

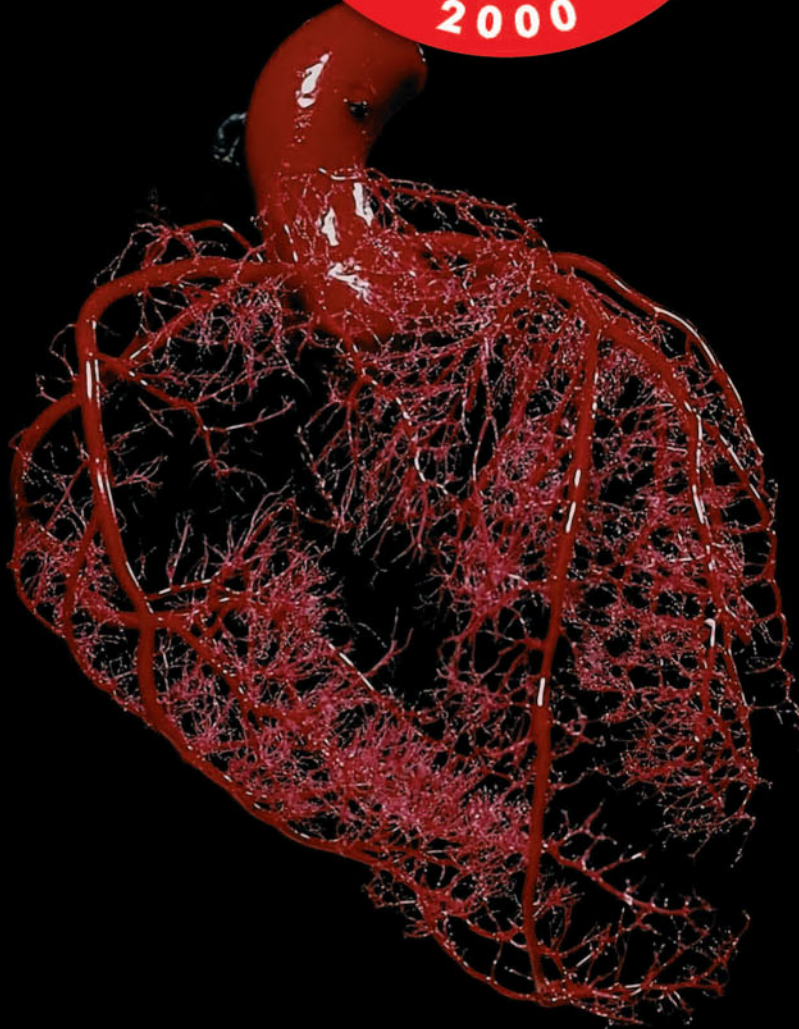
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## CONFLICT OF INTERESTS – WHAT IS IT, DOES IT MATTER, AND HOW TO DEAL WITH IT?

Disclosing of conflict of interests (Col)\* is the part of the editorial policy of the Serbian Journal of Experimental and Clinical Research (see Instruction to authors). Although editors of SJECR advise authors to consult Uniform Requirements for Manuscript Submitted to Medical Journals (1) and Committee on Publication Ethics – COPE (2) about anything related to the technical and ethical (including Col) aspects of preparing the manuscripts, it seems that this issue is practically unknown to the majority of our authors. This is the reason this editorial was born, although I had published several articles dealing with Col earlier (3-6).

\* Some editors prefer the term "Competing interests".

**Definition.** Anyway, what Col in medical publishing means? Let us clarify the term: "Conflicts of interest are those which may not be fully transparent and which may influence the judgment of an author, reviewer, and editors" (2). This means that all actors in the publishing game – authors, reviewers and editors – may have Col, which may bias the professional judgment.

The Col can be financial or academic. In the world of medical publishing, financial Col most often implies relationship with pharmaceutical industry (employment, funding, honoraria, consultations, payment for presentations at scientific meetings etc.). In academia, non-financial Col may be personal, professional, ethical, religious or political.

**Does it matter?** It is important to emphasize that there is nothing wrong with having Col – this is "neither immoral nor unethical" (7). What is wrong is to hide Col, if any. Undisclosed Col may cause suspicions on the integrity of the whole research and publishing process, and make the audience misled or deceived. That is what editors should avoid at any cost!

**How editors should deal with Col.** Since Col could influence what and how research results are presented in biomedical publications, editors of scientific journal should take it with much concern. The best way is to require from authors (and reviewers) the disclosure of Col in the form of Declaration of competing interests, which should be in the Instructions for Authors of any biomedical journal. Declared Col (or its absence) should be published at the end of the article. Since the authors are often unaware about importance and the way of declaring Col, they should be advised to consult the Col policies of the International Committee of Medical Journal Editors (1), Council of Science Editors (8) and World Association of Medical editors – WAME (9).

Since biomedical journals are often valued on the base how they handle Col, I believe that further development of the SJECR editorial policy regarding this issue will contribute to the constant improvement of our journal – the goal we all are attempting to achieve (10).

According to my proposal to publish declaration of Col in every article (and after consulting WAME members whether or not it is ethical to publish in the journal I am editorial board member), I end this editorial by following:

*Declaration of competing interests: The authoress of this editorial is the member of the editorial board of SJECR. She is unpaid for this, and was not involved in the decision-making process, including peer review.*

Ljiljana Vučković-Dekić

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**Figure 4**  
Professor Vladimir Vujic, a few months before his death.



**CORNERSTONES OF SERBIAN MEDICINE: DR VLADIMIR VUJIC**

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**UTEMELJIVAČI SRPSKE MEDICINE: DR VLADIMIR VUJIĆ**

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**ABSTRACT**

Professor Vladimir Vujic was the founder of the school of neuropsychiatry in the former Yugoslavia, and was especially influential in Serbia and Belgrade. He was born in Belgrade in 1894, but his father's service brought the Vujic family to Kragujevac, where he finished his primary school and attended the famous Gymnasium. As a volunteer he took part in the Balkan Wars and as a member of the medical corps he participated in the First World War, which also caused him to suspend his medical studies in Paris and Vienna. Then, in 1919, he went to Prague to study at the Karlov University and worked at the Neurological Clinic of Professor Haskovec where he became interested in neurology. In 1923, having finished his studies, he returned to Belgrade and started working at the Mental Hospital. He spent two years (1924–1925) on advanced professional training in Vienna, with Professor Wagner Jauregg, who received the Nobel Prize for Medicine 1927. At first, Vujic was an Assistant and then, in 1932, he became an Assistant Professor at the Faculty of Medicine in Belgrade. Although absorbed in his work, he managed to come to Kragujevac to celebrate the 20th anniversary of his graduation from the Gymnasium. In 1941 and again in 1945, he refused the position of the Major of Belgrade. He became a full professor of the Faculty of Medicine in 1946. He was elected the first Vice Dean of the Faculty of Medicine in Belgrade, and because of his scientific contribution he became a corresponding member of the Serbian Academy of Science in 1948. Vujic entered into a direct correspondence with many of the outstanding neurologists and psychiatrists of the time: Wartenberg, Cossa, Heuyer, Bersot, Lowenthal, and Levis. Professor Vujic published original works such as "Synesthesia of hallucinated voice and perception of colors," and other works on optical hallucinations in patients with schizophrenia, on optical images in a series of clinical entities, on interpretation of psychastenia, on the disappearance of lunatic ideas and change of faith in the course of cures, on affective intolerance, and many other topics. Professor Vujic also wrote some papers in the field of neurology. For instance, his monograph "Encephalitis Larvata" went through two editions even though it was published in the difficult post-war period (1948-1951). We should also point out his studies of the signs indicating encephalitis during flu epidemics, his "experiment with a book" as an indicator of extrapyramidal disorders, and his experimental

**SAŽETAK**

Profesor Vladimir Vujic je bio osnivač neuropsihijatrijske škole u prethodnoj Jugoslaviji, posebno u Srbiji i Beogradu. On je rođen u Beogradu 1894. godine, ali je službovanje njegovog oca dovelo porodicu Vujic u Kragujevac, u kome je završio osnovnu školu i poznatu Gimnaziju. Učestvuje kao dobrovoljac u Balkanskim ratovima i medicinar u Prvom svetskom ratu, koji mu prekida započete studije medicine u Parizu i Beču. Potom, 1919. godine, odlazi u Prag, da studira na Karlovom Univerzitetu, gde je radio na neurološkoj klinici Profesora Haškoveca i tu se usmerava ka neurologiji. Vraća se po okončanim studijama 1923. god. u Beograd, gde započinje rad u duševnoj bolnici. Dve godine (1924-1925) potom provodi na dodatnom profesionalnom usavršavanju u Beču, kod profesora Wagner Jauregga, dobitnika Nobelove nagrade za 1927. god. Prvo je bio asistent a potom, 1932. godine, je postao docent na Medicinskom fakultetu u Beogradu. Zaokupljen obavezama i naukom ipak stiže da dođe na proslavu dvadesetogodišnjice velike mature u Kragujevcu. Odbio je 1941. god. i 1945. god. da bude gradonačelnik Beograda. Postaje redovni profesor Medicinskog fakulteta 1946. godine. Biran je za prvog prodekana Medicinskog fakulteta u Beogradu, a zbog svog naučnog doprinosa postaje 1948. godine dopisni član Srpske akademije nauka. U direktnoj je prepisci sa velikanima neurologije i psihijatrije onog doba: Wartenberg, Cossa, Heuyer, Bersot, Lowenthal, Levis i dr. Profesor Vujic objavljuje originalne radove kao što je "Sinestezija halucinatornog glasa i precepcija boja", zatim radove o optičkim halucinacijama kod bolesnika sa shizofrenijom, o optičkim slikama kod niza kliničkih entiteta, o tumačenju psihoastenije, o nestajanju sumanutih ideja kao i o promeni vere tokom lečenja, o afektivnoj intoleranciji i dr. Profesor Vujic napisao je više radova iz oblasti neurologije. Njegova monografija "Encephalitis larvata" je u teškim vremenima doživela dva izdanja (1948-1951). Poznati su Vujicevi znaci koji ukazuju na encefalitis tokom gripoznih epidemija, zatim "ogled sa knjigom" kao indikator ekstrapiramidnih poremećaja ali i eksperimentalne studije o spavanju i promeni pritiska likvora. Do svih otkrića profesor Vujic dolazio je bez ikakvih instrumenata, samo blistavom observacijom i neumornim istraživanjem. Veliki patriota, briljantan predavač, izuzetno radan, visokoetičan, kritičar proizvoljnih i netačnih tvrdnji, bio je profesor koji je okupljao asistente i nastavnike uoči predavanja već u 5 h ujutru

