarditis. Having punctured the femoral artery and placed the introducer sheath, a suitable tail catheter was introduced using a guide wire. A catheter with a wire was placed in the abdominal aorta at the place of origin of the renal artery. We used the low-osmolar contrast agent (Ultravist), with prior adequate intravenous hydration of the patient.

MRA was performed for diagnostic purposes in patients in whom secondary causes of hypertension were excluded after initial examination, but who had no adequate response to antihypertensive therapy, according to the protocol. After MRA, DSA was performed in patients with visible RBV stenosis and in patients with high clinical suspicion of RVH, in addition to a normal MRA finding. Also, MRA was done as a control imaging method, after therapeutic revascularization in patients with RVH (autotransplantation, balloon dilatation or stent placement). All MR examinations were performed on a 1.5 T whole-body MRI scanner (Magnetom Aera, Siemens AG, Healthcare Sector, Erlangen, Germany). Gadolinium-based contrast agent was used in the amount of 0.1 ml/kg of body weight.

The data were processed using descriptive statistical methods. For categorical data variables, the number (n) and percentage (%) were calculated.

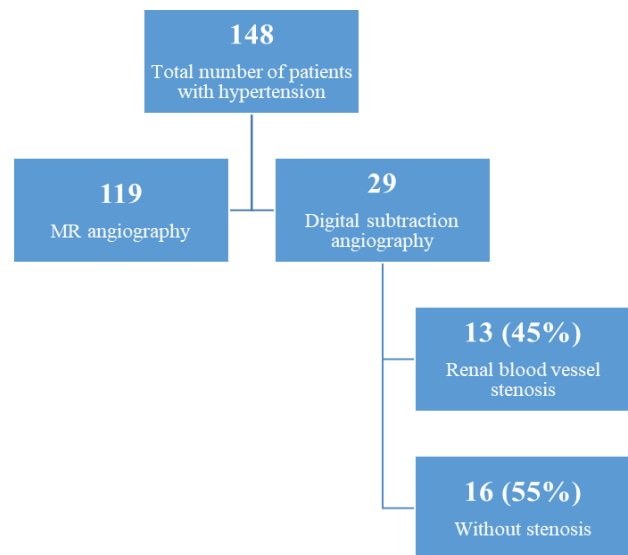
## RESULTS

After the initial tests (clinical examination, laboratory workup and renal Doppler ultrasound), due to a high suspicion of RVH, DSA was performed in 29 out of 148 patients included in the study. In 13 (45%) out of 29 patients, the diagnosis of RVH i.e., RBV stenosis was confirmed. The remaining 16 (55%) patients had normal findings on DSA (**Figure 1**).

MRA was performed in 119 patients, and in 116 (97.5%) patients it was done in diagnostic purposes, whereas it was performed as a control imaging method after therapeutic revascularization in 3 (2.5%) patients. In 4 (3.5%) out of 116 diagnostic MRA, the result indicated RBV stenosis, and in 44 (38%) patients it indicated some other abnormality of the kidney parenchyma and the urinary tract or a variety of kidney blood vessels (**Figure 2**).

Out of the 44 patients with some abnormality/variety on MRA, 25 (57%) had a variety of the RBV, 15 (34%) had some change in the kidney parenchyma, and 4 (9%) had an abnormality of lower parts of the urinary tract (**Figures 3 and 4**).

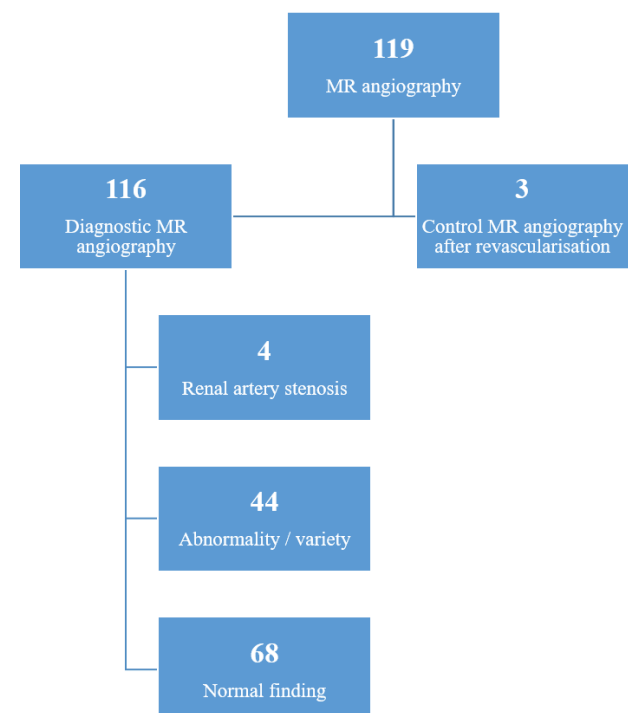
After diagnostic MRA, DSA was performed in 7 (6%) out of 116 patients. In 4 patients it was done due to RVB stenosis observed on MRA, and in 3 patients it was performed due to high clinical suspicion of RVH despite MRA which did not confirm renal artery stenosis, but indicated some of the varieties of RBV (**Figure 5**). In all 7 patients, DSA findings were normal.



**Figure 1.** MR angiography and digital subtraction angiography (DSA) in patients with hypertension

## DISCUSSION

Poorly controlled AH in childhood is one of the strongest predictors of AH in adulthood and its severe sequelae (myocardial infarction, stroke, encephalopathy) (15). Therefore, it is extremely important to diagnose AH in children, find its cause and provide an adequate treatment. RVH occurs as a result of reduced blood flow through one or both renal arteries due to their narrowing, which results in the activation of the renin-angiotensin-aldosterone system (16). Increased blood pressure is a compensatory mechanism that enables blood flow through a narrowed RBV, but over time it also leads to the damage of the target organ.



**Figure 2.** MR angiography in patients with hypertension

<b>Other abnormalities (4)</b>
Neurogenic bladder (2)
Ureter fissus (2)
<b>Parenchyma abnormalities (15)</b>
Cystic changes (11)
• Solitary cyst (5)
• Multiple cysts (6)
Scarring (2)
Agenesis, hypoplasia, dysplasia (2)

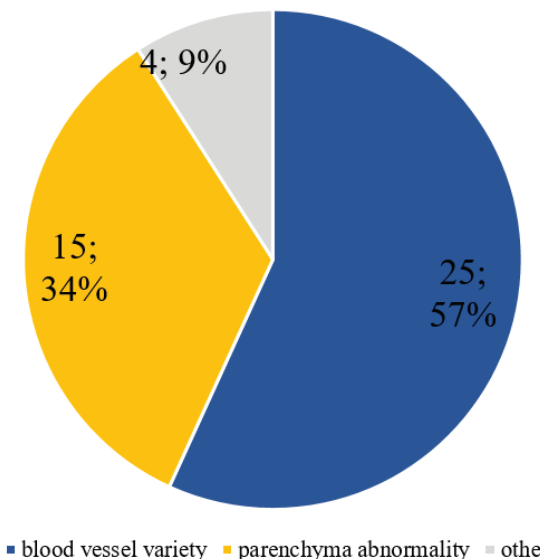
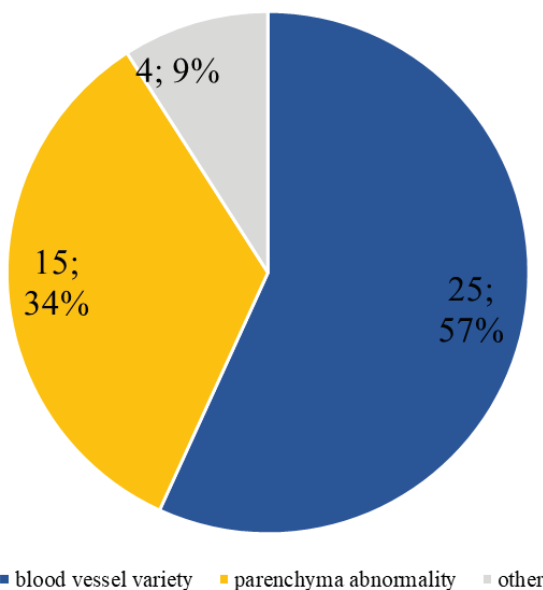


Figure 3. Parenchyma and other abnormalities in MR angiography findings

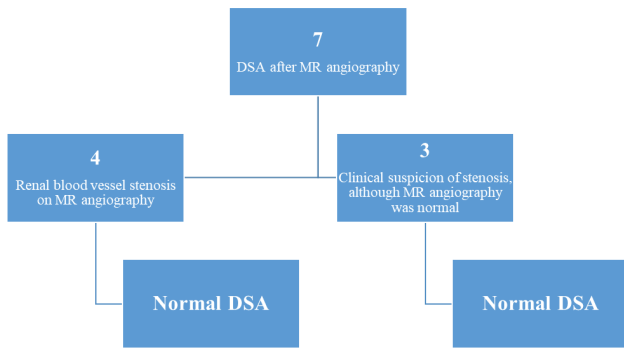
Considering all the specificities of the pediatric population, the clinical course, causes and outcomes of RVH compared to the adult population, the ideal imaging method in the diagnostic algorithm of RVH is still controversial (17). Although a relatively rare cause of secondary AH in children, RVH at this age has great possibilities of being treated with drug therapy, endovascular or surgical procedures (5, 13, 18). Therefore, the sensitivity of non-invasive diagnostic methods must be high, so that children with RVH do not remain undiagnosed and inadequately treated. Some authors consider non-invasive diagnostic methods as adequate screening for RVH (10-12, 16, 19). Results of other studies indicate poor sensitivity of these methods to exclude RBV stenosis, especially in case of intrarenal blood vessel stenosis, therefore it is recommended that DSA should be performed in all patients with high clinical suspicion of RBV stenosis, even when

the results of non-invasive diagnostic methods are normal (9, 20-22). For now, according to the latest data from literature, non-invasive diagnostic methods, renal Doppler ultrasound, CTA and MRA cannot replace DSA, which is currently considered the most reliable diagnostic method for confirming RVH in children (6, 9, 17). The advantages of this method are certainly the best view of the lumen of the RBV, as well as the possibility of a therapeutic endovascular intervention (balloon dilation, stent placement) during the same procedure (9), as well as taking blood from the renal vein in order to measure local renin synthesis in unreliable DSA findings (23). However, it has been shown that the selective collection of venous blood from the renal veins, taken for determining plasma renin activity, as a method for diagnosing RVH has low sensitivity (74%) and specificity (59%), which is why it is not frequently used (6). According to American proto-



<b>Renal artery varieties (25)</b>
Two renal arteries for each kidney (3)
Two renal arteries for left kidney (9)
Two renal arteries for right kidney (5)
Artery diameter difference (3)
Aberrant left renal artery (1)
Gracile accessory branch of right renal artery (1)
Coiling (2)
Early branching of left renal artery (1)

Figure 4. Renal blood vessel varieties in MR angiography findings

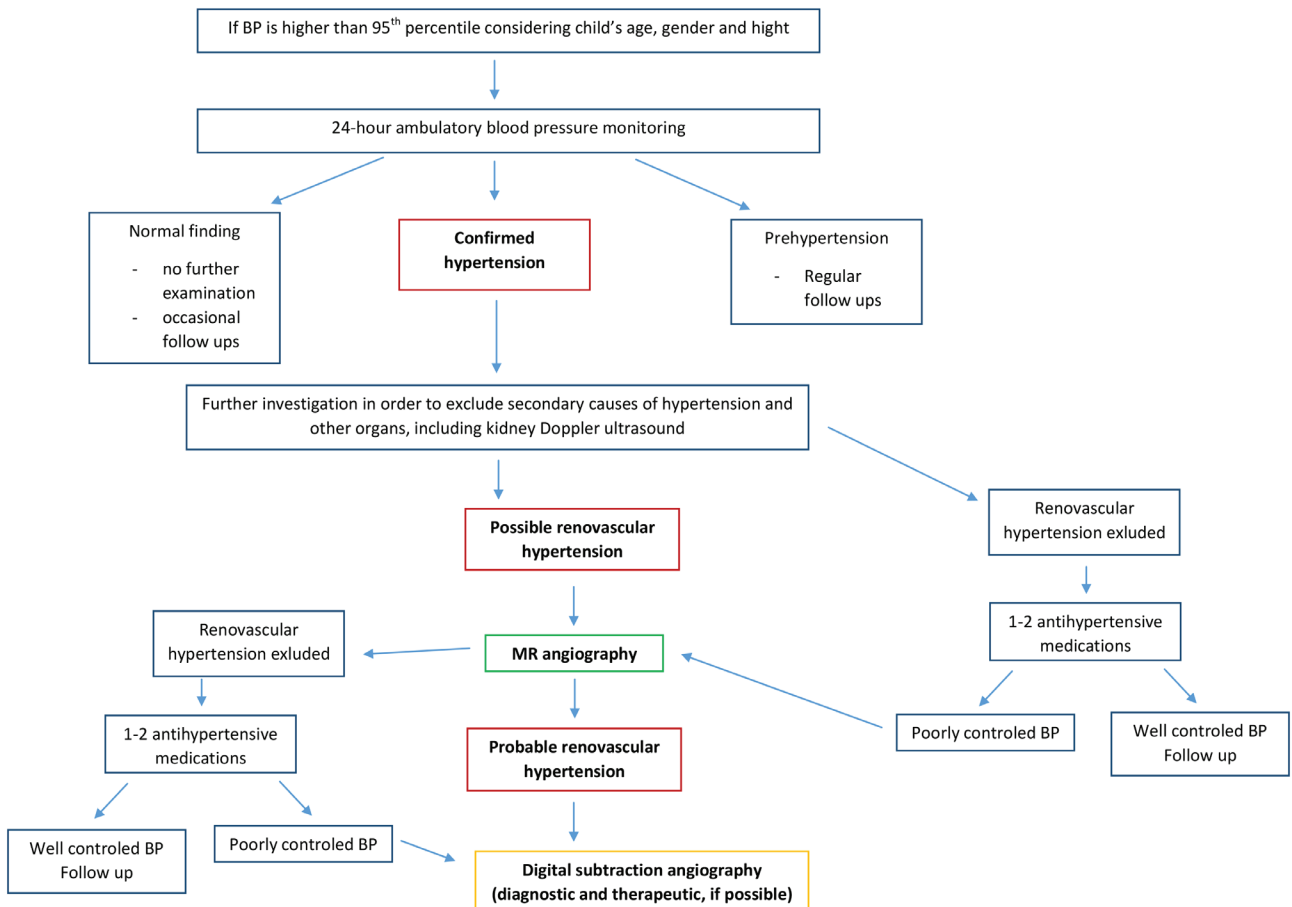


**Figure 5.** Digital subtraction angiography (DSA) after MR angiography

cols for adult patients with AH, blood sampling from renal veins is no longer recommended as a diagnostic method for detecting renal artery stenosis (24). Disadvantages of DSA are radiation to which children are exposed, the risk of arterial blood vessel injury and obtaining only indirect information about the blood vessel wall, which is important only from an etiological point of view (7, 22). According to the valid European and American guidelines for examining pediatric patients with AH (6, 7), it is recommended that patients with suspected RVH, after clinical and laboratory workup along with renal Doppler ultrasound, as the only non-invasive imaging method, should undergo the invasive DSA to definitively confirm

the diagnosis. In children under 10 years of age, the procedure usually requires general anesthesia, while in older patients it is possible to apply local anesthesia (14). When carefully selecting patients, according to data from literature, 40-78% of DSA findings in this population indicate RBV stenosis (9, 25, 26). Our results are consistent with data from literature. In 29 out of 148 patients included in the study due to high suspicion of RVH, after the initial clinical, laboratory examination and renal Doppler ultrasound, DSA was performed. DSA findings confirmed RBV stenosis in 13/29 patients (45%).

The results of MRA in patients with suspected RVH are becoming increasingly more informative over time, and therefore the technical capabilities of MRA device are getting better, which facilitates the interpretation of findings by radiologists (14). A meta-analysis that included 998 adult patients from 25 studies indicated MRA sensitivity of 94% and specificity of 85% (27) for diagnosing the cause of RVH. The use of gadolinium as a contrast agent increased the sensitivity (97%) and specificity (93%) of the method (27-32). A study involving pediatric patients with suspected RVH indicated a lower sensitivity (80%) and specificity (63%) of MRA (9). In this study, MRA was performed in 39 patients, and stenosis of renal blood vessels, later confirmed by DSA, was not diagnosed in 10 patients (6 – main trunk of the renal artery, 2 – main branch of the renal artery, 2 – segmental



**Figure 6.** Recommended protocol for children with arterial hypertension

arteries). False positive results were observed in children with varieties of renal blood vessels (two renal arteries on one side, one of which is gracile but without stenosis on DSA). The authors state that the disadvantage of this study is that it is retrospective and includes patients from many centers around the world, where numerous radiologists worked on technically different devices and interpreted the results of the MRA scans. Louis et al. indicated an extremely low sensitivity (62.5%) and high specificity (100%) of MRA in 25 pediatric patients with fibromuscular dysplasia (19). Out of the 116 diagnostic MRA examinations performed in our patients, the results of the findings indicated suspected RBV stenosis in 4 patients, and some varieties of RBV in 25 patients. In 3 patients, we performed MRA as a control imaging method after DSA and one of the applied methods of revascularization of the stenotic RBV, which is why we intended to avoid an invasive imaging method and re-exposing the patient to radiation. The result of the control MRA was normal in all three patients. As the guidelines for pediatric patients with AH state (6, 7) in 7 patients we performed DSA after the diagnostic MRA, in 4 patients we performed it due to suspected RBV stenosis, and in 3 due to high clinical suspicion of RVH despite the fact that MRA did not indicate stenosis of the renal blood vessel, but some variety of kidney blood vessels. In all 7 patients, the DSA result did not indicate RBV stenosis. MRA has its importance in the diagnosis of RVH, but there are possible false positive or negative findings. MRA finding should always be defined in accordance with the clinical features and is part of the diagnostic workup in children with suspicious RVH.

It should not be forgotten that the most common cause, responsible for 60% of secondary hypertension in the pediatric patient population, is of renal parenchymal origin (glomerular diseases, renal parenchymal scars) (6) and that MRA images ideally show the renal parenchyma, so they represent an excellent non-invasive method for its evaluation (9). In 15/116 patients included in our study who underwent diagnostic MRA, changes in the kidney parenchyma were found. The most common ones were cystic changes in 11 patients, renal scarring in two patients and morphological changes such as agenesis/hypoplasia/dysplasia in two patients.

There is a small number of studies in pediatric population available in literature, which deal with the importance of this non-invasive diagnostic method. The reason for this are the specificities of the pediatric population, primarily in terms of the size of blood vessels, technical artifacts during MRA due to movement, small number of patients per center with technically different capabilities of the MRA device and a large number of radiologists who interpret the findings. Therefore, our opinion is that, despite the mentioned advantages of MRA, this non-invasive diagnostic method that does not require radiation has been insufficiently investigated and used in the pediatric population of patients with AH.