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studies of sleep and changes of liquor pressure. Vujic had no instruments and all the discoveries he made were based solely on his observations and tireless research. He was a great patriot, a brilliant lecturer, a hard-working man, and a highly ethical critic of arbitrary and incorrect scientific claims. As a professor, he frequently gathered his assistants and teachers for consultations and preparations before lectures, even at his house at five o'clock in the morning. He was loved and respected by his students, for whose benefit he once spent his AVNOJ reward. He died prematurely, while serving as the Head of the Psychiatric Clinic in Belgrade. The Psychiatric Clinic of the Faculty of Medicine in Belgrade bears his name.

**Keywords:** neuropsychiatry, Serbia, founders, Vujic's signs

*"I have no fear of death, I am only sorry that my premature death will take away at least ten years of work."*

Professor Vujic,  
a few months before his death

Professor Vladimir Vujic was born February 13, 1894 in Belgrade. It remains unclear precisely when his father's service brought the Vujic family to Kragujevac. His father, Filip, was the Head of the Ministry of the Post Office and, as a civil servant, he was moved from one town to another for the good of the service (1).

The family lived in a small street opposite the famous Gymnasium founded by Serbian Prince Milos Obrenovic in 1833. Here, almost in the shadow of the famous Gymnasium, Vladimir finished his primary schooling and then enrolled in the Gymnasium, which he graduated from in 1912. He acquired his enthusiasm, patriotic spirit and a thirst for knowledge in the Grammar School and town itself. He could have easily been inspired both by professors and students, as he worked with such figures as Djura Jaksic, Radoje Domanovic, Radomir Putnik, and others.

After attending the Gymnasium, he participated in the Balkan Wars (1912–1913) as a volunteer. In 1913, he went to Paris. In the "City of Lights" he enrolled in the Faculty of Medicine and completed his first year there before continuing his medical studies in Vienna in 1914. When the First World War began, Vladimir took part as a member of the medical staff, but soon, at his own request, he was transferred to an infantry regiment. Together with other Serbian soldiers, he crossed into Albania. After the war, in 1919, Vladimir went to Prague. This was one of the crucial years for Vladimir: he was a third-year student of Medicine at the Karlov University, and worked at the Neurological Clinic of professor Haskovec, where, guided by this eminent professor, he became interested in neurology. He finished his medical studies in 1923, and left Prague to return to Belgrade, where he started working at the Mental Hospital in Guberevac (1).

According to Dr. Dusan Stojimirovic, "the state of psychiatry before 1910 was like this. We read Havelock Ellis, Forel, Meiner and Kraft-Ebing, who had just laid the foundation of that branch of medicine. Freud, who became known around 1910, was not taken too seriously, as he might never be, because psychoanalysis is a long lasting and expensive procedure both for the society and the individual. We had already had around 500 patients, who needed urgent and human help. Ease the misery, heal the man, or keep him in hospital for ever—that was our plan, therefore, in these circumstances, there was not much time for Freud's method. There is no superstitious respect for the mad in our culture, as in Turks, but he—the poor man, did not know

u svojoj kući radi dogovora i preslišavanja. On je bio poštovan i voljen od studenata na čiju je ekskurziju znao da potroši svoju AVNOJ-evu nagradu. Umro je prerano 1953. godine kao upravnik Neuropsihijatrijske klinike u Beogradu. Klinika za psihijatriju Medicinskog fakulteta u Beogradu nosi njegovo ime.

**Ključne reči:** neuropsihijatrija, Srbija, utemeljivači, Vujićev znak



what to do. He dragged them from one which doctor to another, from one monastery to another, and then he would often bring them to us to rack our brains about them once their relatives had given up on them. However, it can be said that our people started looking upon mentally ill patients with different, rational attitude even before 1900. From 1850 we were shepherds, then from 1850 we were peasants, and since 1900 we have had yet another social transformation. The cultural level of the country began to rise quickly. People gradually became aware that all illnesses, including mental, belong to the realm of medicine and not witchcraft, and that medicine can offer cure for them. Nevertheless, it must not be kept secret that people were fed up with epileptics and mentally sick and occasionally they were tied up to a wall ring, morally abused and inhumanly treated even by those who were once very fond of them. But since 1900 these abuses were not that common. The Government gave us the necessary credits to accept those who suffered and to take care of them in the Mental Hospital till they are dead or cured. Authorities even sent patients from villages to us in Belgrade, their families brought them to us even from the farthest parts of Serbia. Rich people still took their patients to Vienna or Graz, but there they were not offered more than they would have been in the Belgrade Mental Hospital. The standard of this hospital was the same as of any other mental hospital abroad, furthermore, it was better equipped and organized than other similar hospitals in the Balkans, or even somewhere in Europe. Each patient had three abundant meals, with a variety of food, while patients with severe physical illnesses got absolutely everything they needed."

To a great extent, this was the achievement of Dr. Vladimir Vujic, who worked in the Mental Hospital at Guberevac, Belgrade. His quest for knowledge took him to Vienna in 1924. There, he spent two years (1924-1925) at the clinic of Wagner Jauregg von Paulus (1857–1940), the winner of the Nobel Prize in Medicine in 1927 for his work on the treatment of progressive paralysis by inoculation of malaria. Still young, but experienced (including his time at war and his studies in Paris, Vienna, and Prague), possessing impeccable knowledge of neurology and psychiatry, fluent in French, Czech and German, and with some knowledge of Italian and Greek, he was elected an Assistant at the Faculty of Medicine in Belgrade. In 1923, he was elected an Assistant Professor (1, 2).

In 1932, Vladimir came to Kragujevac for the celebration of the 20th anniversary of his graduation from the Gymnasium, which indicates that he was very fond of Kragujevac and its Gymnasium (figure 1). He was promoted to Associate Professor in 1940. Until 1941 he was the family doctor for the Karadjordjevic royal family. Because of the great respect he enjoyed, he was offered the position of Major of Belgrade in 1941 and then





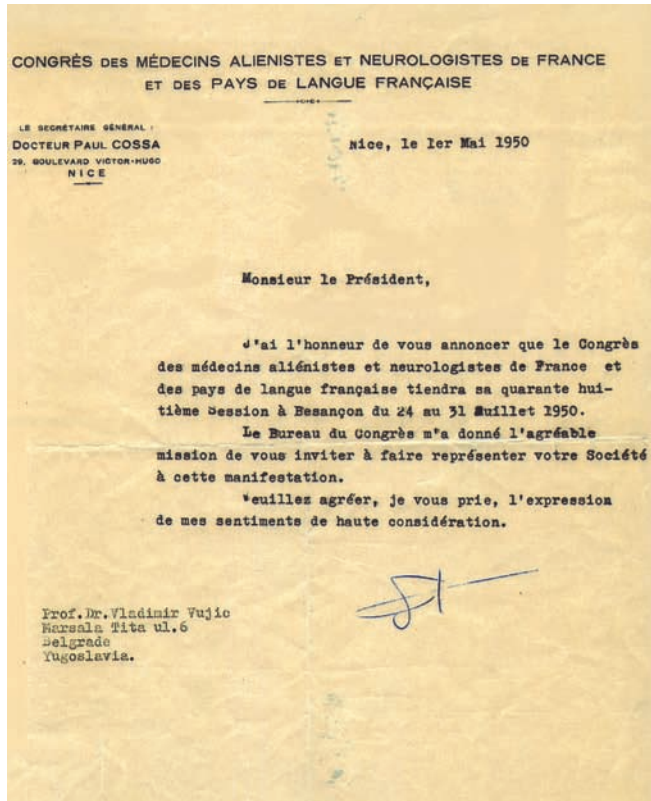
again in 1945, but both times he refused. He was elected a full Professor of Neuropsychiatry in 1946.

He was also elected the first Vice Dean of the Faculty of Medicine in Belgrade after the Second World War. This was a time of great creativity for Vladimir. As an excellent observer, he frequently discovered new phenomena and interpreted them in his own, ingenious way. His excellent teaching approach, which was strict and rigorous, gave him a reputation as both a respected academic and a loved professor.

During the period from 1946 to 1952, he kept in direct correspondence with world-renowned neurologists and psychiatrists like Robert Wartenberg in San Francisco, Paul Cossa in Nice, Georges Heuyer and Henry Bersot in Paris, Milton Lowenthal in New York, Levis in London, etc. To provide an example of these letters, we have chosen a selection written by Robert Wartenberg and Paul Cossa (figures 2 and 3). In the letter dated January 8th, 1951, Wartenberg wrote to Professor Vujic: "We are sole mates as neurologists—we share the same interests... I am interested in everything coming from your pen".

In Prague, in 1921, while still a third-year student, he started his own experimental investigations. Even at this early stage of his career, he published a paper, titled "Synesthesia of hallucinated voice and perception of color" (1). Synesthesia was a phenomenon new to the literature of that time. He continued to investigate the problem of optical perception: he published another paper on optical hallucinations in cases of schizophrenia in 1940, and he presented his original clinical study of optical images in series of clinical entities at the Consortium of French Neuropsychiatrists in 1946.

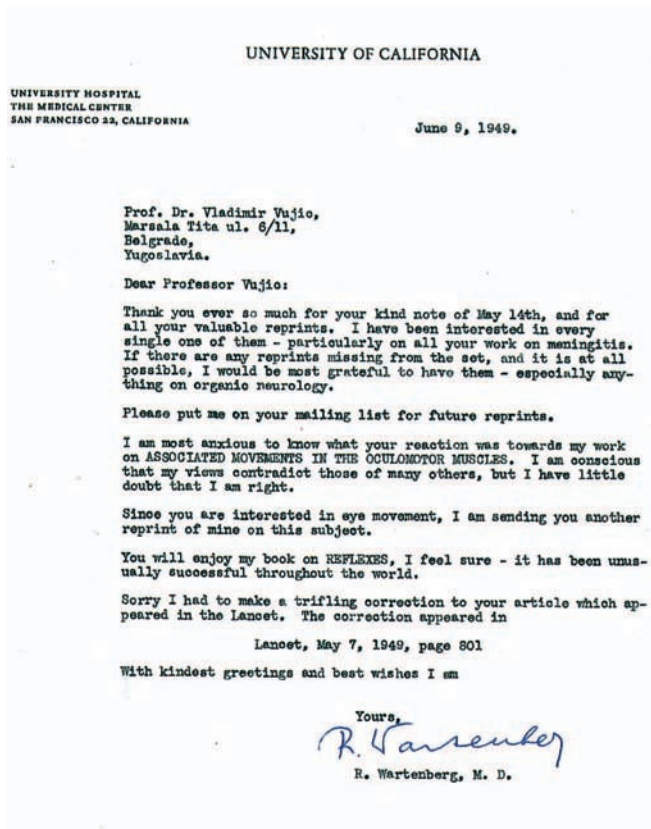
In these years, in light of the theory on changes at the level of psychical tension developed by Bergson, Vujic described paradoxical psychological phenomena such as the "illusory fall of a small object...on magnification and moving-away of objects." He also discussed Bergson's theory with Pierre Janet, giving a diametrically opposite interpretation of psychastenia to the one presented by Janet. He also pointed out the clinical significance of the discovery of the minimal pathology of ocular spectra on the optical pathways. The importance of this observation lies in the fact that the findings can indicate the existence of a brain tumor or intracranial hypertension with various causes. These discoveries were published by Vujic along with K. Levijen in Basel in the book "Die Pathologie des optischen Nachbilder" (3-5). Professor Vujic's areas of interests were very broad and also included the field of special psychiatry. In the period from 1930 to 1938, he investigated progressive pa-



**Figure 2.**  
A private letter from Professor P. Cossa, famous French neurologist, to professor Vujic.



**Figure 1.**  
Professor Vladimir Vujic, sitting the second from the left, at the 20-year anniversary of his Gymnasium graduation.



**Figure 3.**  
A letter from Professor R. Wartenberg asking for a reprint of one of Vujic's articles.





ralysis and published the first paper on disappearance of lunatic ideas in the course of cure and on the change of faith that occurs during the process.

At one of the world consortiums he attended, when one of the participants claimed that hysteria appeared only with still-primitive Serbs in the Balkans, he reacted patriotically but professionally and with dignity, responding, "Gentlemen, my small but heroic people are being offended here, although it is a scientific fact that hysteria exists worldwide. Furthermore, Freud's introduction of deep psychology and psychoanalysis was founded on the study of hysteria." Vujic's study on the frequency of progressive paralysis in different peoples compared to that of Serbs was written during this period. In this study he disputed incorrect and unscientific claims that classified Serbs as a "primitive" people (6).

As noted above, the breadth of Professor Vujic's work was very wide, but special attention must be paid to his debates on affectations and their role in everyday behavior and interpersonal communications. In 1949, at the Scientific Conference of Neuropsychiatry, he introduced a new term in this scientific field: "affective intolerance." Professor Vujic introduced psychology and psychopathology into the field of neuropsychiatry. He had a deep knowledge of psychoanalysis, although he was not an advocate of psychoanalysis in practice.

He was also a talented teacher whose students remember him as an excellent and interesting lecturer, given to demonstrating his skills at hypnosis. No wonder that his lectures were attended not only by students of medicine, but also by students of other faculties, educated people in general, and even laymen. His assistants and teachers were known to come to his office consultations and preparations even at five o'clock in the morning. The result of these brilliant lectures was the exceptional and extraordinary textbook "Medical Psychology with General Psychopathology" used by generations of Serbian students as the basic introduction to psychiatry (7). The shrewdness and wisdom of Professor Vujic can be illustrated by the following example. His close friend, a famous actor Dobrica Milutinovic, once saw a patient with Parkinson's disease and said, "this man looks as if he were holding a tray." Professor Vujic used this brilliant observation in his book "Encephalitis Larvata," and this description is still often cited by many professors in their lectures (8-10).

Professor Vladimir Vujic was also a man of principles, high morality and ethics in science as well as in everyday life. He was merciless in criticizing arbitrary and incorrect scientific claims, including those in the lectures at the Serbian Society of Physicians. His paper about the simulation of nervous and mental disorders is a good example of his critique of others (11).

Professor Vujic wrote numerous papers on a variety of topics in the field of clinical neurology, and these were frequently noted at an international level. In 1925, he described "Paradoxical blinking reflex and convergent eyeball tremor" (12). He also noted the existence of intentional tremor and introduced so-called the "breaking test" for use when finger tremor, a pathognomonic diagnostic sign of pseudosclerosis, appears. Professor Vujic was among the first scientists to discover the cause of polyneuritis epidemics in women, pointing to the use of apiol (parsley camphor) as an abortion agent. He also introduced the "experiment with a book" as a way of diagnosing the dying-out of automatic movements and a possible indicator of extrapyramidal disorders.

Professor Vujic searched for signs of encephalitis during flu epidemics for five years. The result of these investigations was his famous monograph "Encephalitis Larvata" (8). This book went through two editions in the Serbian language (1948, 1951),

even during the hard times after the war, when this was a rarity. American neurologists asked Professor Vujic to write something in memorial of Robert Wartenberg, so he gave a detailed description of his investigations in the field of larval encephalitis. Professor Vujic conducted his share of experimental work. His study on sleeping and change in liquor pressure should be especially remembered (13). It included a great number of clinically treated patients and it provides a basis for determining the existence of epilepsy without epileptic seizures. Throughout, Professor Vujic used no instruments; all his findings were based solely on his observation and investigation (14).

Professor Vladimir Vujic was a man of great morality and enormous erudition (Figure 4). He was a scholar and scientist, but also an extraordinary teacher (he spent his AVNOJ reward to take his 110 students on a traditional excursion to Opatija). From 1945 until his premature death in 1953 he was the Head of the Neuropsychiatric Clinic in Belgrade. He was a corresponding member of the Serbian Academy of Science from 1948 on, and the Psychiatric Clinic of the Faculty of Medicine in Belgrade bears the name of Professor Vladimir F. Vujic in his honor. Professor Vujic was also the founder of the school of neuropsychiatry in the former Yugoslavia, especially in Belgrade and Serbia.

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## SIGNIFICANCE OF NT-PRO-BNP IN EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE CORONARY SYNDROME

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## ZNAČAJ NT-pro-BNP- $\alpha$ U PROCENI FUNKCIJE LEVE KOMORE U BOLESNIKA SA AKUTNIM KORONARNIM SINDROMOM

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### ABSTRACT

**Introduction.** Left ventricle function in patients with acute coronary syndrome (ACS) is crucial in prognosis of the illness. Increased levels of N-terminal prohormone brain natriuretic peptide (NT-pro-BNP) were found in 50-90% of patients with ACS.

**Goal.** The goal of this research was to establish a correlation between the level of NT-pro-BNP and echocardiographic parameters of systolic and diastolic function of the left ventricle in patients with ACS.

**Methods and results.** The experiment included 62 patients with ACS. First, the serum level of NT-pro-BNP and systolic and diastolic function of the left ventricle were measured. According to their NT-pro-BNP levels, patients were divided into two groups: group A (18 patients with levels of NT-pro-BNP from 0 to 14.75 pmol/L) and group B (44 patients with levels of NT-pro-BNP higher than 14.75 pmol/L). Reduced systolic function of the left ventricle (SFLV) was found in 90.09% of patients in group B and 5.6% of patients in group A. Diastolic function of the left ventricle (DFLV) was diminished in 83.3% of patients in group A and 100% of patients in group B.

A strong correlation was found between levels of NT-pro-BNP in group B and all parameters of systolic and diastolic functions of the left ventricle: ejection fraction (EF)  $r=-0.459$ ,  $p<0.01$ ; fraction shortening (FS)  $r=-0.367$ ,  $p<0.05$ ; relation of maximal early (PE) and late (PA) diastolic speed of loading (PE/PA)  $r=-0.469$ ,  $p<0.01$ ; deceleration time of early diastolic flow (DT)  $r=0.582$ ,  $p<0.01$ ; and isovolumetric relaxation time of the left ventricle (IVRT)  $r=0.545$ ,  $p<0.01$ . In group A, a correlation was found only between levels of NT-pro-BNP and some parameters of diastolic function (DT  $r=0.676$ ,  $p<0.01$  and for IVRT  $r=0.586$ ,  $p<0.05$ ).