Current guidelines for examining pediatric patients with AH (6, 7) clearly state that after clinical and laboratory tests along with renal Doppler ultrasound, as the only initial non-invasive diagnostic method, when RVH is suspected, the patient should be referred directly to DSA in order to confirm the diagnosis. According to the data available in literature (9, 25, 26), and according to the results of our study, an average of about 50% of pediatric patients sent to DSA, due to highly suspicious RVH, had a normal finding. Therefore, in our opinion, it is justified to first refer pediatric patients with suspected RVH who are examined according to the above-mentioned guidelines, to MRA (Figure 6). This way, a number of patients with a normal MRA finding would probably avoid DSA as an invasive diagnostic method that requires radiation and carries the already mentioned intervention risks. Certainly, patients with clinically highly suspected RVH, in the first place, and with an unsatisfactory response to two or more antihypertensive drugs, despite the normal findings of MRA, are justified to be referred to DSA. Also, over time, this way, we would have enough patients with highly suspicious RVH and performed MRA to adequately assess the sensitivity and specificity of this non-invasive diagnostic method in terms of diagnosing stenosis of the RBV.

## CONCLUSION

We have presented our experience of using MRA in children with AH. RVH is an important cause of secondary AH in children and adolescents, and it requires a serious multidisciplinary approach by nephrologists, interventional radiologists/cardiologists and vascular surgeons. A clearer prediction of the diagnostic significance of the sensitivity and specificity of MRA in children with suspected RVH would be obtained by planning a prospective study under the same clinical, laboratory and technical conditions. Certainly, a great problem is the relatively small number of pediatric patients with suspected RVH per center, which is why multicenter studies are necessary to contribute to solving this problem.

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None.

## Conflict of interest

None to declare.

## Authors' contributions

Study design: MC, MK. Acquisition: MC, GML, DP, BS, MĐ, PP, IG, TR, IS. Analysis: MC, MK, AP, TG. Data interpretation: MC, MK, AP. Preparing the draft version of



the manuscript: MC, MK, AP. Revising the manuscript: MC, MK, AP, GML, DP, BS, MĐ, PP, IG, TG, TR, IS.

## Ethical approval

This research and publication were approved by the Ethical committee of the University Children's Hospital (approval number 017 16/2).

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## PRIMENA MAGNETNE ANGIOGRAFIJE KOD DECE SA ARTERIJSKOM HIPERTENZIJOM - ISKUSTVO JEDNOG CENTRA

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### Sažetak

**Uvod:** Stenoza renalnog krvnog suda (RKS) uzrok je sekundarne arterijske hipertenzije (AH) kod 10% dece. Digitalna subtraktivna angiografija (DSA) je zlatni standard za postavljanje dijagnoze stenoze RKS. Mnogi autori razmatraju MR angiografiju (MRA) kao adekvatnu neinvazivnu dijagnostičku metodu koja ne zahteva zračenje. Cilj ovog rada je analiza iskustva našeg centra u primeni MRA kod dece sa AH.

**Metod:** U ovu retrospektivnu studiju uključeno je 148 pacijenata hospitalizovanih na Univerzitetnoj dečjoj klinici u Beogradu, zbog AH. Nakon inicijalnih ispitivanja, pacijentima je učinjena DSA i/ili MRA.

**Rezultati:** Prema važećim smernicama kod 29/148 pacijenata zbog visoke sumnje na stenozu RKS učinjena je DSA i dijagnoza je potvrđena kod 13/29 (45%). Dijagnostička MRA je učinjena kod 116/119 (97,5%), a kao kontrolna,

nakon terapijske revaskularizacije kod 3/119 (2,5%) pacijenata. Kod 4/116 (3,5%) nalaz je ukazao na stenozu RKS, a kod 44/116 (38%) pacijenata na neku drugu abnormalnost parenhima bubrega i urinarnog trakta ili varijetet RKS. Posle MRA, DSA je urađena kod 7/116 (6%) pacijenata (4 sa nalazom stenoze RKS na MRA, 3 sa kliničkom sumnjom na stenozu RKS i urednim nalazom MRA). Rezultat je bio uredan kod svih.

**Zaključak:** Prema našim rezultatima, opravdano je deci sa visokosuspektnom stenozom RKS, pre DSA, uraditi dijagnostičku MRA, kako bi se kod jednog broja pacijenata sa urednim nalazom izbegla DSA, kao invazivna procedura sa zračenjem. Pored toga vremenom bismo imali jasniji uvid u senzitivnost i specifičnost MRA kao dijagnostičke metode za stenozu RKS kod dece.

**Ključne reči:** Stenoza renalnog krvnog suda, arterijska hipertenzija, MR angiografija, digitalna subtraktivna angiografija, deca

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## ORIGINAL ARTICLE

# The relationship between functional status, natriuretic peptide levels and echocardiographic parameters in patients with precapillary pulmonary hypertension

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**Competing interests:**

The authors have declared that no competing interests exist

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**Summary**

**Introduction/Aim** While echocardiography plays an important role in the follow-up of patients with precapillary pulmonary hypertension (PH), several studies have identified World Health Organization's functional class (WHO FC), 6-minute walk distance (6MWD) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) as the strongest prognostic markers. We investigated the relationship between echocardiographic indices, functional status and NT-proBNP in patients with precapillary PH.

**Material and Methods** A total of 23 patients were included in this retrospective study. Data were collected from routine risk assessments, including WHO FC, 6MWD, NT-proBNP, standard, strain and three-dimensional echocardiography. The echocardiographic data were analysed in terms of the patients' functional status as determined by WHO FC, 6MWD and NT-proBNP values.

**Results** Patients in WHO FC III or IV had a shorter 6MWD [180 (interquartile range 85-240 m)] than patients in WHO FC I or II [409 (interquartile range 364-494 m),  $p=0.02$ ], while the difference in NT-proBNP was not statistically significant [FC I or II: 1297 (interquartile range 283-3196) versus FC III or IV: 343 (interquartile range 274-598) pg/ml,  $p=0.146$ ]. There were inverse correlations between 6MWD and left and right ventricular longitudinal strain and a direct correlation between 6MWD and pulmonary acceleration time ( $r=0.73$ ;  $p=0.001$ ). NT-proBNP measurements were directly correlated with right heart dimensions and right ventricular strain and inversely correlated with pulmonary acceleration time ( $r=-0.70$ ;  $p=0.004$ ).

**Conclusion** Standard and advanced echocardiographic indices of right ventricular structure, function and hemodynamics correlate with functional status and natriuretic peptide levels in a heterogeneous cohort of patients with precapillary PH and may be useful ancillary parameters in clinical practice.

**Keywords:** pulmonary hypertension, echocardiography, functional status, natriuretic peptides

## INTRODUCTION

Pulmonary hypertension (PH) is characterized by chronic elevation of pulmonary artery pressure (PAP), defined as a mean PAP of  $\geq 20$  mmHg measured invasively by right heart catheterization (RHC) (1). It most frequently results from cardiac, respiratory, and connective tissue diseases, and the current classification has divided PH into five distinct groups based on the underlying mechanism (1). Group 1 (pulmonary arterial hypertension, PAH) and Group 4 (chronic thromboembolic pulmonary hypertension, CTEPH) belong to the spectrum of precapillary PH, which is hemodynamically defined as a mean resting PAP of  $\geq 20$  mmHg, pulmonary capillary wedge pressure (PCWP)  $\leq 15$  mmHg, and pulmonary vascular resistance (PVR)  $> 2$  Wood units (1). Although the understanding of the pathophysiologic mechanisms and therapeutic options of precapillary PH has improved considerably during past two decades, morbidity and mortality rates are still high (2).

While echocardiography and other cardiac imaging modalities play an important role in the follow-up of patients with precapillary PH, several studies have identified World Health Organization's functional class (WHO FC), 6-minute walk distance (6MWD), and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) as the strongest prognostic markers in this population of patients (3,4).

Accordingly, recent guidelines recommend using only these three variables for a simplified four-strata risk assessment during regular follow-up, with additional variables considered as needed (1). It should be noted that in the absence of one variable (WHO-FC, 6MWD or NT-proBNP), risk prediction is still accurate, but when two of these variables are not available, this risk assessment tool is no longer reliable (4,5).

On the other hand, three conventional echocardiographic parameters (right atrial systolic area, the presence of pericardial effusion, and the ratio of tricuspid annular plane systolic excursion (TAPSE) to systolic PAP) are included in a comprehensive risk assessment (three-strata model), but only at the time of diagnosis. Meanwhile, new echocardiographic techniques (e.g., strain-rate imaging and three-dimensional echocardiography) have not only emerged but have also become commercially available (6,7). It has not been fully explored if the parameters derived from advanced echocardiographic techniques are related to functional status and natriuretic peptides. Therefore, in this observational study, we investigated the relationship between conventional and advanced echocardiographic parameters, functional status, and the level of NT-proBNP in patients with precapillary PH.

## METHODS

This retrospective study included 23 patients (21 patients with PAH and 2 patients with CTEPH) diagnosed with precapillary PH or treated with PAH-specific therapies between January 2018 and December 2022 at the Department of Cardiology, Clinical Hospital Centre Zemun, Belgrade, Serbia. All patients were diagnosed and followed up according to the algorithms proposed in the guidelines, including RHC to confirm the presence of hemodynamic criteria (1,8). Risk stratification was routinely performed at the time of diagnosis and reassessed every 6-12 months thereafter, with frequency depending from individual patient characteristics. Data on WHO FC, the 6-minute walk test (6MWT), NT-proBNP, and comprehensive echocardiography were obtained from the hospital electronic medical records and the local PH database. If all key parameters were available, data from the last examination were recorded; otherwise, data from the most complete examination were used for the study. The study was approved by the Institutional Ethics Committee (licence number 21/2022-1).

### WHO functional class

On the basis of the presence or absence of excessive dyspnea or fatigue, chest pain, or near syncope at rest or with varying degrees of exertion, patients were divided into four functional classes. Patients in FC I had no limitation of physical activity, patients in classes FC II and III had mild and marked limitation of physical activity, respectively, whereas patients in class FC IV were unable to perform physical activity without symptoms (1).

Due to a relatively small sample size, instead of comparing patients from all functional groups separately, the comparisons were made between two major groups, assembling patients with no or mild symptoms (WHO FC I and II) and patients with pronounced symptoms (WHO FC III and IV).

### 6-minute walk test

The 6MWT was performed in accordance with international guidelines (9). Patients were instructed to walk along a straight 30-metre corridor for 6 minutes and were allowed to rest if necessary and continue or discontinue the test depending on their condition. The total distance at the end of the test was recorded. The start line was marked on the ground, while the turnaround points were marked with a cone. During the test, patients were directly observed by physicians (K.G., I.V., B.G.) and encouraged using standardized sentences.

### NT-proBNP

NT-proBNP was measured on the day of echocardiographic examination with the Elecsys NT-proBNP assay (Roche

Diagnostic, Mannheim, Germany). The assay was performed in the laboratory of Clinical Hospital Centre Zemun, Belgrade, Serbia. Normal values were below 125 pg/ml.

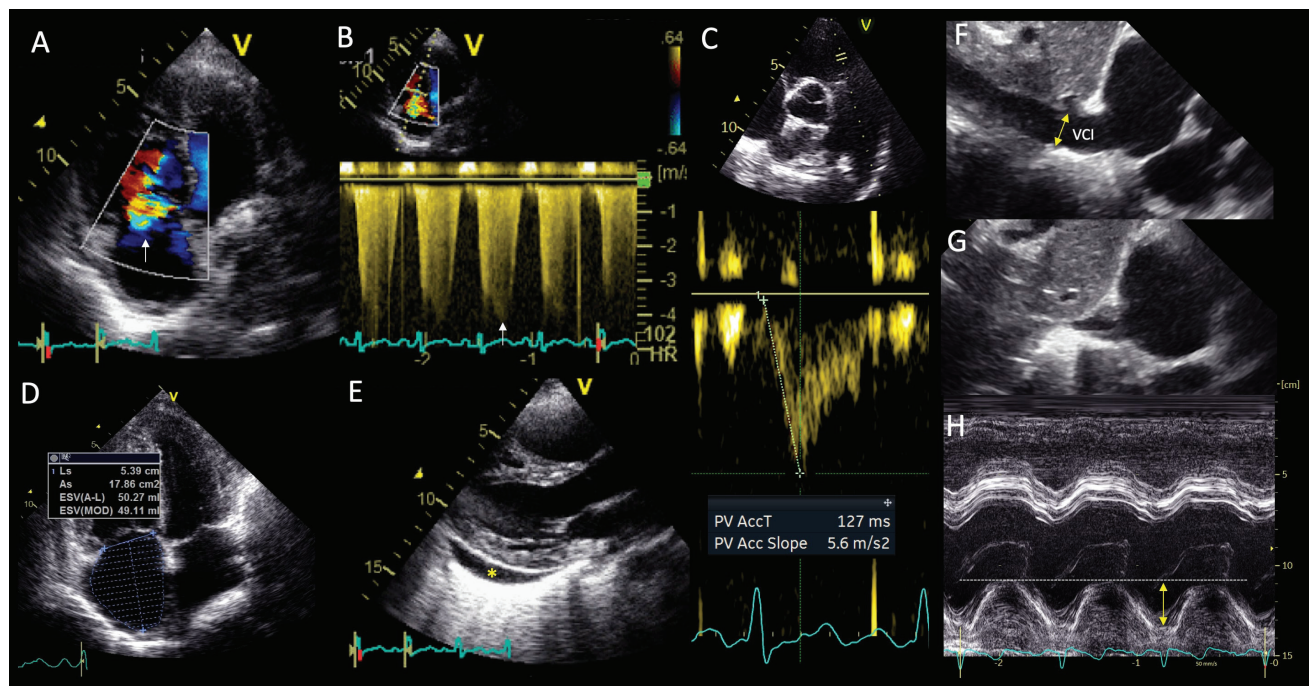
### Standard Doppler echocardiography

Echocardiographic examinations were performed using a commercially available Vivid E9 scanner (GE Healthcare, Horten, Norway). In accordance with hospital protocol, image loops from three consecutive cardiac cycles were digitally stored for further off-line analysis on a dedicated workstation (EchoPac, version 204, GE Healthcare). All measurements (standard and advanced) were performed by a single experienced echocardiographer (I.S.) who was blinded to all other data and complied with guideline recommendations (10,11). Left ventricular (LV) diameter was measured at the end of diastole in the parasternal long-axis view using the two-dimensional (2D) technique. LV ejection fraction (LVEF) was assessed using the modified Simpson rule (biplane disk summation method). Left atrial (LA) volume was determined by manually tracing LA contours in the apical 4- and 2-chamber views at the end of systole, excluding the area under the mitral annulus and the inlet of the pulmonary veins. The obtained value was indexed with the patient's body surface area to calculate the LA volume index (LAVI). The ratio of peak mitral velocity of early filling to early diastolic mitral annular velocity ( $E/e'$ ) was calculated using the average of septal and lateral  $e'$  velocities (11). The basal dimension of the right ventricle (RV) was measured at the end of diastole, while right atrial (RA)

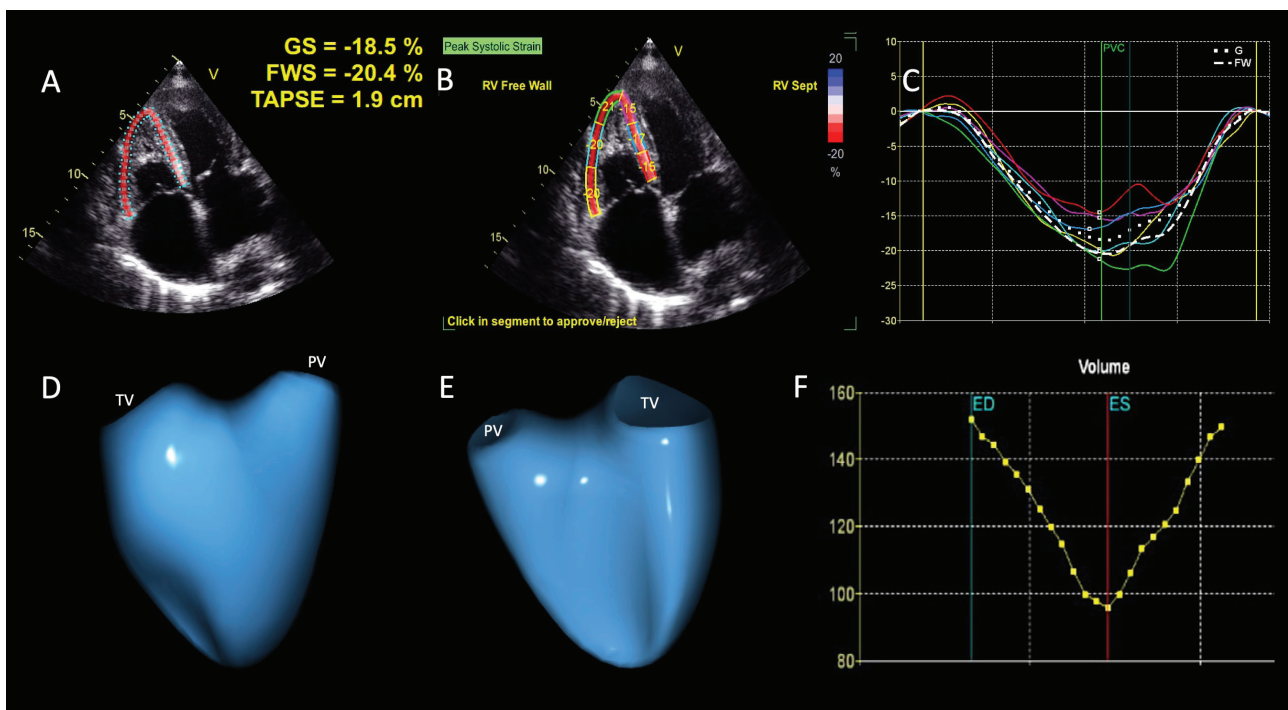
area was traced at the end of systole, excluding the area under the tricuspid annulus; both measurements were made from an RV-focused A4C view (Figure 1). RA volume index (RAVi) was assessed from the same window using the area-length method. RV systolic function was assessed by measuring TAPSE and systolic velocity of the tricuspid annulus ( $s'$ ) using the M-mode and tissue Doppler methods, respectively. Fractional area change of the RV (FAC) was assessed by tracing the endocardial border of the RV at end-diastole and end-systole and dividing the difference of the areas at end-diastole and end-systole by the area at end-diastole. RA pressure (RAP) was estimated from the subcostal view by assessing the diameter of the inferior vena cava (IVC) and its respiratory variations. Tricuspid gradient (TRG) was estimated from the maximum velocity of tricuspid regurgitation ( $4V_{max}^2$ ). Right ventricular systolic pressure (RVSP, also systolic PAP) was estimated by adding the estimated RA pressure to TRG. The ratio of TAPSE/systolic PAP was calculated as a non-invasive marker of RV-PA coupling (1). Acceleration time (AccT) of systolic pulmonary artery flow was measured from the forward velocity profile obtained with pulsed Doppler in the RV outflow tract near the pulmonary valve (Figure 1). PA diameter was measured in the parasternal short-axis view at the level of maximum diameter above the pulmonary root at the end of diastole.