**Conclusion.** In patients with ACS, there is a high correlation between increased levels of NT-pro-BNP and systolic and diastolic function of the left ventricle. NT-pro-BNP is very specific sensitive to changes in systolic and diastolic function of the left ventricle.

**Key words:** acute coronary syndrome, NT-pro-BNP, left ventricular function.

### SAŽETAK

Funkcija leve komore kod bolesnika sa akutnim koronarnim sindromom (ACS) od presudnog je značaja za prognozu bolesti. Povišene vrednosti natriuretskih peptida (NT-pro-BNP- $\alpha$ ) nalaze se u 50-90% bolesnika sa ACS. Istraživanje je imalo za cilj da utvrdi da li postoji povezanost između vrednosti NT-pro-BNP- $\alpha$  i ehokardiografski utvrđene sistolne i dijastolne funkcije leve komore u bolesnika sa ACS. Ispitivanjem je obuhvaćeno 62 bolesnika sa ACS. Nakon hospitalizacije bolesnicima je određena vrednost NT-pro-BNP- $\alpha$  u serumu i ehokardiografski utvrđena sistolna i dijastolna funkcija leve komore. Bolesnici su na osnovu vrednosti NT-pro-BNP- $\alpha$  podeljeni u dve grupe: grupu A (kojoj pripada 18 bolesnika sa povišenim vrednostima NT-pro-BNP- $\alpha$  (vrednosti veće od 14.75 pmol/l)) i grupu B (koja obuhvata 44 bolesnika sa referentnim vrednostima NT-pro-BNP- $\alpha$  (vrednosti od 0 do 14.75 pmol/l)). Kod 91% bolesnika grupe A i 5.6% bolesnika B grupe registrovana je smanjena sistolna funkcija leve komore (SFLV). Kompromitovanu dijastolnu funkciju leve komore (DFLV) imalo je 83.3% bolesnika B grupe i 100% bolesnika grupe A. Dobijen je visok stepen korelacije vrednosti NT-pro-BNP- $\alpha$  bolesnika A grupe u odnosu na sve parametre sistolne i dijastolne funkcije leve komore (za ežekcionu frakciju (EF)  $r=-0.459$ ,  $p<0.01$ ; za frakciono skraćivanje (FS)  $r=-0.367$ ,  $p<0.05$ ; za odnos maksimalne rane (PE) i kasne (PA) dijastolne brzine punjenja (PE/PA)  $r=-0.469$ ,  $p<0.01$ ; za vreme deceleracije ranog dijastolnog protoka (DT)  $r=0.582$ ,  $p<0.01$ ; i za vreme izovolumetrijske relaksacije leve komore (IVRT)  $r=0.545$ ,  $p<0.01$ ) a u B grupi samo za neke parametre dijastolne funkcije (za DT  $r=0.676$ ,  $p<0.01$  i za IVRT  $r=0.586$ ,  $p<0.05$ ). Zabeležen je visok stepen korelacije povišenih vrednosti NT-pro-BNP- $\alpha$  i ehokardiografski utvrđene sistolne i dijastolne funkcije leve komore u bolesnika sa ACS. NT-pro-BNP pokazuje i visoku senzitivnost i specifičnost u odnosu na sistolnu i dijastolnu funkciju leve komore.

**Ključne reči:** akutni koronarni sindrom, NT-pro-BNP, sistolna i dijastolna funkcija leve komore.

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## INTRODUCTION

Brain natriuretic peptide (BNP) was first isolated in brain tissue, but it has since been found in myocardial cells. BNP acts in vasodilation, intensifies natriuresis and decreases aldosterone secretion. Pro BNP (108 amino acids) is synthesised in cardiomyocytes and is split into N-terminal pro BNP (76 amino acids) and C-terminal BNP (32 amino acids) (1). Many studies have shown that patients with hypertension, acute coronary syndrome (ACS), cardiac deficiency (inborn and earned), and fibrillation of atria have increased levels of these peptides (2-7). Some studies show that variations of peptide concentration in a patient's serum can be found before chemodynamic and echocardiographic changes (8). It was also shown that NT-pro-BNP level in serum is proportional to left ventricle load (9, 10).

Acute coronary syndrome (ACS) is an acute phase of ischaemic heart disease, and it includes several clinical forms such as unstable angina pectoris, acute infarct of the myocardium without ST elevation, acute infarct of the myocardium with ST elevation and sudden heart death. Most of these begin with angina pain. Increased pressure on ventricular walls and ischaemic myocardium increases synthesis of natriuretic peptides in cardiomyocytes, which explains the higher levels of natriuretic peptides in ACS patients' serum. Consequently, vasodilation of veins and arteries and a reduction in blood influx to the heart occur. Tonus of vagus is increased, but noradrenaline release and tonus of sympathicus are reduced. There is increased diuresis, and renin angiotensin is inhibited.

Considering the above data, we focused our investigation on a potential diagnostic role of NT-pro-BNP in the evaluation of left ventricular function in patients with ACS.

## METHODS

The subjects for the study included 62 ACS patients (13 females and 49 males), ranging in age from 43 to 75 years (average =  $60 \pm 13$  years of age).

Patients for this study met the following criteria:

**1)** diagnosis of ACS established by WHO (minimum 2 of 3 criteria): existence of chest pain, evolutive electrocardiographic changes (ST elevation or depression  $\geq 1$  mm, or negative T wave), evolutive changes of serum cardiac markers (CK, CK-MB, TnT).

**2)** patients under 75 years of age (because increased levels of NT-pro-BNP were found in patients over 75 years of age without cardiovascular disease).

**3)** patients do not suffer from other disease that can cause an elevation of NT-pro-BNP levels (such as artery hypertension, heart weakness, indigenous or gain heart failure, vestibule fibrillation, hypertension of the lungs, chronic lung diseases, acute and chronic insufficiency of kidneys, ascites, hyperthyreosis, hypothyreosis, Cushing's syndrome, and diabetes).

Concentration of NT-pro-BNP in serum was determined 24 hours after the admission of the patients, when maximal values are expected. The NT-pro-BNP determination kit was manufactured by Hoffman La Roch, Ltd. Normal levels of NT-pro-BNP range from 0 to 14.75 pmol/L. NT-pro-BNP concentration in the serum was determined by electrochemiluminiscent immunoassay application on an Elecsys 2010 analyser (Roche Diagnostics).

Based on these results, we divided patients into two groups. Group A consisted of 18 ACS patients with NT-pro-BNP levels ranging from 0-14.75 pmol/L. Group B included 44 ACS pa-

tients with NT-pro-BNP levels higher than 14.75 pmol/L. The levels of serum cardiac pointers (CK, CK-MB and troponin) were measured. Systolic and diastolic functions of the left ventricle were measured by heart echocardiography using the Asilent Sonos 5500 ultrasound device.

To evaluate systolic function, we determined ejection fraction (EF), left ventricle diastolic dimension (LVEDD), left ventricle systolic dimension (LVESD), left ventricle posterior wall thickness (PWT), septum thickness (ST) and fraction shortening (FS). To evaluate diastolic function, we determined maximal early (PE) late (PA) diastolic load speed, their relation (PE/PA), deceleration time of early diastolic flow (DT), left isovolumetric ventricle relaxation time (IVRT) and peak systolic wall stress (PSWS). Criteria for normal systolic function were  $EF > 50\%$  and  $FS$  in interval of 28-42%. Normal diastolic function measurements should satisfy the following:  $PE/PA \geq 1$  and  $< 2$ ;  $DT > 150$  and  $< 220$  ms;  $IVRT > 60$  and  $< 100$  ms.

A basic statistical program, Student's T test and Pearson's correlation coefficient were used. Group A had  $18-2=16$  degrees of freedom, so its linear correlation coefficient was 0.468 (for the probability of the null hypothesis = 0.05) and 0.590 (for the probability of the null hypothesis = 0.01). However, group B had  $44-2=42$  degrees of freedom, and its linear correlation coefficient was 0.304 (for the probability of the null hypothesis = 0.05) and 0.393 (for the probability of the null hypothesis = 0.01).

The probabilities of  $p < 0.05$  and  $p < 0.01$  were considered significant and highly significant, respectively.

Sensitivity and specificity levels of NT-pro-BNP measurements and echocardiographic parameters of systolic and diastolic function of the left ventricle were determined.

## RESULTS

Table 1 shows the demographic parameters of both groups with ACS. Group A consisted of patients with ACS and normal NT-pro-BNP levels and included 14 males and 4 females aged 43 to 75 years with an average of  $60 \pm 6.6$  years. Their NT-pro-BNP levels ranged from 2.5 to 13.4 pmol/L, with an average of  $5.9 \pm 3.2$  pmol/L.

Group B consisted of 44 patients with ACS and increased NT-pro-BNP levels. There were 35 males and 9 females, aged 54 to 75 years with an average of  $62 \pm 7.3$  years. Their NT-pro-BNP levels ranged from 18.7 to 731 pmol/L, with an average of  $157 \pm 178$  pmol/L.

Table 2 shows the echocardiographic parameters of systolic and diastolic function of left ventricle in both groups. Minimum, average, maximum and standard deviation are shown.

Regarding parameters of systolic function of the left ventricle, group B had considerably lower EF values ( $p < 0.01$ ) than group A. The difference between the groups in FS values ( $p > 0.05$ ) was minor. As far as parameters of diastolic function

Characteristics	Group A		Group B	
	N	A $\pm$ SD	N	B $\pm$ SD
Number of patients	18 (29%)		44 (71%)	
Gender M/F	14 / 4		35 / 9	
Age		$60 \pm 6.6$		$62 \pm 7.3$
NT-pro-BNP (pmol/L)		$5.9 \pm 3.2$		$157 \pm 178$

**Table 1.** Demographic characteristics and levels of NT-pro-BNP of ACS patients.



Parameters	Group A		Group B		p
	Amin-Amox	A±SD	Bmin-Bmax	B±SD	
EF (%)	55-65	56±4	25-65	49±9	p<0.01
LVEDD (cm)	4.7-6.5	5.3±0.5	4.4-6.7	5.4±0.5	p>0.05
LVSDD (cm)	3.2-4.5	3.6±0.4	2.8-5.4	3.8±0.7	p>0.05
ST (cm)	0.9-1.1	1±0.1	0.9-1.3	1.1±0.13	p<0.05
PWT (cm)	0.9-1	1±0.07	0.9-1.2	1.1±0.1	p<0.05
FS (%)	22-37	31±8	12-41	30±7	p>0.05
PE (cm)	0.49-0.6	0.54±0.03	0.42-0.56	0.47±0.03	p<0.05
PA (cm)	0.42-0.61	0.51±0.05	0.48-0.62	0.52±0.06	p>0.05
PE/PA	0.9-1.25	1.1±0.1	0.8-1.1	0.9±0.06	p<0.05
DT (ms)	203-221	213±7	212-239	229±8	p<0.05
IVRT (ms)	89-117	97±7	88-121	112±7	p<0.05
PSWS (g/cm <sup>2</sup> )	55-93	70±13	55-92	83±6.7	p<0.05

**Table 2.** Echocardiographic parameters of systolic and diastolic function of ACS patients.

Ejection fraction (EF), left ventricle diastolic dimension (LVEDD), left ventricle systolic dimension (LVSDD), left ventricle posterior wall thickness (PWT), septum thickness (ST), fraction shortening (FS), maximal early (PE) and late (PA) diastolic load speed, their relation (PE/PA), deceleration time of early diastolic flow (DT), left isovolumetric ventricle relaxation time (IVRT) and peak systolic wall stress (PSWS).

of the left ventricle, PE/PA, DT and IVRT values differ considerably ( $p<0.05$ ) between groups A and B.

Figures 1 and 2 present the degree of correlation between peptide levels and parameters of left ventricle systolic and diastolic function for ACS patients.

In group A, as the NT-pro-BNP level increased, EF value decreased with a statistically minor correlation of  $-0.398$  ( $p>0.05$ ). Also, as the NT-pro-BNP level increased, FS values increased as well, with a positive correlation of  $0.14$ , which was of not statistically significant ( $p>0.05$ ). As for diastolic function of the left ventricle, parameters for NT-pro-BNP and PE/PA showed no considerable correlation ( $r=-0.278$  and  $p>0.05$ ), which is distinct from the high positive correlation found be-

tween increasing NT-pro-BNP levels and DT values ( $r=0.676$  and  $p<0.01$ ) as well as IVRT values. In group B, there is a high correlation between all parameters of systolic and diastolic function of the left ventricle and NT-pro-BNP levels ( $p<0.05$ ,  $p<0.01$ ). Increase of NT-pro-BNP levels is followed by DT and IVRT increase and EF, FS, and PE/PA decrease (fig. 2).

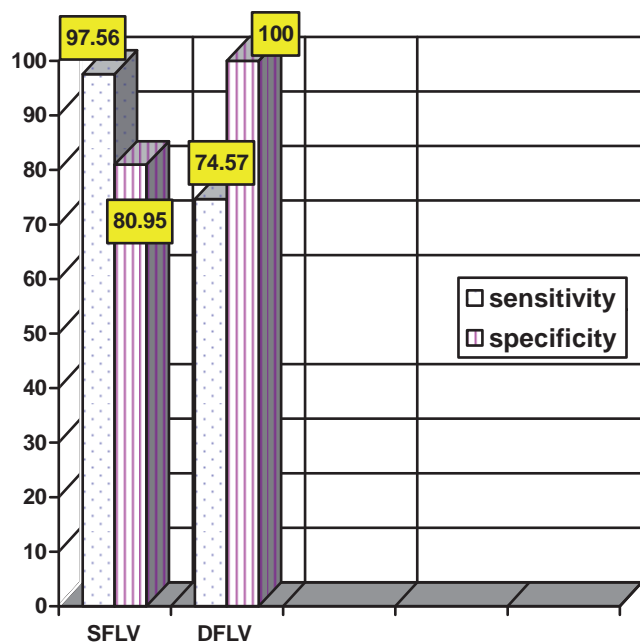
As shown in Table 3, sensitivity and specificity were calculated. NT-pro-BNP sensitivity for SFLV was  $97.56\%$  ( $40/41$ ) and  $74.57\%$  for DFLV. On the other hand, specificity for SFLV was  $80.95\%$  ( $40/41$ ) but  $100\%$  for DFLV (Figure 3). Seventeen patients in group A ( $94.4\%$  of patients in this group) had normal SFLV, but only 4 patients ( $9.1\%$ ) in group B had normal SFLV (table 3). Compromised SFLV was recorded in 1 patient ( $5.6\%$ ) of group A and 40 patients ( $90.09\%$ ) of group B. Three ( $16.7\%$ ) patients in group A and 0 patients in group B had normal DFLV, whereas compromised DFLV was found in 15 ( $83.3\%$ ) group A patients and 44 ( $100\%$ ) group B patients.

Derived NT-pro-BNP sensitivity for SFLV was  $40 / 41 = 97.56\%$  and  $44 / 59 = 74.57\%$  for DFLV (Figure 3).

NT-pro-BNP specificity for SFLV was  $17 / 21 = 80.95\%$  and  $3 / 3 = 100\%$  for DFLV.

**Table 3.** The frequency of diagnosis of normal and compromised systolic and diastolic function of the left ventricle in A and B groups

	A Group	B Group
Normal SFLV	17 (94.4%)	4 (9.1%)
Compromised SFLV	1 (5.6%)	40 (90.09%)
Normal DFLV	3 (16.7%)	0
Compromised DFLV	15 (83.3%)	44 (100%)

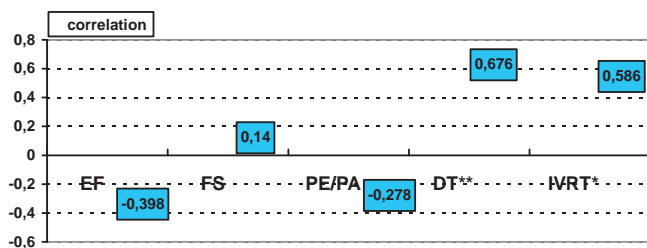


Sensitivity and specificity %

SFLV and DFLV

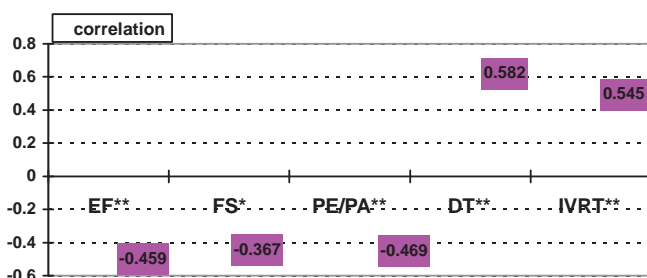
**Figure 3.** Sensitivity and specificity levels NT-pro-BNP and echocardiographic parameters of systolic and diastolic function of the left ventricle, ACS patients.

\*\*  $p<0.01$ ; \*  $p<0.05$



**Figure 1.** Correlation among levels of NT-pro-BNP and echocardiographic parameters of systolic and diastolic function of left ventricle in group A

\*\*  $p<0.01$  \*  $p<0.05$



**Figure 2.** Correlation among NT-pro-BNP levels and echocardiographic parameters of systolic and diastolic function of the left ventricle in group B





## DISCUSSION

According to the demographic data presented in table 1, both groups consisted of more males than females because the research was done in a military facility where the percentage of males is higher. Groups were formed according to NT-pro-BNP levels. Group B (71% of all examinees) demonstrated higher NT-pro-BNP levels and was larger than group A, which was composed of patients with normal peptide levels. This was expected because most of the literature data indicate that NT-pro-BNP levels are elevated in 47 to 96% of patients with ACS (11-13).

NT-pro-BNP levels of patients in group B ( $157 \pm 178$  pmol/L) were significantly higher ( $p < 0.01$ ) than those of patients in group A ( $5.9 \pm 3.2$  pmol/L). A study that included 7800 patients with ACS showed that NT-pro-BNP levels varied from 2.3 to 4320 pmol/L (14). Other research showed that patients with ACS can have normal as well as extremely high levels of this peptide in serum (10, 12).

According to the parameters of SFLV, patients with increased NT-pro-BNP levels had much lower EF ( $p < 0.01$ ) than patients with normal peptide levels (table 2). Since ischaemia is a basic cause of increased NT-pro-BNP levels, it was expected that patients with normal peptide levels would have larger EF values. Only 5.6% of patients in group A had reduced systolic function of the left ventricle, whereas 90.09% of group B patients demonstrated reduced systolic function of the left ventricle. Several studies (15, 16, 17) have shown significant influence of myocardial ischaemia on NT-pro-BNP levels in ACS patients. In addition, there is a major difference in diastolic function parameters between the two groups (table 2). We concluded that reduced diastolic function was characteristic of both groups, but in group B, this function was more severely compromised. There are a high percentage of patients (83.3%) with reduced diastolic function but with average NT-pro-BNP levels, which shows that diastolic function disorder is not necessarily followed by NT-pro-BNP level increase. Changes in NT-pro-BNP concentration are directly related to systolic function disorder, but no relation with diastolic function of the left ventricle was found. Our results are compatible with other research that found that decreased diastolic function of the left ventricle was usually followed by high levels of peptides. However, this was not always the case; sometimes, normal NT-pro-BNP values were found.