### Advanced echocardiography

LV longitudinal strain was assessed by 2D speckle-tracking echocardiography from apical 4-, 2- and long-axis



**Figure 1.** Representative examples of standard Doppler echocardiography for assessment of right ventricular structure, function, and hemodynamics in pulmonary hypertension. A. Tricuspid regurgitation (arrow); B. Continuous wave Doppler profile of tricuspid regurgitation; C. Measurement of pulmonary artery acceleration time (pulse wave Doppler); D. Measurement of right atrial area; E. Pericardial effusion (\*) behind the posterior wall of the left ventricle; F. Measurement of inferior vena cava (VCI) diameter during normal respiration (arrow) and with inspiration (G); H. Tricuspid annular plane systolic excursion measurement (arrow).



**Figure 2.** Advanced echocardiographic assessment of the right ventricle. A. Speckle-tracking echocardiography of the right ventricle (RV) from the focused apical view. B. Longitudinal strain values of six free wall and septal segments are shown as numbers within each segment. C. Longitudinal strain curves of all RV segments (the color of the curve corresponds to the color of the segment shown in panel B). A representative case of right ventricular (RV) quantification using three-dimensional echocardiography (3DE) is shown in panels D and F. After manual placement of six landmark points at two-dimensional views (not shown here), a model of the RV is automatically generated. F. RV volume calculation with 3DE - the curve represents the volume changes during the cardiac cycle. GS - global strain, FWS - free wall strain, PV - pulmonary valve, TAPSE - tricuspid annular plane systolic excursion, TV - tricuspid valve.

views with a temporal resolution of >50 frames per second (fps), using dedicated software (EchoPAC, version 204) and a semi-automated tool (AFI LV). Global longitudinal strain (GLS) was calculated by the software as the average of 18 LV segments (6 segments per view).

Longitudinal RV strain was determined by 2D speckle tracking echocardiography from RV-focused A4C acquisition, with a temporal resolution of >50 fps (6,12). Care was taken to ensure that the region of interest included both the RV free wall and the septum, with width adjusted to cover the thickness of the RV free wall. After checking the quality of the tracking, the longitudinal strain of the RV free wall (FWS) was calculated using the software (EchoPAC, version 204, AFI RV tool) as the average of the strain values of the three segments of the RV free wall, while the global longitudinal strain of the RV was calculated as the average of the six segmental strain values of the RV free wall and the interventricular septum (Figure 2).

For three-dimensional (3D) echocardiography, 6-beat full-volume 3D data sets of the RV (volume rate > 30 volumes/s) were obtained during breath-hold from the focused A4C view of the RV, taking care to encompass the entire RV. Post-processing of the 3D images was done using commercially available software (EchoPAC, 4D AutoRVQ Tool) to calculate RV volumes and ejection fraction (Figure 2).

### Statistical analysis

Normally distributed continuous data are expressed as mean ± standard deviation, while categorical data are summarized by frequencies and percentages. Normally distributed data were compared between groups using unpaired t-tests for continuous variables and Fisher's exact test for categorical variables. Normality assumptions were tested using Shapiro-Wilk and Kolmogorov-Smirnov tests. If the results of either test indicated that the normality assumption was not met, median and interquartile ranges (IQR) and Mann-Whitney U test were used. Correlations between clinical, laboratory and echocardiographic parameters were described using the Spearman correlation coefficient.

### RESULTS

The baseline characteristics of the patients and the breakdown of PH etiologies are shown in Table 1. The majority of patients were female, with arterial hypertension and hypothyroidism being the most common comorbidities. At the time of the study, 87% of patients were symptomatic (WHO FC II-IV), and all but one were receiving at least one PAH-targeted therapy. Two patients received monotherapy, 18 received combination therapy and 2 patients received triple PAH-specific therapy. Long-term oxygen therapy was used by 44% of patients. The

**Table 1.** Characteristics of study population

Age, years	57±17
Female sex, n (%)	17 (74)
Arterial hypertension, n (%)	13 (57)
Hypothyroidism, n (%)	6 (26)
Atrial fibrillation, n (%)	4 (17)
Diabetes mellitus, n (%)	2 (9)
Coronary artery disease, n (%)	2 (9)
WHO functional class	
I, n (%)	3 (13)
II, n (%)	9 (39)
III, n (%)	7 (30)
IV, n (%)	4 (17)
6MWD, m	316±176
NT-proBNP, pg/mL	370 [274-1935]
<b>PH etiology</b>	
Idiopathic, n (%)	7 (30)
Connective tissue disease, n (%)	4 (17)
Congenital heart disease, n (%)	10 (44)
Chronic thromboembolic PH, n (%)	2 (9)
<b>PH specific therapies</b>	
Sildenafil, n (%)	21 (91)
Riociguat, n (%)	1 (4)
Bosentan, n (%)	7 (30)
Ambrisentan, n (%)	2 (9)
Macitentan, n (%)	8 (35)
Selexipag, n (%)	2 (9)

6MWD – 6-minute walk distance; NT-proBNP – N-terminal pro-B-type natriuretic peptide; PH – pulmonary hypertension; WHO – World Health Organization.

6MWT could not be performed in four patients due to their general condition or inability to walk without support. NT-proBNP measurements were not performed in five patients due to unavailability of lab kits or technical issues with the blood samples.

Standard and advanced echocardiographic data on LV and RV morphology and function are summarised in **Table 2**. Standard echocardiographic and speckle-tracking longitudinal strain-derived parameters were available in all patients. RV ejection fraction could not be reliably determined with 3D echocardiography in 35% of patients because of the presence of atrial fibrillation, insufficient patient cooperation during image acquisition, or inability to encompass the entire RV while maintaining adequate volume rates. There were no patients with reduced LVEF (<50%) or with more than mild mitral or aortic valve disease. Pericardial effusion was observed in 30% of patients and was mild in all cases (<10 mm at the end of diastole). In our study population, there was a moderate direct correlation between LV GLS and RV 6-segment strain ( $r=0.47$ ,  $p=0.037$ ), while no significant correlation was observed between LV GLS and RV FWS ( $r=0.17$ ,  $p=0.464$ ). There were significant differences in RV FWS, sPAP, pulmonary AccT and TAPSE/sPAP ratio between asymptomatic or mildly symptomatic patients (WHO FC I and II) and those with marked symptoms (WHO FC III and IV) (**Table 2**). On the other hand, the RA areas were similar ( $p=0.496$ ), and there was no significant difference in the prevalence of pericardial effusion

**Table 2.** Standard and advanced echocardiographic parameters in all patients and with regard to the patient functional status

	All patients (n=23)	WHO FC I or II (n=12)	WHO FC III or IV (n=11)	p-value
LVEDD, mm	44±9	45±5	42±12	0.448
LVEF, %	58±7	57±7	59±6	0.618
LV GLS, %	-17±3	-16.8±2.9	-17.9±2.3	0.391
LAVI, ml/m <sup>2</sup>	32±10	34±9	30±10	0.269
Mitral E/e' ratio	10.5±3.2	10.6±3.5	10.4±2.9	0.899
Pericardial effusion, n (%)	7 (30)	3 (25)	4 (36)	0.667
RV basal diameter, mm	45±9	46±10	45±8	0.917
RA area, cm <sup>2</sup>	23±9	22±8	25±10	0.496
RAVI, ml/m <sup>2</sup>	44±19	44±22	45±18	0.880
TAPSE, mm	19±5	20±5	18±4	0.215
RV FAC, %	34±9	37±8	31±10	0.104
sPAP, mmHg	73±30	58±28	89±25	0.013
TAPSE/sPAP, mm/mmHg	0.31±0.16	0.40±0.17	0.21±0.06	0.002
S', cm/s	11±3	12±3	10±2	0.075
RV FWS, %	-16.5±5.5	-18.9±5.1	-13.9±4.9	0.029
RV 6-segment strain, %	-14.4±4.4	-15.9±4.6	-12.9±3.6	0.108
PA diameter, mm	34±8	34±5	33±10	0.853
PA AccT, ms	88±27	103±29	76±18	0.025

AccT – acceleration time, FAC – fractional area change, FWS – free wall strain, LV GLS – global longitudinal strain of the left ventricle, LAVI – left atrial volume index, LVEDD – left ventricular end-diastolic diameter, LVEF – left ventricular ejection fraction, PA – pulmonary artery, RA – right atrial, RAVI – right atrial volume index, RV – right ventricular, S' – tricuspid annular systolic velocity, sPAP – systolic pulmonary artery pressure, TAPSE – tricuspid annular plane systolic excursion, WHO – World Health Organization.

**Table 3.** Correlations between 6MWD, NT-proBNP values and echocardiographic parameters

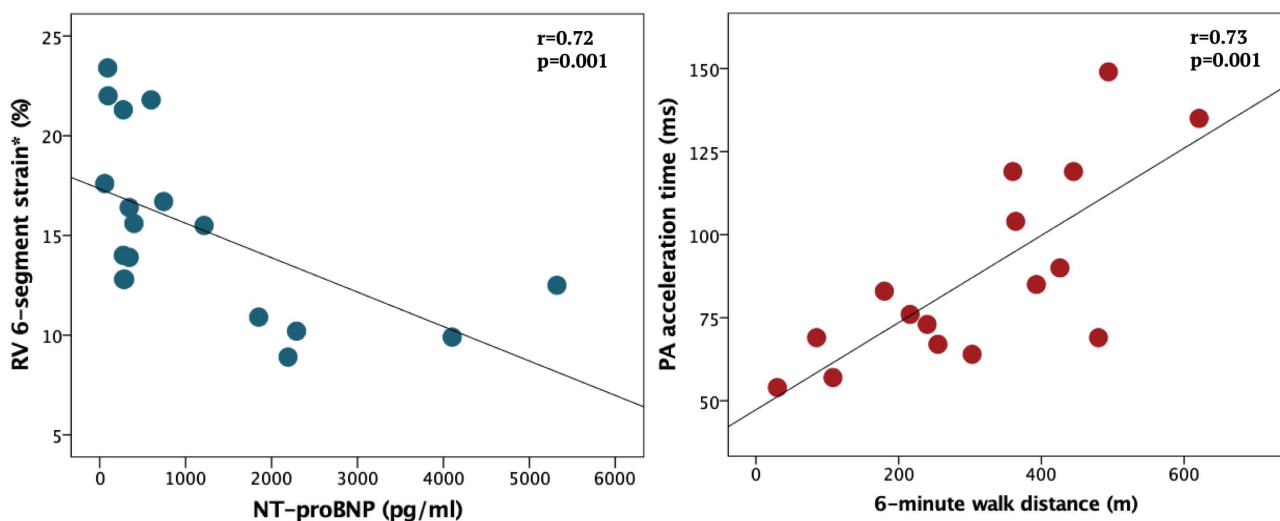
	6MWD, m		NT-proBNP, pg/ml	
LV EDD, mm	r=0.13	p=0.606	r=0.13	p=0.606
LVEF, %	r=0.13	p=0.606	r=-0.11	p=0.653
LV GLS, %	r=-0.53	p=0.030	r=0.33	p=0.180
LAVI, ml/m <sup>2</sup>	r=0.31	p=0.213	r=-0.15	p=0.566
Mitral E/e' ratio	r=-0.15	p=0.587	r=0.09	p=0.741
RV basal diameter, mm	r=-0.02	p=0.994	r=0.53	p=0.024
RA area, cm <sup>2</sup>	r=-0.13	p=0.598	r=0.64	p=0.005
TAPSE, mm	r=0.35	p=0.147	r=-0.38	p=0.125
RV FAC, %	r=0.14	p=0.571	r=0.01	p=0.981
sPAP, mmHg	r=-0.22	p=0.368	r=0.29	p=0.245
TAPSE/sPAP, mm/mmHg	r=0.41	p=0.081	r=-0.41	p=0.089
S', cm/s	r=0.12	p=0.659	r=-0.07	p=0.811
RV FWS, %	r=-0.59	p=0.008	r=0.65	p=0.004
RV 6-segment strain, %	r=-0.55	p=0.015	r=0.72	p=0.001
RVEF, %	r=0.31	p=0.301	r=-0.18	p=0.577
PA AccT, ms	r=0.73	p=0.001	r=-0.70	p=0.004
PA diameter, mm	r=0.31	p=0.261	r=-0.21	p=0.464

6MWD – 6-minute walk distance, AccT – acceleration time, FAC – fractional area change, FWS – free wall strain, GLS – global longitudinal strain, LAVI – left atrial volume index, LV – left ventricular, LVEDD – left ventricular end-diastolic diameter, LVEF – left ventricular ejection fraction, NT-proBNP - N-terminal prohormone of brain natriuretic peptide, PA – pulmonary artery, RA – right atrial, RV – right ventricular, RVEF – right ventricular ejection fraction, S' – tricuspid annular systolic velocity, sPAP – systolic pulmonary artery pressure, TAPSE – tricuspid annular plane systolic excursion, WHO – World Health Organization.

between the two groups (p=0.667). Patients in WHO FC III or IV had a shorter 6MWD [180 (IQR 85-240 m)] than patients in WHO FC I or II [409 (IQR 364-494 m), p=0.02], while the difference in NT-proBNP was not statistically significant [FC I or II: 1297 (IQR 283-3196) versus FC III or IV: 343 (IQR 274-598) pg/ml, p=0.146].

The correlations between 6MWD, NT-proBNP values and echocardiographic parameters are shown in **Table 3**. There were moderately strong inverse correlations

between 6MWD and LV GLS, RV FWS and 6-segment longitudinal strain and a strong direct correlation between 6MWD and pulmonary AccT (**Figure 3A**). Other echocardiographic parameters were not significantly correlated with 6MWD. NT-proBNP measurements correlated moderately with basal RV diameter, RA area and RV FWS; there was a strong direct correlation with RV 6-segment strain and a strong inverse correlation with pulmonary AccT (**Figure 3B**).



**Figure 3.** Scatter plots showing correlations between clinical and echocardiographic parameters. A. Correlation between right ventricular (RV) 6-segment strain and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (\* absolute values of RV strain are shown). B. Correlation between pulmonary artery (PA) acceleration time and 6-minute walk distance.



## DISCUSSION

In this retrospective observational study, we found significant correlations between functional status, standard and advanced echocardiographic indices and natriuretic peptides in patients with precapillary PH. Functional class correlated with strain parameters reflecting RV systolic function and with noninvasive surrogates of pulmonary arterial pressure, pulmonary vascular resistance and RV-PA coupling. In addition, 6MWD correlated with longitudinal strain-derived echocardiographic parameters reflecting left and right ventricular function, whereas NT-proBNP correlated with parameters reflecting structure and function of right heart chambers. Only pulmonary acceleration time, as a surrogate measure of pulmonary vascular resistance, correlated with WHO FC, 6MWD, and NT-proBNP values.

Elevated NT-proBNP is commonly used in cardiology as a biomarker for heart failure and atrial fibrillation and indicates poor prognosis (13). The association between NT-proBNP and right heart function and morphology has been investigated in various patient populations with PH, where right heart chambers were usually assessed by cardiovascular magnetic resonance (CMR), whereas right heart hemodynamics were determined by RHC (14-16). For example, in a study of patients with PAH and CTEPH, NT-proBNP correlated negatively with RVEF, assessed by CMR (14). Furthermore, NT-proBNP correlated with RV volumes determined by CMR and pulmonary pressures assessed by echocardiography in patients with PAH, who had congenital heart disease (atrial septal defect) (15). In addition, NT-proBNP, RV dimensions, systolic PAP, and pulmonary AccT were higher in patients with functional limitations after pulmonary embolism and suspected CTEPH (16). Our data support the notion that NT-proBNP reflects RV structure and function in the precapillary PH and suggest that comprehensive echocardiographic data and NT-proBNP may be clinically useful when CMR and 6MWT are unavailable, impractical, or contraindicated.

Previous studies showed that RV strain imaging can also provide important clinical information (17,18). In chronic PH, RV strain, derived from 2D and 3D speckle tracking echocardiography, and 3D RVEF were lower in patients with pre- and post-capillary PH compared with controls. Advanced echocardiographic indices (e.g. 2D and 3D strain) reflected global and regional RV dysfunction better than conventional echo parameters and were independent predictors of mortality (17). Moreover, it was recently reported that in patients with idiopathic PAH, not only the numerical values of RV strain but also the patterns of the curves might be prognostically important (18). In this patient population, speckle-tracking echocardiography allowed the identification of three phenotypically distinct RV strain-derived post-systolic patterns that were associated with prognosis (18).

In a recent study, RV strain abnormalities were associated with 6MWD, NT-proBNP, and mortality (19). In another report, global RV longitudinal strain predicted long-term prognosis in patients with PAH but showed only a weak correlation with B-natriuretic peptide concentration (20).

In a large study including 575 patients with confirmed or suspected PAH, RV longitudinal strain predicted clinical outcomes and decreased in parallel with functional class, 6MWD, increase in NT-proBNP levels and the presence of RV failure (21). While the association between reduced functional capacity, RV pressure overload, and marked reduction in RV systolic strain was expected, our data showed that 6MWD was also related to LV global longitudinal strain. This observation is prognostically important because it has been demonstrated that reduction in LV GLS was associated with early mortality despite preserved LVEF, underscoring the importance of ventricular interdependence in PAH (22).

3D echocardiography allows not only analysis of RV strain and measurement of RV ejection fraction but also a comprehensive analysis of RV shape. Increased eccentricity, apical rounding, and bulging at the base have been shown to characterize RV shape in PH, but interestingly, the shape changes were not associated with symptoms as assessed by WHO FC (23). Different loading conditions have also been shown to be associated with specific RV curvature changes associated with longitudinal and radial RV dysfunction (7).

In our study, the ratio of TAPSE/systolic PAP was lower in patients with more severe symptoms than in patients with milder symptoms. It has been suggested that this index of RV-arterial coupling can be improved by using RV strain instead of TAPSE (24). In a recent study, the RV strain/sPAP ratio predicted all-cause mortality and heart-lung transplantation and was superior to other established parameters in patients with precapillary PH (24).

In the current study, pulmonary AccT was strongly correlated with patients' functional status and NT-proBNP level. In previous reports, pulmonary AccT was inversely correlated with pulmonary haemodynamics measured with RHC and was able to accurately predict PAP and PVR (25). Furthermore, in the paediatric population, the addition of pulmonary AccT improved the specificity of NT-proBNP for the diagnosis of PH (26). In adult patients, pulmonary AccT <90 ms was a strong non-invasive predictor of PVR >3 WU, which could distinguish patients with pre- and post-capillary PH (27).

Finally, owing to advances in diagnosis and therapy, the majority of patients with CHD reach adulthood (28). In our study, a heterogeneous cohort of patients with adult congenital heart disease (ACHD)-related PAH accounted for more than 40% of the study population. In these patients, RV function may be impaired even without PH because of pressure and/or volume overload (28). While patients with ACHD-related PAH are treat-

ed similarly to other patients with PAH, there are some differences in RV response to PH, including more pronounced RV hypertrophy but also a longer period of stable RV function in patients with Eisenmenger syndrome compared with patients with idiopathic PAH (29). Other predictors of survival in PAH, such as 6MWT, WHO functional class, and NT-proBNP levels, are also applicable in Eisenmenger patients (30).

## LIMITATIONS

Our study is limited by its retrospective, observational design and small number of participants. RV systolic strain was highly feasible, similar to previous reports (20), while RV 3D assessment was feasible in 65% of patients. Feasibility in our study was slightly lower than in a recent report, where feasibility in the focused A4C view using different 3D settings was 72% (31).

The characteristics of our patient population (markedly enlarged right ventricles, patients' inability to hold their breath and prevalent atrial fibrillation) as well as our conservative approach to obtaining reliable 3D sets probably contributed to this discrepancy.

## CONCLUSION

Standard and advanced echocardiographic indices of RV structure, function and hemodynamics correlate with functional status and natriuretic peptide levels in a heterogeneous cohort of patients with precapillary PH and may be useful ancillary parameters in clinical practice.

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None.

## Conflict of interest

None to declare.

## Ethical approval

The study was approved by the Ethics committee of **blinded** (the license number 21/2022-1).

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## POVEZANOST FUNKCIONALNOG STATUSA, NIVOA NATRIURETSKIH PEPTIDA I EHOKARDIOGRAFSKIH PARAMETARA KOD BOLESNIKA SA PREKAPILARNOM PLUĆNOM HIPERTENZIJOM

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### Sažetak

Uvod/Cilj Iako ehokardiografija ima važnu ulogu u praćenju bolesnika sa prekapilarnom plućnom hipertenzijom (PH), više studija je identifikovalo funkcionalnu klasu Svetske zdravstvene organizacije (FK SZO), šestominutnu distancu hodom (6MDH) i N-terminalni prohormon moždanog natriuretskog peptida (NT-proBNP) kao najjače prognostičke parametre. Cilj istraživanja je ispitivanje povezanosti konvencionalnih i naprednih ehokardiografskih parametara, funkcionalnog statusa i NT-proBNP-a kod bolesnika sa prekapilarnom PH.

Materijal i metode Ova retrospektivna studija je obuhvatila 23 bolesnika. Podaci su prikupljeni iz rutinskih ispitivanja procene rizika, uključujući FK SZO, 6MDH i NT-proBNP, kao i standardnu, strejnu i trodimenzionalnu ehokardiografiju. Ehokardiografski podaci su upoređeni sa funkcionalnim statusom bolesnika utvrđenog FK SZO, 6MDH i vrednostima NT-proBNP-a.

Rezultati Bolesnici u FK SZO III ili IV imali su kraću 6MDH

[180 (interkvartilni raspon 85-240 m)] od bolesnika u FK SZO I ili II [409 (interkvartilni raspon 364-494 m),  $p=0,02$ ], dok razlika u NT-proBNP nije bila statistički značajna [FK I ili II: 1297 (interkvartilni raspon 283-3196) u odnosu na FK III ili IV: 343 (interkvartilni raspon 274-598) pg/ml,  $p=0,146$ ]. Uočene su inverzne korelacije između 6MDH i longitudinalnog strejna leve i desne komore i direktna korelacija između 6MDH i vremena plućne akceleracije ( $r=0,73$ ;  $p=0,001$ ). Merenja NT-proBNP-a su bila u direktnoj korelaciji sa dimenzijama desnog srca i strejnom desne komore, i inverznoj korelaciji sa vremenom plućne akceleracije ( $r=-0,70$ ;  $p=0,004$ ).

Zaključak Standardni i napredni ehokardiografski pokazatelji strukture, funkcije i hemodinamike desne komore koreliraju sa funkcionalnim statusom i nivoima natriuretskih peptida u heterogenoj kohorti bolesnika sa prekapilarnom PH i mogu biti korisni pomoćni parametri u kliničkoj praksi.

**Ključne reči:** plućna hipertenzija, ehokardiografija, funkcionalni status, natriuretski peptidi

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## ORIGINAL ARTICLE

# The profile of patients presenting to the department of vitreoretinal surgery and ocular trauma at the university clinic for eye diseases – a two-year retrospective study

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**Competing interests:**

The authors have declared that no competing interests exist

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**Summary**

**Introduction/Aim:** Vitreoretinal diseases can lead to permanent vision loss. The aim of our study was to present the frequency, demographics and treatment options of the patients hospitalized and treated at the tertiary healthcare Department of Vitreoretinal Surgery and Eye Trauma in a two-year period.

**Material and Methods:** The retrospective study was conducted at the Clinic for Eye Diseases, University Clinical Center of Serbia in Belgrade, Serbia in the period between November 30, 2020 and December 4, 2022. [Data on demographics, seasonality and treatment methods were collected from “Heliant” healthcare software and subsequently interpreted.

**Results:** During the study period, a total of 1295 patients were hospitalized. Cataract was the most common reason for hospitalization (n=355, 27.4%), followed by ocular trauma (n=303, 23.4%) and rhegmatogenous retinal detachment (n=287, 22.2%). The majority of patients with eye trauma (n=125, 41.2%, p<0.001) were between 19 and 44 years old. Male predominance was found in ocular trauma (n=261, 86.1%, p<0.001), and also in patients hospitalized for rhegmatogenous retinal detachment surgery (n=166, 57.8%, p<0.001) and surgery due to complications of proliferative diabetic retinopathy (n=41, 71.9%, p<0.001). Patients aged between 45 and 64 years were at the highest risk (n=136, 47.4%, p<0.001) and vitrectomy was performed more often as a treatment of rhegmatogenous retinal detachment (n=193, 67.2%, p<0.001). Rhegmatogenous retinal detachment most commonly occurred in autumn (n=103, 35.9%, p<0.001).

**Conclusion** Further studies focusing more on some of the pathologies included in this study may be beneficial for a better understanding of epidemiology, preventive measures, and optimal treatment methods.

**Keywords:** vitreoretinal diseases, rhegmatogenous retinal detachment, ocular trauma

## INTRODUCTION

Vitreoretinal diseases such as rhegmatogenous retinal detachment (RRD), eye trauma and endophthalmitis can lead to permanent vision loss. Ocular trauma is thought to be the primary cause of monocular blindness and accounts for around 19 million cases of vision loss worldwide (1-4). Rhegmatogenous retinal detachment is a common ophthalmological emergency with an incidence of approximately 10 to 18 per 100 000 (5, 6). On the other hand, the main cause of vision loss in middle-aged people is diabetic retinopathy (7).

Over the last decades, pars plana vitrectomy (PPV) instruments and techniques have evolved. It is now considered the standard treatment for many vitreoretinal disorders (3, 8). Regmatogenous and tractional retinal detachment, vitreal hemorrhage, macular hole (MH), epiretinal membrane (ERM), endophthalmitis, and eye trauma are some of the indications for vitrectomy. If left untreated, many of these diseases lead to blindness (2, 3, 9, 10).

Department of Vitreoretinal Surgery and Eye Trauma of the Clinic for Eye Diseases, University Clinical Center of Serbia in Belgrade admits adults suffering from any kind of ocular trauma who require clinical observation, and conservative or surgical treatment. Emergency and various elective vitreoretinal diseases, as well as senile, complicated and traumatic cataracts are also treated and operated on at this department. The aim of our study was to present the frequency, demographics and treatment options of the patients hospitalized and treated at the tertiary healthcare Department of Vitreoretinal Surgery and Eye Trauma over a two-year period.

## MATERIAL AND METHODS

### Study design and data source

The retrospective study was conducted at the Clinic for Eye Diseases, University Clinical Center of Serbia in Belgrade, Serbia. The study included all patients hospitalized at the Department of Vitreoretinal Surgery and Eye Trauma in the period between November 30, 2020 and December 4, 2022. The patients' data were collected from "Heliant" healthcare software.

All patients hospitalized during the defined period were included in the study, regardless of the need for surgical treatment. The demographic data we tracked were age and sex. Data on seasonality were obtained for diseases that, according to literature, showed a connection with certain seasons. All patients were divided into groups according to the reason for hospitalization: cataract, ocular trauma, RRD, complications of proliferative diabetic retinopathy (PDR), endophthalmitis, ERM/MH, lens (crystalline or artificial intraocular lens) luxation and subluxation, silicon oil removal, secondary in-

traocular lens (IOL) implantation and other. In addition to demographic data, certain information was collected in particular groups. Surgical method was analyzed in the cataract group – phacoemulsification or conventional extracapsular extraction (ECCE) surgery. Seasonality and surgical method data were obtained for RRD and ocular trauma. We divided eye trauma into closed globe injuries (contusions) and open globe injuries (OGI). We further divided open globe injuries into those with intraocular foreign body (IOFB), without IOFB, and globe rupture. The PDR complication group included patients with tractional retinal detachment and vitreal hemorrhage, while the "other" group included those patients who could not be classified into any of the other categories—iris reposition, iridoplasty, or corneal suture removal. We divided all patients into four age categories: – up to 18 years or less, between 19 and 44 years, 45 and 64 years and 65 or older. This study was undertaken according to the tenets of Helsinki Declaration and approved by the hospital's committee.

### Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 29.0.0.0. Descriptive data are presented as absolute numbers (n) and percentages (%). Mean and standard deviation are calculated for continuous variables. Chi-square test was used to examine statistical significance and p-value; the value below 0.05 was considered statistically significant.

## RESULTS

During the study period, a total of 1295 patients were hospitalized at the Department of Vitreoretinal Surgery and Eye Trauma. The details regarding age distribution in specific groups are shown in Table 1. The average age of all patients was  $61.16 \pm 15.87$  years with the youngest patient being 15 and the oldest 90 years old. Cataract was the most common reason for hospitalization (n=355, 27.4%), followed by ocular trauma (n=303, 23.4%) and RRD (n=287, 22.2%). One hundred forty-three patients (11%) were hospitalized for silicon oil removal. Fifty-seven (4.4%) patients required vitrectomy for complications of PDR, while 40 (3.1%) and 39 (3%) of all patients were hospitalized for treatment of ERM/MH and lens luxation/ subluxation, respectively. Twenty-four (1.9%) secondary IOL implantations were performed, while 25 (1.9%) patients were hospitalized for other reasons. Endophthalmitis was the rarest of all and it accounted for 1.7% (n=22) of the entire examined population.

The youngest patient with cataract was 34, and the oldest was 90. The average age was  $70.04 \pm 9.76$ . The majority of them (n=265, 74.6%) were 65 years or older,  $p < 0.001$ . Details of the age range in cataract group

**Table 1.** Age distribution in different study groups

Age n (%)	≤18	19-44	45-64	≥65	Total	P value
Group						
Cataract	0 (0%)	7 (2%)	83 (23.4%)	265 (74.6%)	355 (100%)	<b>&lt;0.001</b>
Ocular trauma	10 (3.3%)	125 (41.2%)	83 (27.4%)	85 (28.1%)	303 (100%)	<b>&lt;0.001</b>
Rhegmatogenous retinal detachment	2 (0.7%)	25 (8.7%)	136 (47.4%)	124 (43.2%)	287 (100%)	<b>&lt;0.001</b>
Complications of PDR	0 (0%)	4 (7%)	25 (43.9%)	28 (49.1%)	57 (100%)	<b>&lt;0.001</b>
Endophthalmitis	0 (0%)	1 (4.5%)	10 (45.5%)	11 (50%)	22 (100%)	<b>0.016</b>

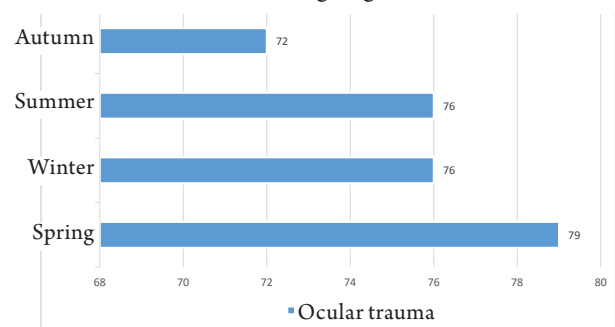
Results are presented in the form of absolute numbers and percentages (n, %). The level of significance <0.05. Abbreviation: PDR: proliferative diabetic retinopathy.

are shown in **Table 1**. Similar numbers of males and females were observed (n=179, 50.4% and n=176, 49.6% respectively, p=0.873). Phacoemulsification was the most common surgical technique (n=323, 91%) compared to ECCE (n=27, 7.6%), p<0.001. Five (1.4%) patients were not treated surgically due to poor general condition or technical issues.

The age range of ocular trauma was from 15 to 88 years, with a mean age of 49.32 ± 18.78 years. A statistically significant majority of patients (n=125, 41.2%) were between 19 and 44 years old, p<0.001. Details of the age range in ocular trauma are shown in **Table 1**. A statistically significant male predominance was found in both open and closed globe injuries, as well as in the entire group of ocular trauma. Detailed information on the gender distribution in ocular trauma are shown in **Table 2**. The largest number of eye injuries were OGI (n=175, 57.8%), while there were 128 (42.2%) closed globe injuries, p=0.006. The most common ocular globe injuries were those without IOFB (n=86, 49.6%), followed by ocular globe injuries with IOFB (n=50, 28.6%) and globe rupture (n=39, 22.3%), p<0.001 respectively. In almost all OGI, operations were performed (n=171, 97.7%), p<0.001. Only 4 (2.3%) patients were treated conservatively and all of these were OGI without IOFB. Early primary PPV was the method of choice in 28 (16%) patients with OGI, while the majority of patients with open globe injury (143, 81.7%) were treated with some other surgical intervention (primary wound repair or different surgeries other than PPV), p<0.001. Statistical significance regarding the treatment method was also found in closed globe injuries. Most of those patients (n=64, 50%) were treated conservatively, while 49 (38.3%) patients required surgery. Laser photocoagulation was the treatment

method in 13 (10.2%) patients and 2 (1.6%) patients were hospitalized only for observation without any treatment, p<0.001. Ocular trauma occurred more often in spring (n=79, 26.1%) compared to other seasons, still with no statistical significance, p=0.955. The analysis related to the seasonality of ocular trauma is shown in **Figure 1**.

The youngest patient with RRD was 17 years old and the oldest was 85. The average age was 60.91 ± 12.66.



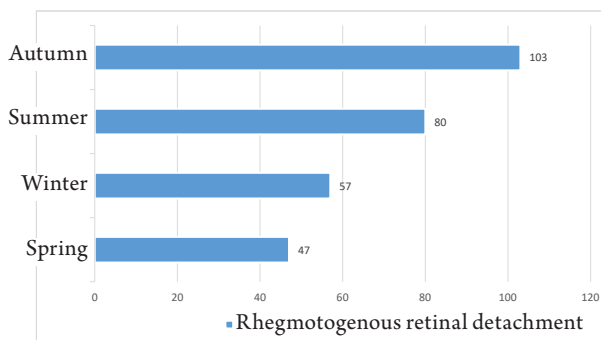
**Figure 1.** Seasonality of ocular trauma. Results are presented in the form of absolute numbers and percentages (n, %). The level of significance <0.05.

The patients aged between 45 and 64 years were at the highest risk of RRD (n=136, 47.4%), p<0.001. More information on age distribution of RRD is presented in **Table 1**. Among 287 patients hospitalized for RRD surgery, 166 (57.8%) were male, while 121 (42.2%) were female, p=0.007. Vitrectomy was performed more often (n=193, 67.2%) compared to scleral buckle surgery (n=73, 25.4%), p<0.001. The remaining patients were treated either with laser photocoagulation (n=5, 1.7%) or were not operated on due to poor general condition or technical issues (n=16, 5.6%). It was found that rhegmatogenous retinal detachment was most common in autumn (n=103,

**Table 2.** Analysis of gender distribution in ocular trauma

Gender	Male	Female	Total	P-value
Diagnosis				
Open globe injuries	151 (86.3%)	24 (13.7%)	175 (100%)	<b>p&lt;0.001</b>
Closed globe injuries	110 (85.9%)	18 (14.1%)	128 (100%)	<b>p&lt;0.001</b>
Total	261 (86.1%)	42 (13.9%)	303 (100%)	<b>p&lt;0.001</b>

Results are presented in the form of absolute numbers and percentages (n, %). The level of significance <0.05.



**Figure 2.** Seasonality of rhegmatogenous retinal detachment. Results are presented in the form of absolute numbers and percentages (n, %). The level of significance  $<0.05$ .

35.9%),  $p < 0.001$ . The analysis related to the seasonality of RRD is presented in **Figure 2**.

The age range for patients with complications of PDR was from 36 to 84 years, with a mean age of  $63.07 \pm 10.65$ . Almost half of these patients ( $n=28$ , 49.1%) were 65 years old or older,  $p < 0.001$ , details are presented in **Table 1**. Men were more often affected ( $n=41$ , 71.9%) compared to women ( $n=16$ , 28.1%),  $p < 0.001$ . Vitreous hemorrhage was observed in 49 (87.5%) patients, while tractional retinal detachment was found in 7 (12.5%) of all the patients with PDR,  $p < 0.001$ .

The minimum age of patients admitted for endophthalmitis treatment was 33 years and the maximum was 87 years. Mean age was  $62.05 \pm 15.02$ . Half of them ( $n=11$ ) were in the age group of 65 years and older,  $p < 0.016$  (details are given in **Table 1**). Endophthalmitis was more common in men ( $n=14$ , 63.6%) than in women ( $n=8$ , 36, 4%),  $p=0.201$ . Post-traumatic endophthalmitis accounted for 54.5% ( $n=12$ ), while postoperative endophthalmitis accounted for 45.5% ( $n=10$ ),  $p=0.677$ .