Jernberg and associates compared the results of a few clinical trials regarding NT-pro-BNP and discovered that increasing NT-pro-BNP was followed by a decrease in systolic and diastolic heart functions, but the correlation between NT-pro-BNP values and SFLV parameters was higher than the correlation of NT-pro-BNP and echocardiographic parameters of diastolic function (17).

By using linear correlating, we tried to determine if there is a connection between NT-pro-BNP levels and parameters of systolic and diastolic function of the left ventricle in ACS patients. In patients with normal NT-pro-BNP levels, we concluded with a high probability that the systolic function of the left ventricle is not compromised, which is not the case in diastolic function. In addition, we found that normal NT-pro-BNP levels are not correlated with left ventricle systolic and diastolic function.

Linear test correlation of the parameters of systolic and diastolic function shows major differences between the two groups

(fig. 2). These results demonstrate a high correlation between NT-pro-BNP levels and SFLV and DFLV levels ( $p < 0.01$ ). This shows that increased NT-pro-BNP levels are directly related to parameters of left ventricle systolic and diastolic function, which is not the case for normal peptide levels.

Pfister and Scoltz's study (10) of 150 patients shows this negative linear correlation between NT-pro-BNP level and left ventricle systolic function (10). Khan and associates studied 356 patients with ACS and discovered a high correlation between NT-pro-BNP levels and systolic function of the left ventricle (LV) ( $p < 0.0001$ ) in patients with ACS (diastolic function in LV was not considered) (18, 19).

In fig. 3, we show NT-pro-BNP sensitivity and its specific role in systolic and diastolic LV function. NT-pro-BNP sensitivity for SFLV was 97.56%, whereas its specificity was 80.95%. NT-pro-BNP sensitivity for DFLV was 74.57%, whereas its specificity was 100%.

Emdin and associates found high sensitivity of NT-pro-BNP for SFLV (98%), and the specificity of NT-pro-BNP for SFLV reached 86% (20). Lubien and colleagues studied 294 patients with ACS and found high specificity (83%) and sensitivity (85%) of NT-pro-BNP for DFLV (21). Footea and associates also found high sensitivity of NT-pro-BNP (90%) as a predictor of compromised systolic function of the LV (22).

According to our results, we conclude that ACS patients with normal NT-pro-BNP levels have considerably less compromised systolic and diastolic LV function than patients with increased levels of this peptide. However, peptide levels do not correlate with SFLV values, whereas diastolic function correlation was found in two out of three parameters of DFLV. High degrees of correlation between increased NT-pro-BNP values and systolic and diastolic functions of the LV were found in ACS patients. NT-pro-BNP shows high sensitivity and specificity to systolic and diastolic LV function. Considering our results, which are supported by similar clinical investigations, we suggest that serum NT-pro-BNP levels are of great clinical importance in the evaluation of left ventricular function.

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## HAEMOSTATIC AND LIPID PROFILE CHANGES IN WOMEN DURING MENOPAUSE

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## PROMENE LIPIDNOG PROFILA I PARAMETARA HEMOSTAZE KOD ŽENA U MENOPAUI

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### ABSTRACT

The values of follicle-stimulating hormone (FSH), estradiol, serum lipids, tissue type plasminogen activator antigen, plasminogen activator inhibitor type 1 antigen and coagulation factor VII were examined in females during menopause. The study was comprised of a total of 107 women divided into three groups based on their menstrual cycle, level of FSH hormone and level of 17- $\beta$  estradiol (E2) hormone. The control group included 30 women with regular menstrual cycles. The second group consisted of 37 women in perimenopause with irregular menstrual cycles and FSH plasma levels under 25 mIU/ml. The third group consisted of 40 women in postmenopause, defined as not having a menstrual cycle for more than 12 months. Hormone levels were determined by radioimmunological methods. Fibrinolytic enzymes were determined using a sandwich enzyme-linked immunosorbent assay. Lipid levels were determined using a colorimetric-spectrophotometric method, and factor VII concentrations were determined using the deficiency plasma method. Statistical analysis showed there was a significant increase in LDL cholesterol, plasminogen activator inhibitor type 1 antigen and factor VII in both perimenopausal and postmenopausal women compared to the control group ( $p < 0.001$ ), but there was a significant decrease in HDL cholesterol and plasminogen activator antigen ( $p < 0.001$ ) during perimenopause and postmenopause.

**Key words:** factor VII, fibrinolysis, hormones, lipids, menopause

### SAŽETAK

Ispitane su vrednosti folikulostimulativnog hormona (FHS), estradiola, serumskih lipida (ukupnog holesterola, triglicerida, HDL i LDL holesterola), tkivnog plazminogen activator antigena (TPA Ag), plazminogen activator inhibitor antigena tipa 1 (PAI-1) i faktora koagulacije VII, kod žena, u periodu menopauze. U studiji je uključeno ukupno 107 žena, podeljenih u tri grupe: kontrolna grupa, grupa žena u perimenopauzi i grupa žena u postmenopauzi na bazi sledećih kriterijuma: redovnost menstrualnog ciklusa, i nivo hormona FSH i 17  $\beta$  estradiola (E2). Kontrolnu grupu sačinjavaju 30 žena, u reproduktivnom periodu, sa redovnim menstrualnim ciklusom. Druga grupa je sastavljena od 37 žena u perimenopauzi, sa neredovnim menstrualnim ciklusom i nivoom FSH hormona u plazmi, ispod 25 miU/ml. Treća grupa uključuje 40 žena u postmenopauzi, kod kojih menstrualni ciklus izostaje više od 12 meseci. Nivo hormona je određivan originalnom radioimunološkom metodom (CIS-RIA). Koncentracija fibrinolitičkih enzima je određena sendvič imunoenzimskom metodom (INNOGENETIC). Nivo lipida je utvrđen kolorimetrijsko-spektrofotometrijskom metodom (MERCK) a faktor koagulacije VII je valoriziran metodom deficijentne plazme. Statistička analiza rezultata pokazuje značajan porast nivoa LDL holesterola, PAI-1 Ag, i faktora VII kod perimenopauznih žena i grupe žena u postmenopauzi u poređenju sa kontrolnom grupom ( $p < 0,001$ ), no i značajno smanjenje nivoa HDL holesterola i TPA Ag, ( $p < 0,001$ ) u toku perimenopauze i postmenopauze. Na bazi naših rezultata zaključujemo da postoji slaba pozitivna korelacija između TPA Ag i HDL holesterola, s jedne i estradiola s druge strane, kao i slaba negativna korelacija između estradiola i PAI-1 Ag, odnosno faktora koagulacije VII.

**Ključne reči:** menopauza, hormoni, lipidi, fibrinoliza, faktor VII

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## INTRODUCTION

Cardiovascular disease, especially of the coronary blood vessels, and cerebrovascular disease are among the leading causes of death in menopausal women. Numerous investigations have pointed to the relation between estrogen status and the process of haemostasis (1, 2). The mechanism through which estrogens exert their effect is still unclear. Former studies have mainly been focused on the possibility of estrogen induction of hypercoagulability through complex alterations of coagulation and fibrinolysis systems (3). Haemostatic factors, such as high levels of plasma fibrinogen, plasminogen activator inhibitor type 1 antigen (PAI-1 Ag) and tissue type plasminogen activator antigen (TPA Ag) are associated with thromboembolic disorders, whereas metabolic factors, such as glucose intolerance, increase of abdominal fat tissue, high levels of androgen hormones and low levels of 17- $\beta$  estradiol (E2) hormones are associated primarily with atherosclerotic complications (4). PAI-1 is a characteristic marker of fibrinolysis that, when levels are increased, serves as a marker of decreased fibrinolysis. Endothelial cells also participate in the process of atherogenesis and thrombogenesis via several markers: plasma von Willebrand factor (vWf) is an endothelial marker associated with thromboembolic complications of the central nervous system, coronary disease and peripheral arterial disease; P-selectin is increased in atherosclerosis; and both soluble thrombomodulin and tissue plasminogen activator play an important role in atherosclerosis (5).

Coagulation factor VII (proconvertin) is one of the risk factors for onset of cardiovascular disease (6). This glycoprotein, synthesized in the liver, participates in both the intrinsic and extrinsic pathways of coagulation activation. In the non-activated form, it is built of a single peptide chain with molecular mass of 45-53 kiloDaltons (kD) and composed of 408 amino acids. Glutamic acid residues are carboxylated and calcium ions are bound. Factor VII is converted from its non-activated form into an activated form (VIIa) by thrombin, activated factor X (Xa) or activated factor XII (XIIa). The activated form is an enzyme with two peptide chains, with an active enzyme site on the heavy chain. In vivo, the strong triad of endothelial factors regulates thromboresistance and vascular tone. Stimulation of endothelial receptors (purinergic, muscarinic, kinin) leads to release of prostacyclin (PGI<sub>2</sub>), nitric oxide (NO) and TPA. The alliance of these three factors acts upon protection of platelet deposition on the walls of blood vessels. Activation of the process of fibrinolysis by TPA through plasmin synthesis is supplemented with inactivation of thrombocytes by PGI<sub>2</sub> and selective inhibition of PAI-1 release from thrombocytes through NO (7). Extensive investigations have indicated that estrogens markedly reduce the risk of thromboembolic complications and cardiovascular disease in women in the reproductive period and before menopause, but the mechanism of the protective effect of estrogens has not been entirely clarified. One component of the vascular protective effect of estrogens is due to activation of the process of fibrinolysis, whereas another component is accomplished by direct action on the receptors of the endothelial cells in blood vessels. E2 may modulate vascular function by stimulation of the enzyme endothelial nitric oxide synthase (eNOS) and increased production of NO, a powerful vasodilator (8).