## DISCUSSION

In our study, elective surgeries (ERM/MH, secondary IOL implantation, most of the silicon oil removals and lens luxations or subluxations and other reasons) altogether accounted for only 20.9% of all patients admitted to the Department of vitreoretinal surgery and ocular trauma. On the other hand, Gupta et al. showed in their study that macular surgeries were performed in 11% (11), which is significantly more than in our study (3.1%). The lower frequency of elective procedures could be a result of COVID-19 pandemic, taking into account that a relevant time period of our study was affected by the pandemic. This assumption is supported by previous research from our Clinic, which reported a significant reduction in elective surgeries during the quarantine in 2020 due to COVID-19, compared to the same period in 2019 because most elective interventions were then postponed (12).

Cataract surgery is one of the most commonly performed eye surgeries and the numbers are still increas-

ing, in accordance with the results of our study, given that it was the most common reason for admission. Indications for cataract surgery are expanding to younger patients as operative techniques and visual outcomes improve (13). Although the majority of the cataract patients in this study were older than 65 years, almost a third of the patients were younger than this age. Previous studies and systematic reviews have shown that phacoemulsification compared to ECCE results in better postoperative visual acuity and a lower complication rate, and has thus become the technique of choice in cataract management (14-16). In our study, we also observed a trend towards phacoemulsification as the surgical method of choice, which is important for minimizing potential complications and achieving the best long-term outcome.

Ocular trauma was an important cause of hospitalization in our study. The mean age of our patients was slightly higher compared to other studies, which may be due to the fact that our study did not include the pediatric population (17, 18). However, a 15-year-long retrospective study of ocular trauma from Portugal that included children, reported the mean age of 48.9 years, which is almost the same as ours (19). When comparing the results of studies, it is useful to keep in mind that different age ranges were used in different studies. However, nearly two-thirds of our patients were between 18 and 65 years old, which is consistent with most previous studies (17-20). Male predominance found in this research was also observed in other studies (17-23). In our research, OGI represented the majority of all eye trauma cases. Studies that exclusively included hospitalized patients produced the same results (18, 19). These results are opposite from some studies that included both inpatient and outpatient eye trauma, where closed globe injuries occurred either more frequently or equally frequently to open globe injuries (21, 24). Alem et al. in their two-year study concluded that among OGI, the most common were OGI without IOFB, followed by IOFB and globe rupture, which is all in accordance with our findings (24). However, there are studies that observed a higher incidence of globe ruptures and a lower incidence of IOFB compared to this study (18, 19). Our preferred surgical method for OGI was primary wound repair, which did not differ from results from other studies, which also performed vitrectomy and other operations as a second operation (18, 19, 24). The majority of closed globe injuries in our study were treated non-surgically, which is supported by the Helsinki Ocular Trauma Study (21). In our study, the occurrence of eye trauma did not show seasonality to be statistically significant, either in all cases of eye trauma or in closed and open globe injuries separately. It was almost equally distributed over the four seasons. Literature data are controversial, reporting peaks in different seasons and months – summer (July, September) and the period between May and October (20, 22, 23).

In the study by Gupta et al. as well as the study by Xu et al., the mean age of patients with RRD was  $60.07 \pm 13.92$



and  $60 \pm 14$ , respectively, which is practically the same as in our findings (11, 25). Others obtained different results regarding the mean age of patients with RRD, ranging from 53 to 61.8 years (5, 6, 26-28). However, this supports our findings that RRD mainly affects people aged between 45 and 64 years. A significant male predominance was found in this study, as in other studies, while the opposite results were not found in literature (5, 6, 11, 26, 28). Some authors believe that greater axial length in men and differences in basal vitreoretinal adhesion, i.e. posterior migration of the posterior border of the vitreous base in men, may contribute to a higher incidence of RRD (29). In contrast to our results where vitrectomy was performed more frequently in the treatment of RRD compared to scleral buckling, a 4-year-long study of 24,928 patients revealed a slightly higher incidence of scleral buckling (45.6%) compared to vitrectomy (42.5%) in treating RRD (1). However, other researchers reported vitrectomy as a more common primary surgical method (6, 11, 27, 28). This may be attributed to the surgeon's preference for one type of surgery, but vitrectomy has also grown in popularity over the past decades due to its better ergonomics and recent technological advances. In this study, a significantly higher incidence of RRD was observed in autumn. It occurred least frequently in winter, which is in accordance with an American study that found a reduced incidence of surgery due to RRD during holidays, especially during winter months (5). Another study also reported results consistent with ours, with the highest number of cases in September and the lowest in December (30). However, a study from France showed that RRD was most common in July and least common in August (31).

The second most common indication for vitrectomy in the study by Gupta et al. was diabetic vitrectomy due to nonclearing vitreous hemorrhage and tractional retinal detachment, as in our study. They reported 10-year lower mean age in Caucasians with PDR complications compared to our study, but the same findings regarding male predilection (23). Another study showed PDR as the second most common reason for vitrectomy, with a higher incidence of vitreous hemorrhage compared to tractional retinal detachment, all consistent with our findings (32). However, most of their patients were 50 to 60 years old, while in our study almost half of the cases were older than 65 years. This discrepancy may be the result of several factors. During the research period, partly affected by the pandemic, only the most complicated cases were hospitalized, which can be related to older age i.e., longer duration of diabetic retinopathy. On the other hand, it may be due to negligence, non-acceptance of the health condition but also due to poor awareness of the complications of diabetes among the younger population.

The rarest, but very important reason for hospitalization in our study was endophthalmitis. The largest number of patients with endophthalmitis were 65 and older, while almost all patients included in this study were older than 45 years. Two previous studies observed an even higher mean age compared to our results (33, 34). Although there are studies that reported significantly lower mean age, they included the pediatric population, which was not the case in our study (35, 36). We found a higher risk of endophthalmitis in men. This was also confirmed by previous studies (33, 35, 36). However, no statistical significance regarding gender distribution was confirmed in this study. These findings may be explained by the higher incidence of OGI in men, which was also shown in our study. Post-traumatic endophthalmitis accounted for slightly more than 50% of the cases. Data from the literature on the causes of endophthalmitis are diverse. In a study by Yang et al. post-traumatic endophthalmitis accounted for as much as 82.6% of all cases, while Almarzouki et al. reported only 7.2% of all cases as a result of OGI (35, 37). Post-traumatic endophthalmitis was most common in a study from Philippines (55.4%), while a Korean study reported that postoperative endophthalmitis was the most common in their sample (33, 36).

The limitations of our study are the absence of the pediatric population, the retrospective nature of the study, and the pandemic period included in the research.

## CONCLUSION

Our results showed that cataract was the most common reason for hospitalization, followed by ocular trauma and RRD. The preferred surgical method for cataract was phacoemulsification, vitrectomy for RRD, and primary wound repair for OGI. Patients of 65 years of age and older accounted for a significant majority of cataract, PDR and endophthalmitis cases. Ocular trauma was the most common in the age group between 19 and 44 years, while RRD mostly affected people between 45 and 64 years. Men had a significantly higher risk of ocular trauma, RRD and complications of PDR. They were also at a higher risk of endophthalmitis, yet statistical significance was not found. Further studies focusing more on some of the pathologies included in this study may be beneficial for a better understanding of epidemiology, preventive measures, and optimal treatment methods. Our findings could enable better evaluation strategies for dealing with ocular trauma and vitreoretinal patients, and provide a substrate for investment and development of a medical system which would care for these patients.

**Conflict of interest:** None to declare.

**Ethics:** Principles of the Declaration of Helsinki were respected in this study.

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## PROFIL PRIMLJENIH PACIJENATA NA ODELJENJE VITREORETINALNE HIRURGIJE I OČNE TRAUME NA UNIVERZITETSKOJ OČNOJ KLINICI - DVOGODIŠNJA RETROSPEKTIVNA STUDIJA

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### Sažetak

**Uvod/Cilj:** Vitreoretinalna oboljenja mogu dovesti do trajnog oštećenja vida. Cilj naše studije bio je da prikazemo učestalost, demografske karakteristike i metode lečenja pacijenata hospitalizovanih i lečenih u tercijarnoj ustanovi na Odeljenju za vitreoretinalnu hirurgiju i traumatologiju oka u periodu od dve godine.

**Metod:** Sprovedena je retrospektivna studija na Klinici za očne bolesti, Univerzitetskog Kliničkog centra Srbije, Beograd, Srbija, u periodu od 30. novembra 2020. godine do 4. decembra 2022. godine. Demografski podaci, podaci o sezonalnosti i metodama lečenja prikupljeni su iz „Heliant“ zdravstvenog softvera i nakon toga interpretirani.

**Rezultati:** U toku studijskog perioda hospitalizovano je ukupno 1295 pacijenata. Katarakta je bila najčešći uzrok hospitalizacije (n=355, 27.4%), zatim povrede oka (n=303, 23.4%) i regmatogena ablacija retine (n=287, 22.2%). Ve-

ćina pacijenata sa povredom oka (n=125, 41.2%, p<0.001) bila je između 19 i 44 godine starosti. Veća učestalost kod muškaraca uočena je među povredama oka (n=261, 86.1%, p<0.001), kao i kod pacijenata hospitalizovanih radi hirurgije regmatogene ablacije retine (n=166, 57.8%, p<0.001) i hirurgije komplikacija proliferativne dijabetične retinopatije (n=41, 71.9%, p<0.001). Pacijenti starosti između 45 i 64 godine bili su u najvećem riziku (n=136, 47.4%, p<0.001), a vitrektomija je izvođena češće u lečenju regmatogene ablacije retine (n=193, 67.2%, p<0.001). Regmatogena ablacija retine bila je najčešća tokom jeseni (n=103, 35.9%, p<0.001).

**Zaključak:** Dalje studije koje bi se više fokusirale na pojedina oboljenja uključena u ovu studiju mogle bi biti korisne za bolje razumevanje epidemiologije, preventivnih mera i optimalnog metoda lečenja.

**Ključne reči:** vitreoretinalna oboljenja, regmatogena ablacija retine, povrede oka

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## ORIGINAL ARTICLE

# The impact of covid-19 pandemic on diagnosing and treating adult patients with glaucoma in Serbia

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**Competing interests:**

The authors have declared that no competing interests exist

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**Summary**

**Aim.** The aim of this study is to summarize the continuity of diagnostic procedures and surgical treatment of patients with glaucoma during the first two years of COVID 19 pandemic in a tertiary ophthalmology center of the Republic of Serbia - the Clinic for Eye Diseases of the University Clinical Center of Serbia, and to compare the results with those from the period before the pandemic was declared.

**Material and methods.** In this retrospective study, we collected data from the protocol of performed diagnostic procedures –visual field testing, optical coherence tomography and clinical examinations, as well as from the protocol from the operating theatre.

**Results.** The number of examined patients, the number of diagnostic procedures related to glaucoma, as well as the number of laser interventions (Nd: Yagiridotomies) and glaucoma surgeries (trabeculectomy) decreased from 20% to 66% during the period of COVID-19 pandemic.

**Conclusions.** COVID-19 pandemic has led to a drastic reduction in the number of examinations, laser interventions and surgeries in the category of people suffering from glaucoma.

**Keywords:** COVID-19, pandemic, glaucoma

## INTRODUCTION

COVID-19 pandemic has an impact on practically every person in the world, on potential or actual patients, and medical professionals (1). Apart from the changes it brought to our everyday life, the field of providing health services has also changed drastically - the majority of diagnostic procedures for chronic diseases, as well as procedures during follow-up of already diagnosed patients, were put on hold. The majority of surgeons worldwide temporarily stopped performing elective surgeries. All this, along with the specificities of the specialty, affected ophthalmology as well.

One of the most prevalent eye diseases in the world is glaucoma – a chronic optic neuropathy characterized by slow degeneration of retinal ganglion cells resulting in deterioration of visual function, and the third most prevalent cause of preventable blindness worldwide (2).

The aim of this study is to present and analyze data related to the diagnosis and treatment of people suffering from glaucoma during the first two years of COVID-19 pandemic in Serbia, in order to try to overcome the consequences, and to get prepared for possible future similar events.

## MATERIAL AND METHODS

This retrospective study was conducted at the Clinic for Eye Diseases of the University Clinical Center of Serbia in Belgrade. We extracted the data from Heliant health-care information system, for the period of two years before the pandemic was declared, and for the period of two years during the pandemic (2018,2019, 2020, 2021).The data on the number of visual field testing (VF), optical coherence tomography of the optic nerve head (OCT) and clinical examination in Glaucoma clinic, along with the number of laser glaucoma treatments (Nd: Yagiridotomies) and surgeries (trabeculectomy) were analyzed.

The outcomes we followed are the differences we found comparing the results from the same time of these two periods (the years 2018 and 2019 versus the years 2020 and 2021), but since the samples gathered in 2018 and 2019 did not differ significantly from each other (p=0.0001) for any of the collected variables, only the data related to 2019 were considered for statistical analysis.

The study was approved by the Clinic’s Ethical Committee. All data were collected anonymously and according to the tenets of the Declaration of Helsinki. Patients at the admission to the Clinic for Eye Disease signed the informed consent for any surgical treatment and data processing.

**Statistical analysis.** Descriptive results were reported in the form of percentage for categorical variables and as mean±Standard Deviation (SD) for quantitative ones. Chi-Square test and T test for independent means were

used, respectively, to compare categorical and quantitative variables between the two periods. The analysis was done using STATA 16.0 (StataCorp, Texas, USA). Statistical significance was considered for the selected level of significance from 0.05.

## RESULTS

Between January 1th, 2020 and December 31th 2020, 102 glaucoma surgeries (trabeculectomies) were performed compared to 172 surgeries carried out during the previous year, in the period before the pandemic. Therefore, the surgical volume of glaucoma dropped by 40.7% in the first year of the pandemic. As for the year 2021, the drop of glaucoma surgeries was even higher (56.5%). The drop in the number of diagnostic procedures ranged from 21% to 51%. Results are shown in **Table 1**, **Table 2** and **Figure 1** and **Figure 2**.

**Table 1.** Number of diagnostic procedures, laser interventions and glaucoma surgeries in pre-pandemic 2019, and pandemic 2020, 2021

	Before pandemic 2019	During pandemic 2020	During pandemic 2021	P
Clinical examination	6199	2106	2129	<0.0001
Visual field testing	9371	4528	4535	<0.0001
Optical coherence tomography	5606	3349	4422	<0.0001
Laser iridotomy	524	286	241	<0.0001
Trabeculectomy	172	102	77	<0.0001

## DISCUSSION

The general impression is that COVID-19 pandemic has significantly worsened global health.

Extended lockdowns and the cease of routine outpatient visits led to a multi-layered deterioration of the health of our patients suffering from glaucoma (3). The extent of glaucoma problem during the pandemic in terms of how many people it affected can be estimated based on the facts that it is predicted that the number of adults with glaucoma will reach 112 million by 2040 (4, 5). There are no reliable data on the prevalence of glaucoma in Serbia, since this disease is not subject to mandatory reporting, but we assume that currently around 150.000 people suffer from glaucoma. Glaucomatous visual field loss may significantly affect functional daily living activities, as reading, driving, and everyday household activities. Unfortunately, most of glaucoma cases do not present with signs and symptoms that patients can recognize, so this is a disease that must be actively looked for, with regular examinations of people who are at risk of getting it (ophthal-

**Table 2.** Variation in the number of diagnostic procedures, laser interventions and glaucoma surgeries in pre-pandemic 2019, and pandemic 2020, 2021

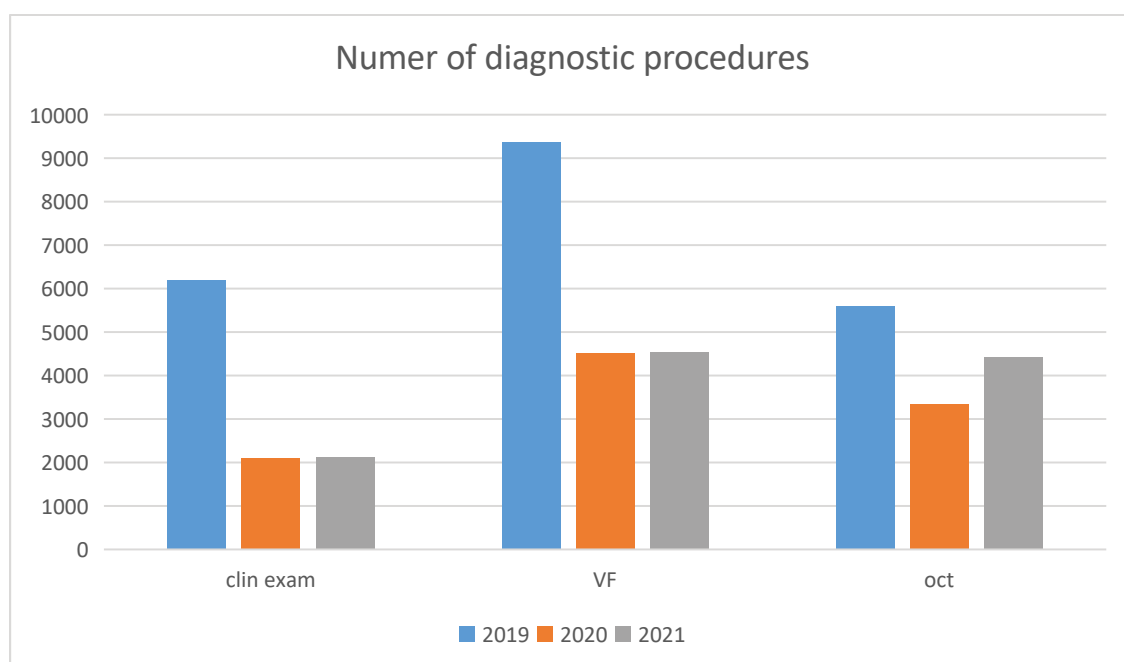
	Variation 2019/2020	Variation 2019/2021	P 2019/2020	P 2019/2021
Clinical examination	-66.03	-65.66	<0.0001	<0.0001
Visual field testing	-51.68	-51.61	<0.0001	<0.0001
Optical coherence tomography	-40.29	-21.12	<0.0001	<0.0001
Laser iridotomy	-45.42	-54.01	<0.0001	<0.0001
Trabeculectomy	-40.7	-56.5	<0.0001	<0.0001

mological examination with intraocular pressure measurement, VF testing, and OCT). Having that in mind, we can assume the depth and complexity of the problems associated with glaucoma and COVID-19 pandemic.

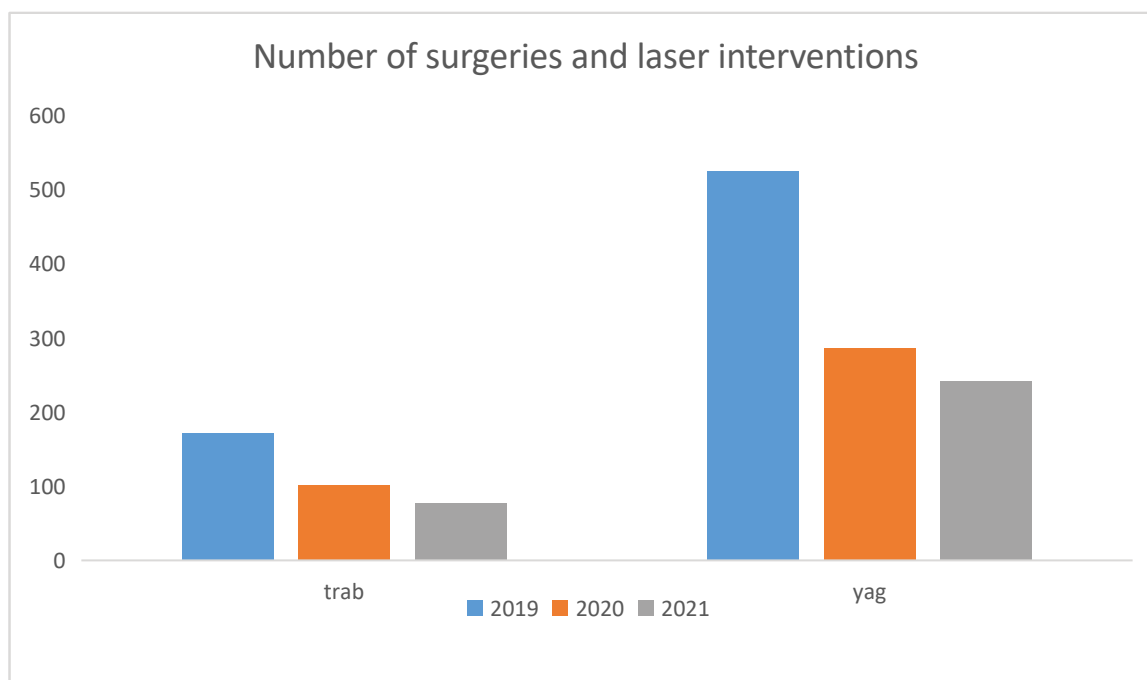
The state of emergency in the Republic of Serbia lasted from March 15 to May 6, 2020, but the disruption in the daily functioning of the health service lasted much longer, and only emergency ophthalmological cases were treated during 2020 and 2021 (6). The “first wave” of COVID-19 pandemic in Serbia led to mobilization of medical staff (both doctors and nurses) exclusively for the management of COVID-19 patients. Ophthalmologists and ophthalmic and scrub nurses, including all authors of this study, were transferred to specialized COVID-19 institutions, which resulted in cancelling and rescheduling of elective surgical procedures. Only ophthalmological emergencies were treated, since the ophthalmological services in Serbia followed WHO recommendations given in the early months of 2020 that ophthalmologists should stop performing all interventions except for the urgent ones (7). Furthermore, ophthalmic staff was at high risk of contracting the infection due to very close distance (8) but from ophthalmologists’

point of view, the greatest harm was done to our chronic patients, who during the pandemic and lockdown could not be followed-up regularly. The consequences that the COVID-19 pandemic has left on the diagnosis and follow-up of glaucoma patients will probably be felt to the full extent in the future. Glaucoma patients need to have regular follow-up examinations for the rest of their lives, their treatment regimen often has to be adjusted, and they have to go through periodical visual field testing and imaging procedures of their optic nerve heads. In addition, they need to be constantly reminded of the importance of regular instillation of eye drops to lower the eye pressure, and their adherence and compliance must be checked periodically. All of this was interrupted during the first years of the pandemic. No less of a problem was the fact that the unavailability of ophthalmology services during the pandemic led to the delay in the diagnosis of new glaucoma cases in a certain percentage of patients.

In spite of all objective difficulties, glaucoma team of the Clinic for Eye Diseases, University Clinical Center of Serbia, prioritized interventions and surgery on patients with elevated IOP uncontrolled by maximal medical therapy and fast progressing glaucoma, so the priority



**Figure 1.** Number of diagnostic procedures (VF-visual field, OCT – optical coherence tomography)



**Figure 2.** Number of surgeries and laser interventions (trab – trabeculectomy, yag – Nd:Yagiridotomy)

criteria changed according to the circumstances. Unfortunately, as expected, overall, the number of diagnostic procedures, along with interventions (Nd: Yag laser iridotomies) and glaucoma surgeries, dropped excessively, from 20% to over 50%. All patients who underwent glaucoma surgery were monitored after the operation according to the generally accepted protocol, during 3 postoperative months. None of them showed symptoms of the COVID-19 infection in early postoperative period.

The results of our study are only an introduction into the analysis of the severity of the COVID-19 pandemic, i.e. only a part of the insight into the consequences that the pandemic and the reduction of health care had on general population, considering that glaucoma is a disease that must be diagnosed early and treated adequately, so as to avoid possible drastic and irreversible aftermath on the patient's vision and quality of life. Patients, on the other hand, were in dilemma whether to miss their regular follow-up visit because of the possibility of contracting SARS-CoV-2 during in-person visits (9, 10). Regardless of this pandemic, it is well known that ophthalmologists and their patients are at heightened risk for contracting many respiratory diseases from each other. At the Clinic for Eye Diseases, from the moment the pandemic was declared until today, all instructions related to the protection of staff and patients have been conscientiously followed (11).

Our data are different from those reported by a tertiary-level Italian center (12), which reported a slight increase in the number of glaucoma surgeries performed during the first month of the pandemic, but other relevant studies show similar results to ours (3,9,13).

It will probably take us many years to be able to analyze the problem of the COVID-19 pandemic realistically

and in detail, but that is precisely why it is worth noting the data we gained during our analysis.

A relative limitation of this study can be the fact that it is retrospective and monocentric, since we analyzed only the data from one clinical center, the Clinic for Eye Diseases, University Clinical Center of Serbia. We must emphasize that this is the referent facility for glaucoma diagnostics and treatment in the Republic of Serbia, and the leading one in the number of glaucoma diagnostic procedures, interventions and operations, and that it covers the entire territory of the Republic of Serbia. In addition, we do not have data from private ophthalmology clinics in our study. Despite the limitations, we believe that our study provides valid information for further clinical research on the impact of the pandemic on the treatment of ophthalmic patients.

In addition, this is an excellent opportunity to highlight the need for and importance of introducing telemedicine in ophthalmology (14, 15). The combination of online and face-to-face ophthalmology care in which patients have the primary consultation online, and only those requiring further assessment or surgical procedures come to hospital for in-person management seems to be most appropriate to use in cases of any pandemic (16, 17).

## CONCLUSIONS

COVID 19 pandemic has caused tectonic disturbances in the provision of diagnostics and treatment for glaucoma patients in Serbia, since during the first two years of the pandemic, almost every other person suffering from glaucoma could not get to their ophthalmologist. Despite the undoubted damage that the pandemic has brought to all



of us, the benefit that can be derived from this situation is a lesson for future similar scenarios in order to practice effective, safe and conscientious ophthalmology.

### Conflict of interest:

None to declare.

### Author Contributions:

MB conceived and wrote the paper, IM revised it for important intellectual content, LR and TK conducted the search and collected data, VM and JV reviewed other studies in this field, extracted and analyzed data. All authors approved the final version of the manuscript before submission

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## UTICAJ PANDEMIJE KOVIDA 19 NA DIJAGNOSTIKU I LEČENJE ODRASLIH OSOBA OBOLELIH OD GLAUKOMA U SRBIJI

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### Sažetak

**Cilj rada.** Cilj ovog rada je da se sumira kontinuitet dijagnostičkih procedura i hirurškog lečenja pacijenata obolelih od glaukoma tokom prve dve godine pandemije kovida 19 u tercijarnom oftalmološkom centru Republike Srbije – Klinici za očne bolesti Univerzitetskog kliničkog centra Srbije, kao i da se broj obavljenih dijagnostičkih procedura, kliničkih pregleda i operacija uporedi sa periodom pre proglašenja pandemije.

**Metode.** U ovoj retrospektivnoj studiji prikupili smo podatke iz protokola obavljenih dijagnostičkih procedura – kompjuterizovanog vidnog polja, optike koherentne

tomografije i kliničkih pregleda, kao i protokola iz operacione sale.

**Rezultati.** Broj pregledanih pacijenata, broj urađenih dijagnostičkih procedura vezanih za glaukom, kao i broj laserskih intervencija (Nd:Yagiridotomija) i operacija glaukoma (trabekulektomija) opao je od 20% do 66% tokom prve dve godine pandemije kovida 19.

**Zaključak.** Pandemija kovida 19 dovela je do drastičnog smanjenja broja pregleda, laserskih intervencija i operacija osoba obolelih od glaukoma.

**Ključne reči:** kovid 19, pandemija, glaukom

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## ORIGINAL ARTICLE

# The effect of hand-arm vibrations on distal forearm bone mineralization

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**Competing interests:**

The authors have declared that no competing interests exist

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**Summary**

A prolonged, mainly professional, exposure to hand-arm vibration (HAV) may cause a complex chronic disorder of the upper extremities known as Hand-Arm Vibration Syndrome (HAVS).

Besides vascular and neurological injuries, such exposure to HAV may cause various bone disorders in the form of cystic changes, exostoses, aseptic necrosis, osteoarthritis, spontaneous fractures and osteoporosis.

The objective of this study was to examine whether there were any changes in the bone mineral density in the distal forearm in persons professionally exposed to HAV.

In a group of 31 workers professionally exposed to vibrations (29 men and 1 woman) with neurological and/or vascular signs of HAVS, the bone mineral density of the distal part of the radius of both hands was examined by dual X-ray absorptiometry (DXA). The control group consisted of 25 healthy subjects with no history of HAV exposure. Osteopenia was found in 14 subjects (45.16%), which makes a statistically significant difference compared to the control group ( $p=0.017$ ), where osteopenia was found in 3 subjects (12.0%). Osteoporosis was not found in any of the subjects. Analyzing the value of T score for the dominant ( $-0.81\pm 0.58$  SD) and non-dominant hand ( $-0.62\pm 0.68$ SD) in our patients, we found no statistically significant difference in the average T score values of the dominant and non-dominant hand ( $p=0.269$ ).

Changes in bone density at the distal radius are common in persons occupationally exposed to HAV. Distal forearm DXA examination in workers occupationally exposed to HAV can help diagnose HAVS.

**Keywords:** Vibration disease, bone density, DXA

## INTRODUCTION

A prolonged, mainly professional, exposure to hand-arm vibration (HAV) may cause a complex chronic disorder of the upper extremities known as Hand-Arm Vibration Syndrome (HAVS) (1). Besides vascular and neurological injuries, such exposure to HAV may cause damage to bones, joints, muscles and tendons of the upper extremity (2,3).

HAVS related impairment is disabling, since patients experience functional, social, emotional, and psychological disability (4). Prevalence among vibration exposed workers varies between 8.4% and 18.1% depending on the vibration exposure factors (vibration magnitude, frequency, direction, and exposure duration), environmental factors (temperature, moisture), biomechanical factors (hand coupling forces, hand and arm postures), and individual factors (genetics, tobacco use, age, sex, hand and arm injury history) (5,6).

Various bone disorders, in the form of cystic changes, exostoses, aseptic necrosis, osteoarthritis, spontaneous fractures and osteoporosis are caused by vibration (7,8). Changes are most common in bones and joints of the wrist, metacarpophalangeal and elbow joints, while changes in the shoulder joint, spine, and other joints are less common, depending on the direction of vibration propagation. Low-frequency impact vibration can be transmitted to the upper arm and cause symptoms in the elbow and shoulder, while high-frequency impact vibration can cause symptoms in the wrist and hand (9,10).

Bone-joint changes are diagnosed by X-ray examination, primarily of the hands and wrists, elbow and shoulder joints. Changes in bone mineral density (BMD) can be determined by dual X-ray absorptiometry (DXA) testing (11).

The objective of this study was to examine whether there were any changes in the bone mineral density in the distal forearm in people professionally exposed to HAV.

## MATERIAL AND METHODS

A group of 31 workers professionally exposed to hand-arm vibrations (29 men and 1 woman), with average exposure to vibrating tools of  $23.23 \pm 7.11$  years, have undergone distal forearm dual x-ray absorptiometry (DXA) in order to evaluate bone mineral density of the distal part of the forearm of both hands, using an OsteoSys DEXXUM-T osteometer. The distal part of the forearm is divided into 3 regions of interest (ROIs): the "ultra-distal" radius consisting of a 15-mm section adjacent to the end plate of the radius; the proximal region termed the "33%" radius consisting of a 20-mm section one-third of the distance between the ulnar styloid and the olecranon; and the intermediate region consisting of the remaining section between the 2 aforementioned sites (12). In our study, we evaluated bone mineral density of the "ultra-distal" radius. All patients had been previously investigated for

vibration-related symptoms and signs by an occupational medicine specialist and had shown neurological and/or vascular signs of HAVS. The control group consisted of 25 healthy subjects with no history of hand-arm vibration exposure.

Demographic information including gender, age, hand dominance, vibration exposure, smoking status, and alcohol consumption were recorded.

The World Health Organization (WHO) criteria for the diagnosis of osteoporosis were applied, according to which a normal finding means bone density is reduced by 1 SD compared to the values for healthy adults (T-score  $\leq -1$ ), reduced bone mass (osteopenia) means bone density is reduced by 1 to 2.5 SD compared to the values for healthy adults (T-score  $-1$  to  $-2.5$ ), and osteoporosis means bone mass is reduced by 2.5 SD or more from values for healthy adults (T-score  $\leq -2.5$ ) (13).

This retrospective, case-control study was performed in accordance with the Helsinki Declaration procedures and Strengthening the Reporting of Observational Studies in Epidemiology (Strobe) Guidelines. The Institutional Ethical Committee approved this study (Protocol No 02/618-1), and subjects were informed of the objective and the procedure of the study and gave their written consent.

## Statistical analysis

Data were presented in the form of arithmetic mean and standard deviation, that is, in the form of absolute and relative numbers. The comparison of categorical variables was performed using the Chi-square test. The comparison of age and T-score in relation to the studied groups was performed using the t-test. The hypothesis was tested with a significance threshold of  $p < 0.05$ . Statistical data processing was performed in the SPSS 21.0 software package.

## RESULTS

Patients and healthy controls did not show any relevant age or gender differences, with male gender being dominant in both groups. Descriptive characteristics of the study sample are presented in **Table 1**.

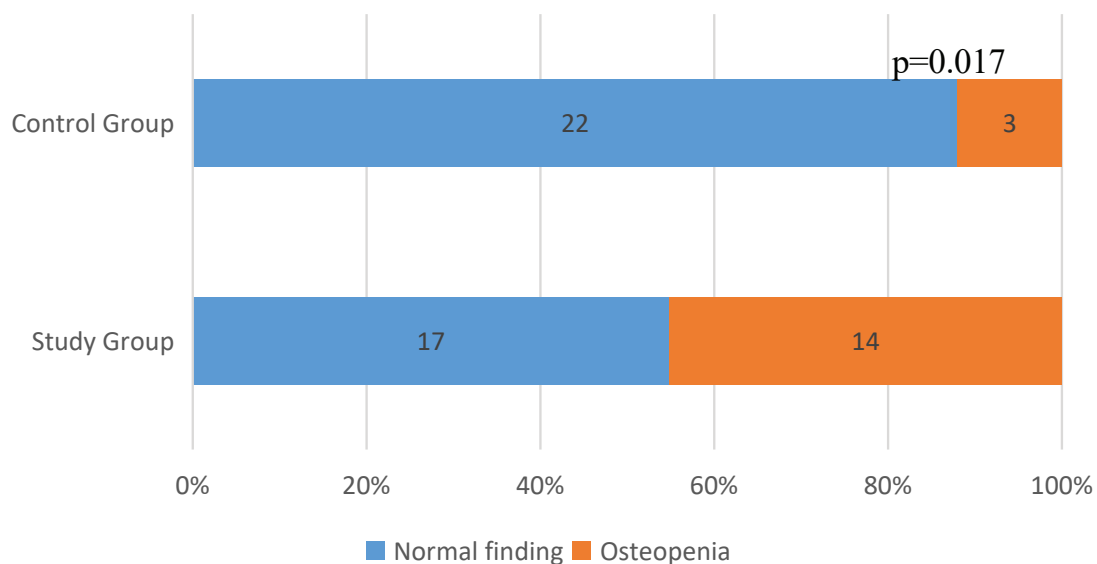
Osteopenia was found in 14 subjects professionally exposed to vibrations (45.16%), which makes a statistically significant difference compared to the control group ( $p = 0.017$ ), where osteopenia was found in 3 subjects (12.0%). Osteoporosis was not found in any of the subjects (**Figure 1**).

Analyzing the value of T score for the dominant hand ( $-0.81 \pm 0.58$  SD) and for the non-dominant hand ( $-0.62 \pm 0.68$  SD) in subjects professionally exposed to vibrations, we found no significant difference in the average T score values of the dominant and non-dominant hand in our study ( $p = 0.269$ ) (**Table 2**).

**Table 1.** Demographic and clinical characteristics

Characteristics	Total	Number of subjects (%) or mean $\pm$ SD		p <sup>1</sup>
		Study Group n=31	Control Group n=25	
<b>Gender</b>				
Male	52 (92.86%)	29 (93.55%)	23 (92.0%)	1.000 <sup>1</sup>
Female	4 (7.14%)	2 (6.45%)	2 (8.0%)	
Age (years)		49.5 $\pm$ 6.1	49.6 $\pm$ 5.6	0.949 <sup>2</sup>
<b>Dominant hand</b>				
Right	51 (91.07%)	29 (93.55%)	22 (88.0%)	0.801 <sup>1</sup>
Left	5 (8.93%)	2 (6.45%)	3 (12.0%)	
<b>Smoking status</b>				
Non-smoker	21 (37.50%)	11 (35.48%)	10 (40.0%)	0.944 <sup>1</sup>
Smoker	35 (62.50%)	20 (64.52%)	15 (60.0%)	
<b>Alcohol consumption</b>				
Yes	40 (71.43%)	19 (61.29%)	21 (84.0%)	0.116 <sup>1</sup>
No	16 (28.57%)	12 (38.71%)	4 (16.0%)	

<sup>1</sup> the Chi-squared test, <sup>2</sup> t-test

**Figure 1.** Frequency of osteopenia in the study and control group**Table 2.** T score values of the dominant and non-dominant hand in study group

T score	Dominant hand N=31	Non-dominant hand N=31	p <sup>1</sup>
Mean $\pm$ SD	-0.81 $\pm$ 0.58	-0.62 $\pm$ 0.68	0.269
Min-Max	-2.3 - -0.2	-1.7 - 0.7	

<sup>1</sup> t-test

## DISCUSSION

Since the time of the first observations of the effect of vibrations on workers' body, which were described by Lariga in 1911, there have been numerous authors who have studied problems related to professional exposure to vibrations and vibration sickness (14).