Estrogens also regulate the balance between prostacyclins and thromboxane, favouring prostacyclin actions that have potent anti-aggregate and vasodilator effects (8).

Estrogens have an indirect protective effect on the blood vessels by regulating the ratio between serum lipids, especially the HDL/LDL index that is an important predictor of coronary disease. There is clear evidence that high levels of LDL-C increase the risk of cardiovascular disease; in contrast, high levels of HDL-C decrease the risk of cardiovascular disease. In all age groups of women, except in those that are postmenopausal, HDL-C concentration is higher compared to the male population (9). Estrogens probably contribute to this difference through 2 basic mechanisms:

- The increase of HDL-C synthesis;
- The decrease of HDL-C catabolism; that is, through suprimation of activation of hepatic lipase (a lipolytic enzyme that degrades HDL-C).

Estrogens also prevent accumulation of cholesterol and oxidized LDL particles on arterial walls.

The aim of this study was to 1) evaluate plasma concentration of fibrinolytic enzymes (TPA Ag, PAI-1 Ag) and coagulation factor VII in women during reproductive life, in perimenopause and in postmenopause; 2) determine the level of serum lipids (HDL-C, LDL-C, total cholesterol and triglycerides) in the same groups of women; and 3) examine the correlation between estradiol status, fibrinolytic enzymes, factor VII and lipids in each of the three groups of women.

## METHODS

The study included a total of 107 female subjects, divided into 3 groups based on the regularity or irregularity of their menstrual cycle, the concentration of serum FSH and the concentration of E2. The control group was comprised of healthy women (n = 30) with regular menstrual cycles. Hormone levels were determined in the late follicular phase (from day 10-13 of the cycle). The second group was comprised of women in perimenopause (n = 37) with medical histories of irregular menstrual cycles, serum FSH levels under 25 mIU/ml and E2 levels above 35 pg/ml. Hormone levels were determined in the late follicular phase of the cycle.

The third group consisted of postmenopausal women (n = 40), with anamnestic data for at least 12 months from the last menstruation, serum FSH levels above 25 mIU/ml and E2 levels below 35 mIU/ml.

Women who did not meet criteria for one of the three groups mentioned above were excluded from the study as were those who suffered from a disease that could interfere with and influence the values of all examined parameter, such as diabetes, familial hyperlipidemia, thyroid dysfunctions, and adrenal gland dysfunction.

Blood samples were collected from an antecubital vein between 8:00 and 9:00 AM after an overnight fast, with subjects in the supine position. For determination of plasma levels of PAI-1, TPA antigen and factor VII, blood was anticoagulated with 3.8% trisodium citrate (9:1, vol/vol) and kept on crushed ice until centrifugation. The remaining blood samples were taken without using anticoagulant agent (for obtaining serum) and used to determine the concentration of FSH and E2 hormones as well as HDL-C, LDL-C, total cholesterol and triglycerides. After centrifugation at 3000 rpm for 5-10 minutes,





plasma and serum samples were separated and stored at -20°C for further examination.

Hormone concentration was determined with standardized tests using the radioimmunological method. TPA Ag and PAI-1 Ag levels were determined by a sandwich technique known as enzyme-linked immunosorbent assay (INNOGENETIC). The concentration of factor VII was determined using the deficient plasma method, and the serum lipid concentration was determined using the method of fractionation sedimentation according to the specific weight. Measurements were done on a spectrophotometer (BECKMAN) at wavelength - 500 nm. Data were entered into a database and statistically analyzed, with  $p < 0.05$  being considered a statistically significant difference. Correlation analysis (Pearson's coefficient) was used for assessing the relationships between the examined parameters.

## RESULTS

The investigation showed differences in the levels of hormones, fibrinolytic enzymes (TPA Ag, PAI-1 Ag) and factor VII among the three groups of women.

Table 1 presents the mean values of serum concentration of FSH and estradiol as well as plasma concentrations of fibrinolytic enzymes and factor VII in the three groups of women.

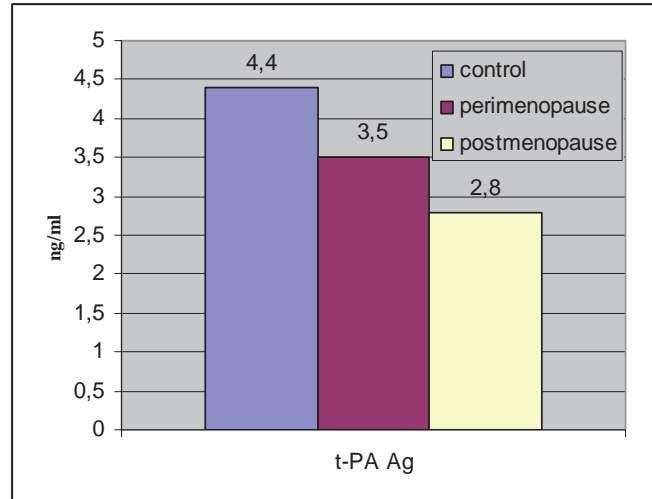
It is evident there is a statistically significant ( $p < 0.001$ ) increase in serum concentration of FSH, decrease ( $p < 0.001$ ) of serum concentration of E2, decrease ( $p < 0.001$ ) of TPA Ag, increase ( $p < 0.001$ ) of PAI-1 Ag plasma concentration and increase ( $p < 0.05$ ) in the concentration of coagulation factor VII in different phases of the reproductive life of the women.

Plasma concentrations of TPA Ag revealed an apparent decrease in postmenopausal women compared to perimenopausal and control women. The average concentration of this enzyme was  $4.5 \pm 2.5$  ng/ml and  $3.5 \pm 1.8$  ng/ml in the control group and in perimenopausal women, respectively, whereas it was  $2.8 \pm 1.3$  ng/ml in postmenopausal women, which was statistically significant. There was no statistical significance in the concentration of this enzyme between the perimenopausal and postmenopausal groups of women, which

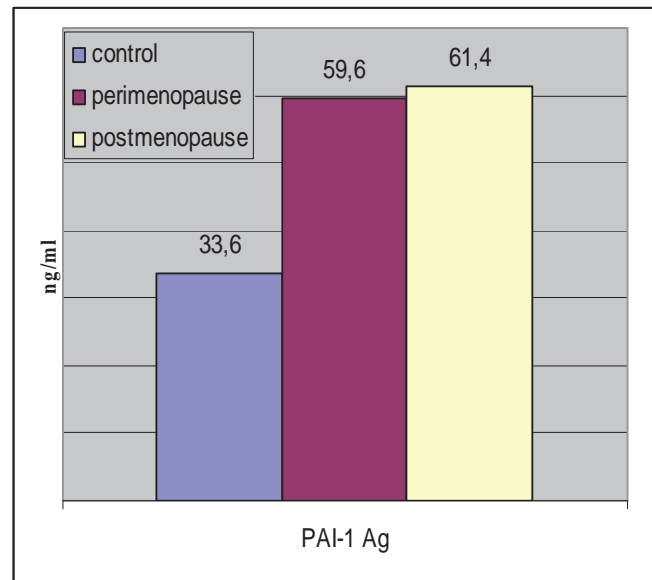
**Table 1.** CONCENTRATION OF REPRODUCTIVE HORMONES, TPA Ag, PAI-1 Ag AND FACTOR VII IN WOMEN BEFORE, DURING, AND AFTER MENOPAUSE (n = 107)

	Control group n=30	Perimenopause n=37	Postmenopause n=40	P
FSH				
mIU/ml	$4.6 \pm 3.6$	$17.2 \pm 10.5$	$70.5 \pm 21.1$	$< 0.001$
E2				
pg/ml	$101.9 \pm 58.6$	$36.2 \pm 23.2$	$10.2 \pm 8.6$	$< 0.001$
TPA Ag				
ng/ml	$4.5 \pm 2.5$	$3.5 \pm 1.8$	$2.8 \pm 1.3$	$< 0.001$
PAI-1 Ag				
ng/ml	$33.6 \pm 9.4$	$61.4 \pm 24.6$	$59.6 \pm 22.5$	$< 0.001$
Factor				
VII %	$80.4 \pm 8.5$	$87.2 \pm 16.9$	$110.1 \pm 12.9$	$< 0.05$

Each value is an arithmetic standard value  $\pm$  standard deviation of 107 single examinations.



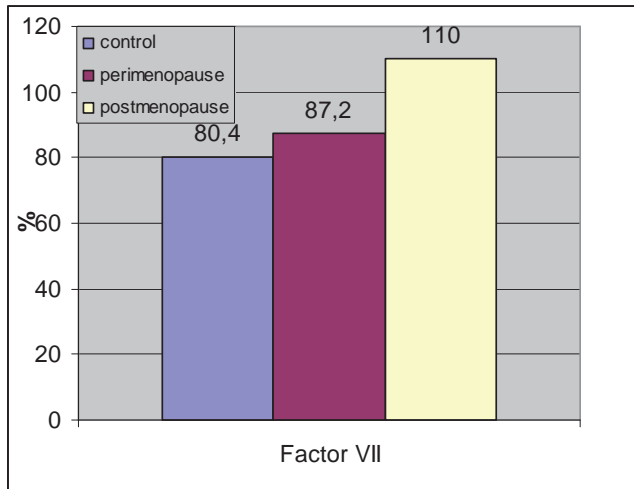
**Figure 1.** t-PA Ag levels before, during, and after menopause



**Figure 2.** PAI-1 Ag levels before, during, and after menopause

		r	r	r
		Control	Perimenopause	Postmenopause
E2	TPA Ag	0.014	0.05	0.10
E2	PAI-1 Ag	0.108	-0.17	-0.16
E2	Factor VII	-0.10	-0.13	-0.065
E2	HDL-C	0.23	0.199	0.091
E2	LDL-C	0.024	0.095	0.010
E2	Total cholesterol	-0.15	-0.13	-0.14
E2	Triglycerides	0.063	-0.034	0.026

**Table 2.** CORRELATION BETWEEN TPA Ag, PAI-1 Ag, FACTOR VII, SERUM LIPIDS AND E2 LEVELS IN WOMEN BEFORE, DURING, AND AFTER MENOPAUSE



**Figure 3.** Factor VII levels before, during, and after menopause

means that even small changes in E2 levels induce big changes in fibrinolytic potential. It has to be taken into consideration the effect of estrone, since it dominates in the period of postmenopause despite its weak biological activity (Figure 1).