In our study, there was no statistically significant difference between the examined groups in the distribution of subjects according to the age structure. The average age in the experimental group was 49.5 $\pm$ 6.1 years with the variation interval of 32-61 years, and in the control group it was 49.6 $\pm$ 5.6 years with the variation interval of 35-59 years. This age structure corresponds to the working population.

In the distribution of subjects according to gender, there was a significantly higher number of men (92.9%) in our study in comparison with women (7.1%), while there was no statistically significant difference in the number of subjects according to gender between the examined groups, as male gender was dominant in both groups. This correlates with data in other countries. In

Great Britain male/female ratio of new cases for HAVS from 2010 to 2019 shows that out of 5620 cases 99.7% were male (15). The difference probably reflects a smaller number of women working in job positions that involve exposure to HAV.

Cigarette smoking has been shown to lead to significant bone loss, and is recognized as an independent risk factor for the development of osteoporosis. It has been shown that long-term cigarette smoking can lead to an imbalance in bone turnover, further contributing to a reduction in bone mass and bone length, and an increased risk of fractures (16). However, smoking did not affect the results of our study, considering that the difference between the groups in relation to the smoking habit was not significant, with significantly higher number of smokers, in both examined groups.

Based on the results of a meta-analysis, alcohol consumption was shown to be a risk factor for osteoporosis. Negative effects of alcohol on bone health mainly interfere with the balance of calcium, a vital nutrient for bone health. There is linear association between greater alcohol consumption and bone density loss over time. (17). In our study, the number of subjects who consumed alcoholic drinks was significantly higher than those who did not consume alcohol at all, and even more so in the control group (84.0%) than in the experimental group (54.3%). This could have influenced the DXA findings, but in our study a greater loss of bone mineral density was not registered in the subjects of the control group.

Previously, it has been reported that vibration altered the bone remodeling and affected bone mineralization (18,19). Some studies reported that low frequency (<40 Hz) vibrations of high magnitude might be associated with abnormal radiological findings in the wrist and elbow joints (20,21). Fialova et al., investigated osteoporosis in the proximal segments of the upper extremities by evaluating chest X-ray findings in a group of 107 chainsaw workers. Their results showed a statistically significant difference in the degree of mineralization of the clavicle, compared to a group of 107 healthy men who had never worked with vibrating tools. The authors concluded that osteoporosis was not a rare finding in patients with vibration disease and that it affected both distal and proximal segments of the upper extremities (22). The results of a study by Peelukhana et al. showed that the structural damage was significant for cortical bone while it remained

insignificant for the trabecular bone. Furthermore, the results of this study showed that structural damage was significant at 5D time point for the cortical bone while the trabecular bone remained largely unaffected, with a change in trabecular spacing observed at 20D time point (23). Our results correlate with these data.

This observational study, with its moderate sized, carefully designed groups and well-constructed analysis, is the first one in Serbia that showed the correlation between HAV and low mineral density in the distal part of the forearm. Measuring the bone mass density of the distal radius using DXA, osteopenia was found in 14 subjects (45.16%) in our study according to the WHO criteria, which makes a statistically significant difference compared to the control group ( $p < 0.01$ ), where osteopenia was found in 3 subjects (12.0%). This would confirm the possibility of applying the distal forearm DXA examination in occupationally exposed HAV, bearing in mind that the distal radius is predominantly composed of the cortical bone.

## CONCLUSIONS

Changes in bone density at the distal forearm are not uncommon in people occupationally exposed to vibrations. Distal forearm DXA examination in workers occupationally exposed to HAV can contribute to the diagnosis of HAVS. The appropriate assessment and diagnosis ensure adequate treatment primarily in terms of timely cessation of vibration exposure, since, similarly to neurological and vascular disorders, bone mineralization can be repaired upon cessation of exposure to vibration.

## Author Contributions:

Conception, interpretation, and work design: Marija Hrković, Tamara Filipović, Anđela Milovanović, Aleksandar Milovanović. Data acquisition and analysis: Dejan Nikolić, Ljubica Nikčević, Jovana Kojović Avramović. Aleksandar Filipović. All authors approved the final version of the manuscript.

## Conflict of Interest:

Authors declare no conflict of interest.

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## UTICAJ LOKALNIH VIBRACIJA NA MINERALNU GUSTINU KOSTIJU DISTALNE PODLAKTICE

Marija Hrković<sup>1,2</sup>, Tamara Filipović<sup>1,2</sup>, Dejan Nikolić<sup>1,3</sup>, Ljubica Nikčević<sup>1,4</sup>, Jovana Kojović Avramović<sup>1,2</sup>, Aleksandar N. Filipović<sup>1,5</sup>, Andjela Milovanović<sup>1,6</sup>, Aleksandar Milovanović<sup>1,7</sup>

### Sažetak

Produžena, uglavnom profesionalna, izloženost gornjih ekstremiteta vibracijama može izazvati složen hronični poremećaj poznat kao vibraciona bolest. Pored vaskularnih i neuroloških poremećaja, ovakva izloženost lokalnim vibracijama može izazvati razne poremećaje na kostima u vidu cističnih promena, egzostoza, aseptične nekroze, osteoartritisa, spontanih preloma i osteoporoze.

Cilj ovog istraživanja bio je da se ispita da li postoje promene mineralne koštane gustine na nivou distalne podlaktice kod osoba koje su profesionalno izložene lokalnim vibracijama.

U grupi od 31 radnika profesionalno izloženih vibracijama (29 muškaraca i 1 žena) sa neurološkim i/ili vaskularnim znacima vibracione bolesti DXA metodom ispitana je mineralna koštana gustina na nivou distalnog radijusa. Kontrolnu grupu činilo je 25 zdravih ispitanika koji nisu

bili izloženi lokalnim vibracijama. Osteopenija je utvrđena kod 14 ispitanika (45,16%), što čini statistički značajnu razliku u odnosu na kontrolnu grupu ( $p=0,017$ ), gde je osteopenija utvrđena kod 3 ispitanika (12,0%). Osteoporoza nije utvrđena ni kod jednog ispitanika. Analizirajući vrednost T skora za dominantnu ( $-0,81 \pm 0,58$  SD) i nedominantnu ruku ( $-0,62 \pm 0,68$ SD) kod naših ispitanika, nismo pronašli statistički značajnu razliku u prosečnim vrednostima T skora dominantne i nedominantne ruke ( $p=0,269$ ).

Promene mineralne koštane gustine na nivou distalnog radijusa su česte kod osoba koje su profesionalno izložene vibracijama. DXA pregled distalnog radijusa kod radnika koji su profesionalno izloženi lokalnim vibracijama može pomoći u dijagnostici vibracione bolesti.

**Ključne reči:** Vibraciona bolest, gustina kostiju, DXA

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**Medicinska istaživanja 2023; 56(2):93-97**





**CASE REPORT**

# Mutaf one-stage technique for congenital constriction rings – safe and effective

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**Summary**

**Introduction:** Congenital constriction ring is a rare congenital malformation that especially affects the limbs. It is associated with fibrous bands that could encircle, strangle, or amputate some parts of the fetus. However, there are only a few techniques described for the correction of this anomaly. We aim to present a successful treatment of congenital constriction ring by means of the one-stage Mutaf technique.

**Patient Review:** In our report, we presented two infants with congenital constriction rings. In the first case, we presented an infant with a constriction band on the right arm accompanied by deformity of the distal part and lymphoedema. In the second case, we presented an infant with multiple constriction bands on the distal part of the right leg with clubfeet and severe lymphoedema. They were both treated by the one-stage Mutaf technique using rectangular dermofat grafts to fill the groove. Using this technique we obtained a normal limb contour, with no oedema or neurovascular compromise. Filling the groove with the rectangular dermofat flaps parallel to the relaxed skin tension lines provides a better scar in comparison with multiple Z- or W-plastics techniques. Additionally, advantages of the one-stage procedure are reduction of surgical and psychological trauma in patients and their parents, less time spent under general anesthesia and lower amount of anesthetic the patient receives, and lower treatment costs.

**Conclusion:** We find the Mutaf technique to be an effective and safe technique for the treatment of congenital constriction rings.

**Keywords:** Amniotic Band, Surgery, Technique

## INTRODUCTION

Constriction ring syndrome (CRS) is a complex of congenital anomalies that occurs in a variety of combinations, especially affecting the limbs and rarely the head and the trunk. (1-10) There are several synonyms for this condition such as amniotic band syndrome (ABS), amniotic constriction bands (ACB), congenital constriction band syndrome (CCBS), annular band, and Streeter dysplasia. (7-18) This congenital malformation occurs with an incidence of approximately 1:1200 to 1:15000 live births. (2,7,14,18) It is characterized by fibrous bands -congenital constriction rings (CCR) - that could cause acrosyndactylies, circular constrictions in the extremities of varying degree, and terminal transverse defects. (1-3,5-7,9) There are several classification systems of this anomaly. (2,6,7) Patterson diagnostic criteria established a classification system of CCR: type 1 – simple constriction rings; type 2 – constriction rings accompanied by deformity of the distal part, with or without lymphoedema; type 3 – constriction rings accompanied by fusion of distal parts, ranging from mild to gross acrosyndactyly (type I, II, and III); and type 4 – intrauterine amputations. (2,4-7) Hall, Winzweig, Hüsler, Hannigan and Homer presented their classifications of CRS. (2,6,7)

The CRS is an independent group of congenital anomalies that occurs sporadically without a genetic background. (1,7) The etiology of this syndrome is still unknown. (1-3) There is no data about the inheritance pattern or chromosomal disorder and there is no difference in morbidity concerning gender and ethnicity. (1-9) The most common etiologies that have been discussed are the intrinsic theory (the umbilical cord causes pressure on the fetal tissue acting like constricting band and thus interfering with normal limb development) and the extrinsic theory (external maternal injury can cause an oligoamnion which can allow a closer contact between the fetus and the amnion). (3,4) However, no single pathogenic conclusion has been made to explain different findings seen in this syndrome. (1,3,7)

Soft tissue, lymphatic vessels and, superficial vascular circulation are usually partially obstructed and oedema with cyanosis could be distally present causing pain. (2,5,7-9) The prenatal ultrasound scan can show swelling of digits or limbs distal to the constriction with amniotic bands attached to the fetus and a reduction in fetal movements. (8)

There are several reports presenting the fetoscopic release of CCR. (20) However, in most cases the treatment of CCR occurs after birth. (1,5,9,11-19) When there are shallow grooves, surgery is not required. (1,2,11) In case of vascular or lymphatic obstruction, constriction bands must be surgically treated to prevent gangrene or auto-amputation and to save the function and development of the affected limb. (9-12,14,15,18) A surgical treatment is usually performed as a one-stage or two-stage procedure,

including multiple Z-plastics, W or Y-to-V plastics (with a variety of techniques proposed by different authors), direct closure, and rectangular-plastic technique (a one-stage Mutaf procedure). (1,9,11,12,14-19).

We present our results using the one-stage Mutaf technique in two patients with limb obstructions caused by CCR.

## Surgical technique

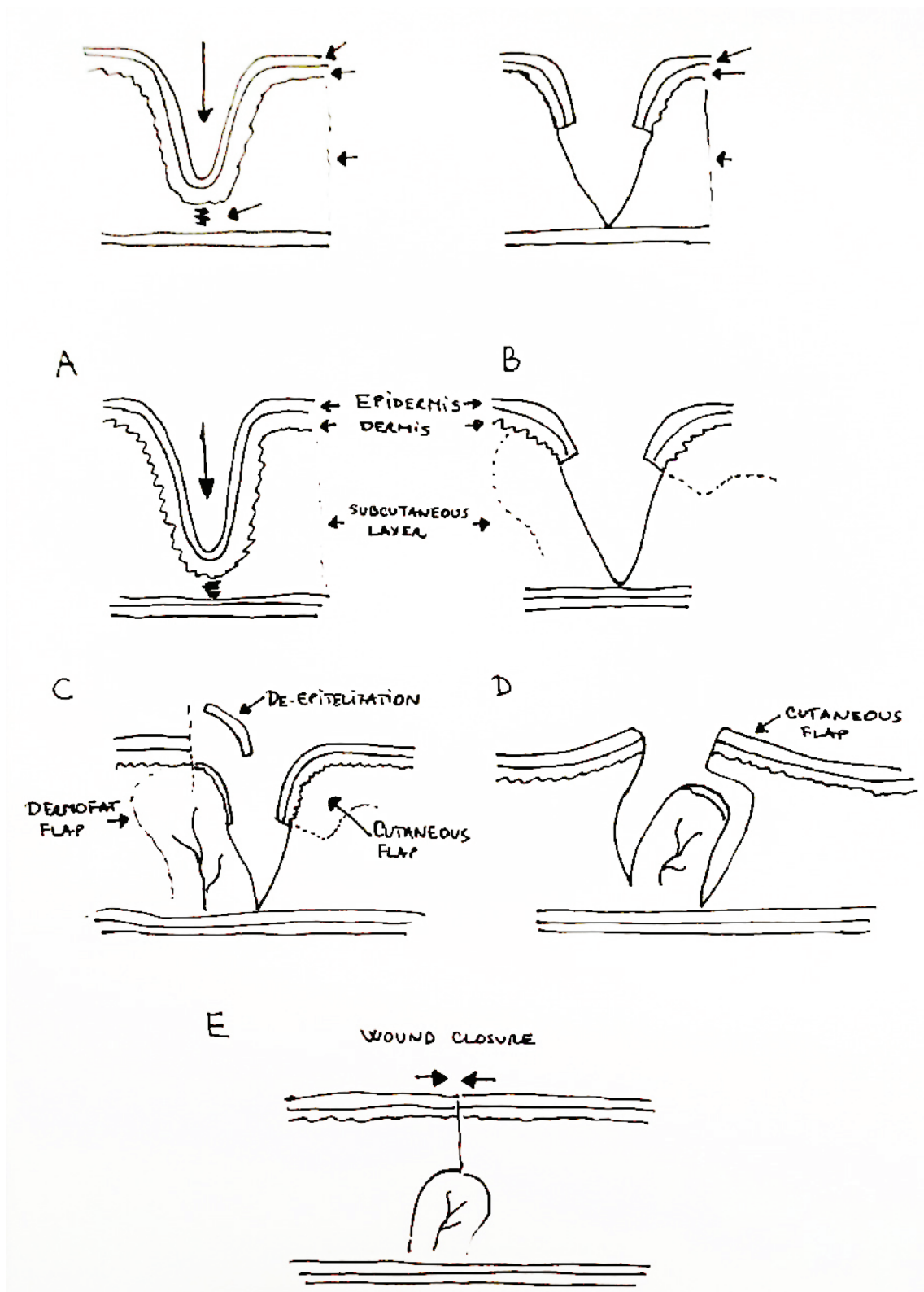
We performed surgery under general anesthesia with a tourniquet application. The scheme of the Mutaf technique is shown in **Figure 1**. Constriction rings were identified intraoperatively and carefully excised (all fibrotic tissue had to be excised) (**Figure 1a,b**). Rectangular flaps were designed on both sides of the groove. The height of these flaps was extended up to the border of the normal limb contour, and the width of each flap was about twice as big as its height. Flaps were de-epithelialized in an alternating pattern on each side while the opposite flaps stayed intact (**Figure 1c**). The de-epithelialized rectangular flaps were elevated as dermofat flaps and turned over from both sides toward the groove and sutured to the subcutaneous tissue of the opposing rectangular skin flaps (**Figure 1d**). According to this technique, the groove was filled with a soft tissue bracelet created by the turned-over dermofat flaps. The skin closure was obtained with rectangular cutaneous flaps opposing the dermofat flaps (**Figure 1e**).

## CASE REPORT 1

We present our first patient with CCR on the distal part of the right forearm with circumferential swelling of the right hand and arm distal to the constriction. According to Patterson, this was CCR II type (**Figure 2a**). Due to conspicuous lymphoedema and functional impairment of the hand, we decided on the one-stage Mutaf technique under general anesthesia. All neurovascular structures were identified and a constriction ring with all fibrotic tissue was excised. After excision, we designed rectangular turn-over dermofat flaps to fill the groove (**Figure 2b**). Ultimately, the skin closure was obtained with rectangular cutaneous flaps opposing the dermofat flaps. There were no problems with circulation or innervation in the postoperative period, and the functional and aesthetic outcome was satisfying (**Figure 2c**). We have continued follow-up for 6 years and here we present the result (**Figure 2d**).

## CASE REPORT 2

Our second patient had type III CCR with associated multiple foot and hand anomalies. Multiple constriction

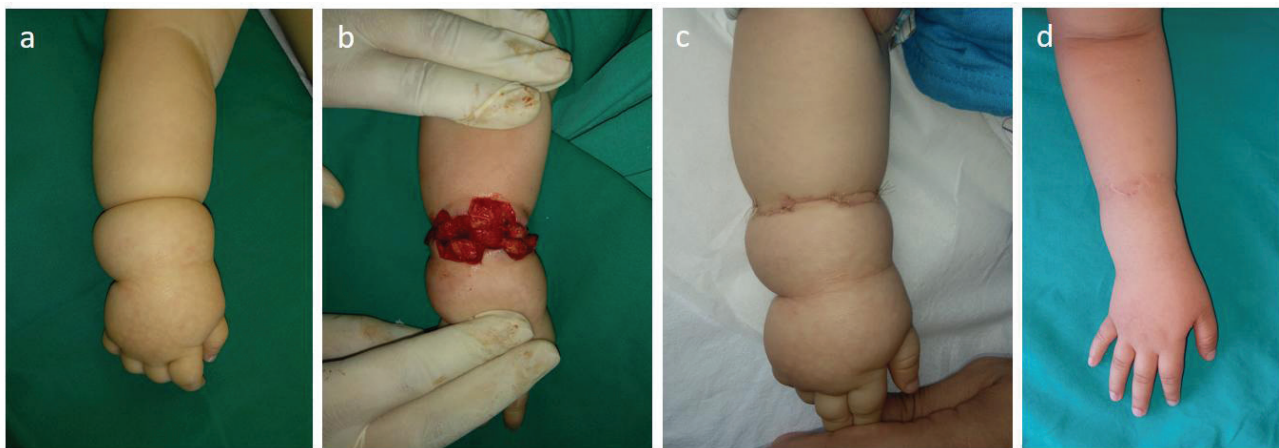


**Figure 1.** Schematic presentation of the one-stage Mutaf technique and its basic principles

- a. Congenital constriction ring;
- b. Excision of the ring;
- c. De-epithelization of the dermofat flap;
- d. Elevation of the dermofat as a cutaneous flap;
- e. Result

bands on the distal part of the right leg with clubfeet were present (**Figure 3a**). Due to vascular compromise and lymphoedema, we decided to perform the one-stage

Mutaf procedure. An extremely strong and thin constrictive ring was present and the preparation of the neurovascular structures was extremely delicate (**Figure 3b**).



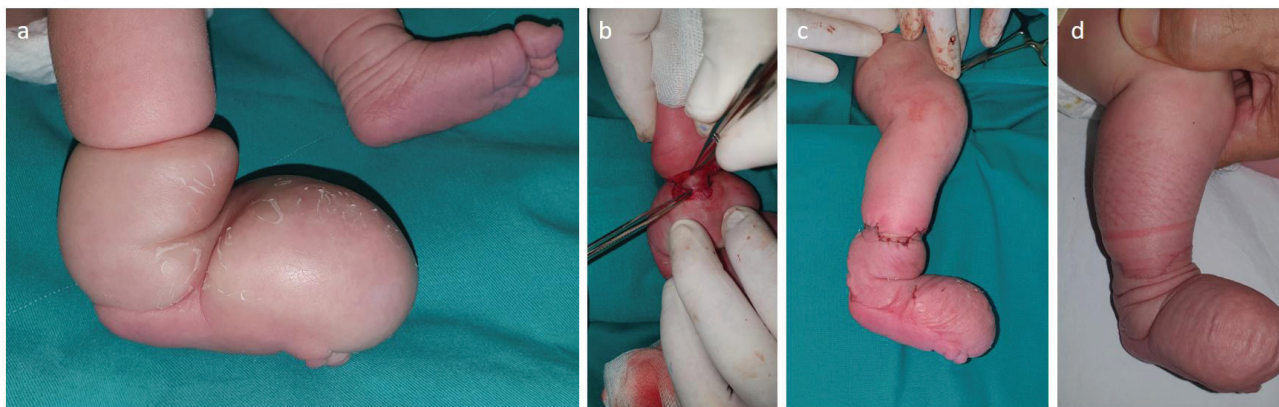
**Figure 2.** Case presentation of a patient with type II congenital constriction ring of the right arm  
 a. Congenital constriction ring of the right arm with distal lymphoedema  
 b. Intraoperative view with rectangular skin and dermofat flaps  
 c. Result after two weeks postoperatively  
 d. Result after six years of follow up.

Additionally, conspicuous lymphoedema was intraoperatively identified. We designed rectangular flaps according to Mutaf (Figure 3c). We got satisfying results immediately after the procedure, with no present neurovascular compromise. Postoperatively, excess skin was present on the dorsum of the right foot. Here we present results after six months (Figure 3d). The patient is still on compressive therapy, and further reconstructive procedures (skin reduction) of the right foot are planned.

**Discussion**

The time and the approach to the management of CCR depend on clinical presentation and range from fetal surgery and urgent postnatal surgery to multiple-stage surgeries performed later in life. (1,3,9,10,12,14,15,18,20) In cases where circulation or innervation is compromised, and where there is a risk of gangrene autoamputation surgery has to be performed as soon as possible.

(1,2,9,11,15) This was the case with our patient N<sup>o</sup>2. Some authors performed surgeries immediately after birth. (14,16) On the other hand, several studies showed very good results in patients who started with surgeries a few months after birth or even later. (3,7) In our report of the first case we had a lower risk of neurovascular obstruction, so we performed surgery at a later date, while the patient described in the second case had a high risk of neurovascular obstruction and surgery was performed a few days after birth. There are several options for the treatment of CCR such as multiple Z- or W- plastics, one-stage circular resection and primary circular suture without Z-plastics, simple linear hemi-circumferential excision without Z-plastic, rectangular-plastic technique (the one-stage Mutaf procedure), and multiple continuous opposing Y-to-V-plastics in a single or staged manner. (9-19) Regardless of the technique used, the key to success is a complete resection of all constricting rings and fibrous tissue, and linear incisions of the deep fascia. (1,



**Figure 3.** Case presentation of a patient with type III congenital constriction rings of the right leg  
 a. The large oedema of the distal part of right leg as a consequence of congenital constriction ring  
 b. Excision of fibrous band which cause the oedema  
 c. Immediate postoperative result with the Mutaf technique  
 d. Result after six months of follow up

-3,7,9,10,12-18) Straight circular sutures at the limbs are generally avoided because of possible scar contractures and circular constrictions, however, this technique is still used by some authors. (1-9,16,17,18) To reduce the risk of scar contracture some authors advocate multiple Z- or W-plastics and according to their experience transposition of two or more flaps allow additional relief of skin tension by redistribution of a relative excess of adjacent skin. (1-7,9-14,18) The main disadvantage of Z-plastic is the undesirable course of scars and the rest of contour deformity. (1) In our point of view using rectangular flaps according to the Mutaf technique can both reduce skin tension and obtain better aesthetic results than Z- or W-plastics.

In the CRS we make soft tissue deficiency up with similar tissue to obtain normal contour of limbs. The Mutaf technique advocates using well-vascularized turn-over dermofat flaps elevated in an alternating fashion from each side of the ring to fill the groove. (9) The incisions made this way are parallel to the relaxed skin tension lines. When the groove is filled rectangular skin flaps are sutured and suture lines are parallel to the relaxed skin tension lines.

Some authors advocate the two-stage “sine plastic” technique with a one-week interval between stages claiming that the known technique is not effective in the elimination of contour deformity. (16) In our point of view using the Mutaf procedure we can also achieve a similar aesthetic outcome in one stage resolving contour deformity as shown in Case 1. The benefits of one-stage procedures are a reduction in surgical and psychological trauma of patients and their parents, less time spent under general anesthesia and a lower amount of anesthetics the patient receives, and lower costs of hospitalization.

In the cases we present here, we achieve satisfactory results in correcting constriction rings in the arm and the

leg. Hence, we think that the Mutaf technique is very reliable when it comes to the correction of constriction rings in the upper and lower extremities. On the other hand, this technique does not seem to be feasible for correcting constriction rings located at the acral parts of the foot and hand because of the lack of dermofat tissue for harvesting adequate flaps. (9)

## CONCLUSION

We find the Mutaf technique to be an effective and safe one-stage technique for the treatment of congenital constriction rings.

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## Conflict of interest:

None to declare.

## Author Contributions:

All authors contributed to the study conception and design. Aleksandar Vlahović is in charge of the design, concept, main idea and the guarantor of integrity of the entire study. Milana Živković is in charge of the study concepts, design and manuscript preparation. Ninoslav Begović is in charge of the material preparation, analysis and editing. Ivan Dizdarević is in charge of the study design and manuscript preparation. Nataša Vlahović is in charge of the study concepts, data acquisition and manuscript preparation. All authors declare that the details of any figure can be published.

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## JEDNOAKTNA PROCEDURA PO MUTAFU ZA UROĐENE KONSTRIKTIVNE PRSTENOVE - BEZBEDNA I EFIKASNA

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### Sažetak

**Uvod:** Sindrom amnionskih brida predstavlja retku kongenitalnu malformaciju koja najčešće zahvata ekstremitete, ređe glavu i trup. Nastaje zbog fibroznih brida koje se tokom intrauterinog razvoja obmotavaju oko ploda, pri čemu može doći do akrosindaktilije, kompresije na ekstremitetima, sa ili bez kompromitovanja vaskularizacije, ili u najtežim slučajevima do amputacije različitih delova ekstremiteta. Postoji nekoliko hirurških tehnika za rešavanje ove anomalije. U ovom radu, prikazali smo naše rezultate koristeći tehniku po Mutaфу u jednom aktu.

**Prikaz pacijenata:** Prikazali smo dva deteta sa sindromom amnionskih brida. U prvom slučaju, prikazano je dete sa konstriktivnim bridama na desnoj ruci sa izraženim limfedemom i deformitetom distalno od mesta kompresije. U drugom slučaju, prikazano je dete sa multiplim konstriktivnim bridama na distalnim delovima desne potkolenice sa deformitetima stopala i izraženim

limfedemom uz kompromitovanje vaskularizacije. U oba slučaja primenjena je Mutafova tehnika u jednom aktu u opštoj anesteziji. U cilju obezbeđivanja normalne konture ekstremiteta, dizajnirani su pravougaoni "turn-over" režnjevi potkožnog masnog tkiva. Za rekonstrukciju defekta kože, korišćeni su pravougaoni kožni režnjevi. U oba slučaja postoperativni period je protekao uredno. Postignut je zadovoljavajući estetski rezultat. Sa obzirom na to da se radi o tehnici koja se izvodi u jednom aktu, najveća prednost ogleda se u manjem stresu kod roditelja i deteta, kraćem trajanju anestezije i manjim troškovima hospitalizacije u odnosu na multiple procedure.

**Zaključak:** Mutafova tehnika predstavlja efektivnu i bezbednu tehniku za rešavanje sindroma amnionskih traka u jednom aktu, kojom se postiže normalna kontura ekstremiteta bez limfedema, uz zadovoljavajući izgled ožiljka.

**Ključne reči:** Sindrom amnionskih traka, hirurgija, tehnika

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**CASE REPORT**

# Pregnancy and delivery in a patient with an ectopic kidney transplant and bilateral hearing loss

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**Summary**

**Introduction:** Pregnancy management and the choice of delivery method in kidney transplant patients are still a matter of debate. The goal is to achieve the balance between mother's underlying disease treatment and optimal conditions for fetal development and maturity.

**Case study:** The patient is a 36-year-old woman whose first pregnancy was complicated by kidney transplantation 11 years ago. During hospitalization, the values of all renal function parameters and cyclosporine concentration in the blood were regularly monitored, and nephrologists and urologists were regularly consulted. Having in mind the pelvic presentation of the fetus, ectopic localization of the transplanted kidney and comorbidities such as deafness, gestational diabetes and gestational hypertension, the delivery was completed by caesarean section with the presence of a urologist and a healthy male child was born.

**Conclusion:** By following the trends in current literature and applying team work, intensive supervision and adequate therapy for the mother and the fetus, it is possible to manage pregnancy in complicated transplanted patients and achieve outcomes equal to those of a physiological pregnancy.

**Keywords:** transplanted kidney, pregnancy, delivery mode

## INTRODUCTION

Owing to the progress of medicine, in recent years the number of pregnant women with chronic diseases has increased. A special challenge for perinatologists is balancing the well-being of the mother in treating her chronic disease while maintaining optimal conditions for fetal development and bringing the pregnancy as close to the due date as possible. The method of delivery is an additional dilemma in such pregnancies. It is necessary to involve all relevant specialists in the management of such pregnancy.

Nowadays, more and more patients get a chance for survival and good quality of life owing to organ transplantation, and some of these patients decide to get pregnant. One of the most frequently transplanted organs are kidneys. Pregnancy management and delivery method in kidney transplant patients are still a matter of debate among experts (1).

In this case study, we present a patient who achieved her first pregnancy 11 years after renal transplantation indicated for congenital renal anomaly requiring nephrectomy and subsequent hemodialysis and who delivered a baby by caesarean section in the 37th week of gestation (GW).

## CASE STUDY

The patient is a 36-year-old female who was admitted to the Clinic for Gynecology and Obstetrics of the University Clinical Center of Serbia (CGO UCCS) in the 33rd GW of a desired spontaneous pregnancy complicated by kidney transplantation performed 11 years ago.

Kidney transplantation was performed in 2001 after nephrectomy due to congenital kidney disease, after which the patient was included in the hemodialysis program for the next three years. The patient's mother was the donor.

In addition to the kidney transplant, the patient underwent spina bifida surgery during her childhood. After nephrectomy, the patient reported impaired hearing, which is why she has had hearing aid implanted in both ears.

The pregnancy was regularly controlled at the local level, and then at the CGO UCCS. Combined screening of the first trimester showed 1:184 probability chromosome 21 trisomy, and values of bHCG and PAPP<sub>A</sub> were 4.28 MoM and 1.88 MoM respectively. Bearing in mind the use of immunosuppressive therapy during the entire pregnancy, including the first trimester, the patient was presented to the Genetic counseling board of the CGO UCCS, after which she opted for further diagnostics in the form of cordocentesis because other types of genetic diagnostics were unavailable at the gestational age the patient presented to the CGO UCCS. Cordocentesis showed a normal male karyotype (46, XY).

At the time of admission and during hospitalization, the patient was with no complaints. The patient's height at admission was 150 cm with BMI 22.22 kg/m<sup>2</sup>.

During hospitalization, specialists in nephrology, surgery and urology were consulted on several occasions.

The values of kidney function parameters (urea, creatinine, eGFR, uric acid, albumins, proteins, ionogram, p/c ratio in the morning sample and 24h urine) as well as the level of cyclosporine in the blood were monitored, and the dose of the drug was increased as needed. On several occasions, the patient received transfusion with filtered erythrocytes. Bacteriological analyzes were performed regularly, with an emphasis on a urine culture to prevent the development of pyelonephritis. Abdominal ultrasound scan showed that the right kidney was located in iliac fossa and apart from that it was a normal finding.

Due to approximately two-fold increase in pancreatic amylase, a general surgeon was consulted on several occasions. After examining abdominal ultrasound scans, as well as clinical signs and symptoms, continued monitoring of the mother and the fetus was indicated, with no signs of acute pancreatitis.

During hospitalization, gestational hypertension developed, which was well controlled with methyldopa, as well as gestational diabetes, which was well controlled by means of antidiabetic diet. Due to the risk of preterm birth, fetal lung maturation was performed with dexamethasone according to the protocol.

Delivery method was chosen according to obstetric indications. Considering the pelvic presentation of the fetus, while taking into account previous surgeries and comorbidities, it was decided to end the pregnancy by caesarean section with the presence of a urologist.

A caesarean section was performed in the 37th GW with the presence of urology consultants and the patient gave birth to a live male child measuring 46cm/2270g/33cm, with Apgar score 8/9. Intraoperatively, it was established that the transplanted kidney was ectopic, placed in the right iliac fossa, polycystically altered and with a dilated ureter. The procedure went smoothly, there was no lesion of the urinary tract and hemostasis was correct.

## DISCUSSION

In addition to challenges in managing pregnancy after kidney transplantation, the localization of the transplanted kidney in the iliac fossa represents an additional predisposition to the development of typical complications such as hydronephrosis and pyelonephritis due to the pressure of pregnant uterus. Moreover, this localization represented an additional intraoperative risk, and during the caesarean section, urologists were called in for consultation, a practice that is known and recommended in other centers (2). This kind of cooperation, as well as



regular consultations of nephrologists make good team work which is essential for optimal pregnancy management and well-directed delivery.

Multiple consultations with nephrologists enabled precise monitoring of allograft function with the aim of preventing its rejection. Generally, patients who had good creatinine clearance before pregnancy should not have an increase in serum creatinine during pregnancy, and a subtle increase in creatinine levels may be overlooked as an early sign of allograft rejection. However, most studies (1, 3, 4) show that pregnancy is not a predisposing factor for graft rejection, and if there is any suspicion, kidney biopsy is recommended to detect the cause of allograft dysfunction (5).

According to recent research by Kattah and the authors (6), hyperfiltration that exists in physiological pregnancy can lead to glomerular hyperfiltration injury, which in some cases progresses to glomerulosclerosis worsening the quality of life postpartum. Hydration and regular monitoring of eGFR values in order to prevent hyperfiltration injury was therefore another task of the nephrology team.

In a recent paper by Shwartz et al. (7) eGFR before pregnancy correlated with GW at delivery and with the percentage of eGFR decline during pregnancy. The age of transplantation (time after transplantation + age of the donor at the time of donation) was not correlated with the percentage of graft loss during pregnancy, which was also confirmed in our patient whose transplantation was performed 11 years before pregnancy. An eGFR of less than 40 mL/min/1.73 m<sup>2</sup> before pregnancy was not only associated with a high risk of loss of graft function, but also with a high risk of fetal or perinatal death of the offspring. According to this study, an eGFR of 40 mL/min/1.73m<sup>2</sup> marks the lower limit of a reasonably planned pregnancy.

The most common maternal complications in pregnant women with kidney transplants are the development of gestational hypertension, preeclampsia or gestational

diabetes due to a chronic use of corticosteroids (8). Our patient developed gestational hypertension in the last trimester, which was successfully controlled with methyldopa and did not require a preventive use of aspirin in order to prevent the development of preeclampsia (9). The same applies to gestational diabetes mellitus, which was well controlled by a diet without elements of fetal macrosomia, although data in the literature show that 10% of patients on calcineurin inhibitor therapy require insulin therapy during pregnancy (8,10).

A question that is raised in this case could be the examination of hereditary factors or *in utero* exposure of the patient, given her characteristic comorbidities such as spina bifida and extremely short stature.

## CONCLUSION

This is a case of a female patient who was admitted to a tertiary level health care institution for pregnancy management after a kidney transplant 11 years before with comorbidities such as bilateral hearing loss and extremely short stature, and whose pregnancy was complicated by breech presentation of the fetus. With successful teamwork and cooperation between perinatologists, nephrologists and urologists, the patient had a successful delivery by means of caesarean section, giving birth to a healthy child with an Apgar score of 8/9 at full-term. By following current literature and applying team work, intensive supervision and adequate therapy for the mother and the fetus, it is possible to manage pregnancy in complicated transplant patients and achieve outcomes equal to those in a physiological pregnancy.

## Conflict of interest:

None to declare.

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## TRUDNOĆA I POROĐAJ KOD PACIJENTKINJE SA EKTOPIČNIM TRANSPLANTIRANIM BUBREGOM I BILATERALNOM NAGLUVOŠĆU

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### Sažetak

**Uvod:** Održavanje trudnoće i izbor načina porođaja kod pacijentkinja sa transplantiranim bubregom su i dalje predmet debate gde je cilj postići balans između lečenja osnovne bolesti majke i postizanja optimalnih uslova za razvoj i dosezanje zrelosti ploda.

**Studija slučaja:** Radi se o pacijentkinji uzrasta 36 godina čija je prva trudnoća komplikovana stanjem nakon transplantacije bubrega pre 11 godina. Tokom hospitalizacije redovno su praćene vrednosti svih parametara bubrežne funkcije i koncentracije ciklosporina u krvi, i redovno obavljane konsultacije nefrologa i urologa.

**Cljučne reči:** transplantirani bubreg, trudnoća, porođaj

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Imajući u vidu karličnu prezentaciju ploda, ektopičnu lokalizaciju transplantiranog bubrega i komorbiditete u vidu nagluvosti, gestacionog dijabetesa i gestacione hipertenzije, porođaj je završen carskim rezom uz prisustvo urologa i rođeno je zdravo muško dete.

**Zaključak:** Uz aktuelno praćenje literature, timski rad i intezivan nadzor i adekvatnu terapiju kod majke i ploda, moguće je kod komplikovanih transplantiranih pacijentkinja trudnoću voditi i svesti na nivo ishoda kao kod fiziološke trudnoće.



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