There was a pronounced increase in the plasma concentration of PAI-1 Ag in perimenopausal women ( $61.4 \pm 24.6$  ng/ml) and postmenopausal women ( $59.6 \pm 22.5$  ng/ml) compared to the control group ( $33.6 \pm 9.4$  ng/ml), but there was no significant difference between perimenopausal and postmenopausal women (Figure 2).

The concentration of coagulation factor VII was significantly increased in postmenopausal women ( $110.1 \pm 12.9\%$ ) as compared to the control group ( $80.4 \pm 8.5\%$ ) and perimenopausal women ( $87.2 \pm 16.9\%$ ). There was also a significant difference between the control group and the perimenopausal group (Figure 3).

Table 2 shows the correlation between TPA Ag, PAI-1 Ag and E2 concentration in the control group, perimenopausal group and postmenopausal group.

It is obvious that there was a weak positive correlation between estradiol levels and TPA Ag concentrations (Figure 4).

It is also apparent that there was a weak negative correlation between estradiol levels and concentrations of PAI-1 Ag and factor VII. This clearly confirms the direct relation between fibrinolytic parameters and estradiol levels (Figures 5, 6).

	Control group n=30	Perimenopause n= 37	Postmenopause n=40	P
HDL-C				
mmol/l	$2.2 \pm 0.5$	$1.4 \pm 0.4$	$1.2 \pm 0.2$	0.001
LDL -C				
mmol/l	$2.4 \pm 0.9$	$3.2 \pm 1.2$	$4.6 \pm 1.3$	0.01
Triglycerides				
mmol/l	$2.2 \pm 0.7$	$2.8 \pm 1.5$	$2.2 \pm 1.5$	N.S.
Total cholesterol				
mmol/l	$6.9 \pm 1.5$	$6.3 \pm 1.3$	$7.3 \pm 2.5$	N.S.

Each value is an arithmetic mean value  $\pm$  standard deviation of 107 single examinations.

**Table 3.** SERUM LIPID LEVELS IN WOMEN ACCORDING TO MENOPAUSAL STATUS (n= 107)

There is also a positive correlation between E2 and HDL-C concentrations (Figure 7).

Our results have also shown that there were differences in the levels of HDL-C and LDL-C among the three groups of women, but that there were no differences in total cholesterol and triglycerides.

Mean values of concentrations of serum lipids (HDL-C, LDL-C, total cholesterol, triglycerides) in women during different phases of the reproductive life are presented in Table 3.

When compared to the control group, perimenopausal and postmenopausal women had a significant decrease ( $p < 0.001$ ) in the serum concentration of HDL-C and a significant increase ( $p < 0.01$ ) in the level of LDL-C. There was no significant difference in the level of triglycerides or total cholesterol among the three groups.

The serum HDL-C level decreased substantially from  $2.4 \pm 0.9$  mmol/l in the control group to  $1.4 \pm 0.4$  mmol/l in perimenopausal women and  $1.2 \pm 0.2$  mmol/l in postmenopausal women. There was a profound increase in the LDL-C level from  $2.4 \pm 0.9$  mmol/l in the control group to  $3.2 \pm 1.2$  mmol/l in perimenopausal women and to  $4.6 \pm 1.3$  mmol/l in postmenopausal women. There was an apparent insignificant difference in the level of these two lipid levels between perimenopausal and postmenopausal women (Figure 8).

The triglycerides level varied from  $2.2 \pm 0.7$  mmol/l in the control group to  $2.8 \pm 1.5$  mmol/l in the group of perimenopausal women and to  $2.2 \pm 1.5$  mmol/l in the group of postmenopausal women, which was not statistically significant. Total cholesterol ranged from  $6.9 \pm 1.5$  mmol/l in the control group to  $6.3 \pm 1.3$  mmol/l in perimenopausal women and  $7.3 \pm 2.5$  mmol/l in postmenopausal women, but with no statistical significance (Figure 9).

## DISCUSSION

Blood coagulation and creation of intravascular thrombi are very important in the development of acute coronary thrombosis (10, 11). Activity of PAI-1 and TPA Ag plays a key role in the development of thrombi and is associated with coronary heart disease. Increased levels of PAI-1 and TPA antigen are positively correlated with myocardial infarction and increased death rates in cardiovascular disease (12).

Our study revealed a significant difference in the concentration of PAI-1 and TPA antigen between the control group and both perimenopausal and postmenopausal groups of women. Notably, there was no statistical significance between the groups of perimenopausal and postmenopausal women. Thus, changes in the fibrinolytic process related to decrease of fibrinolytic activity (TPA Ag) and increase of fibrinolytic inhibitors (PAI-1 antigen) appear much earlier than the first objective signs of menopause. Perimenopause is the adequate period for prevention of numerous diseases associated with disorders of fibrinolysis.

A group of authors (5) have examined the relation between E2 levels and fibrinolytic potential by determination of TPA and PAI-1 Ag. They have concluded that women in the fertile period (with high concentrations of E2) have greater fibrinolytic potential (lower levels of PAI-1) than women in menopause. Postmenopausal women who are receiving hormone replacement therapy with estrogens have lower levels of PAI-1 than

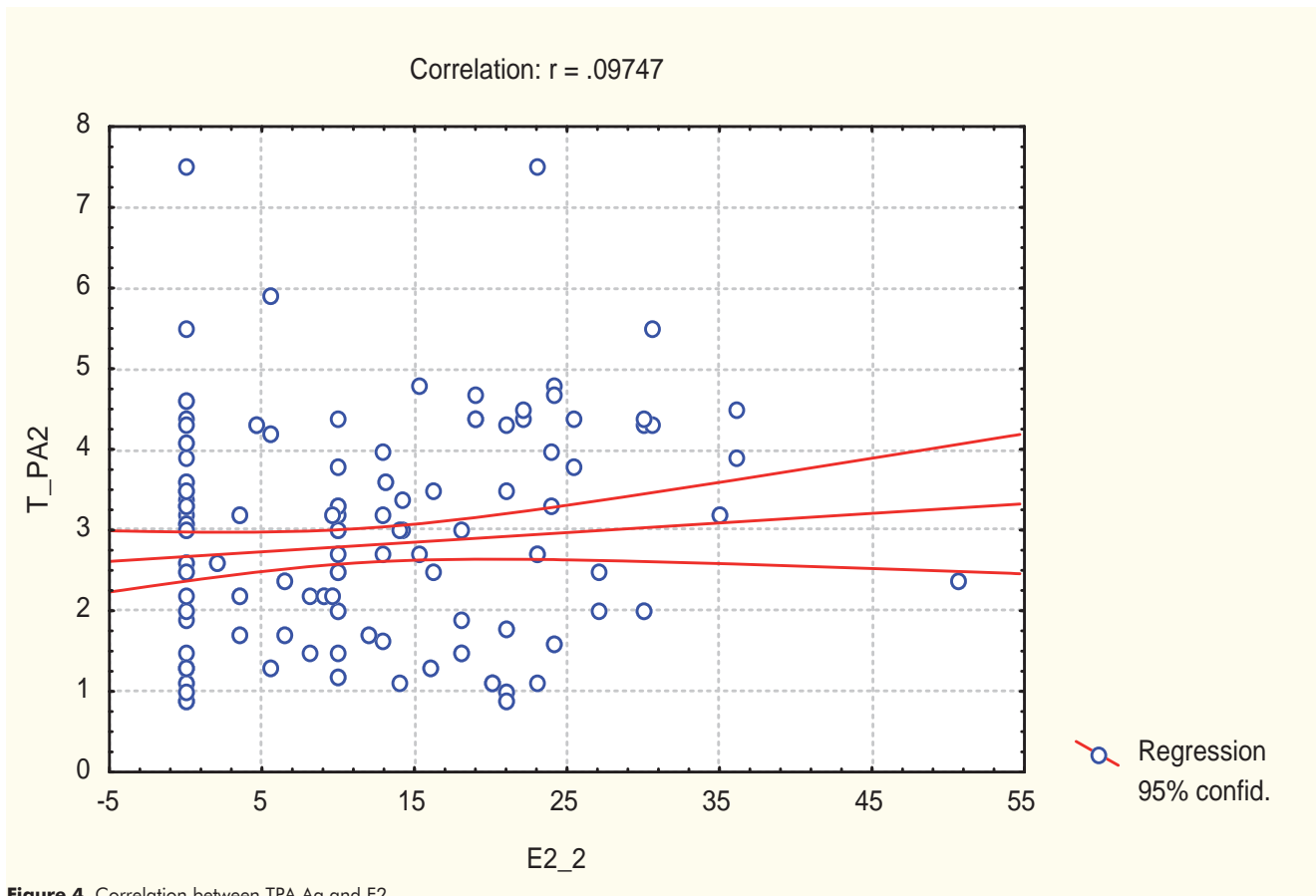


Figure 4. Correlation between TPA Ag and E2

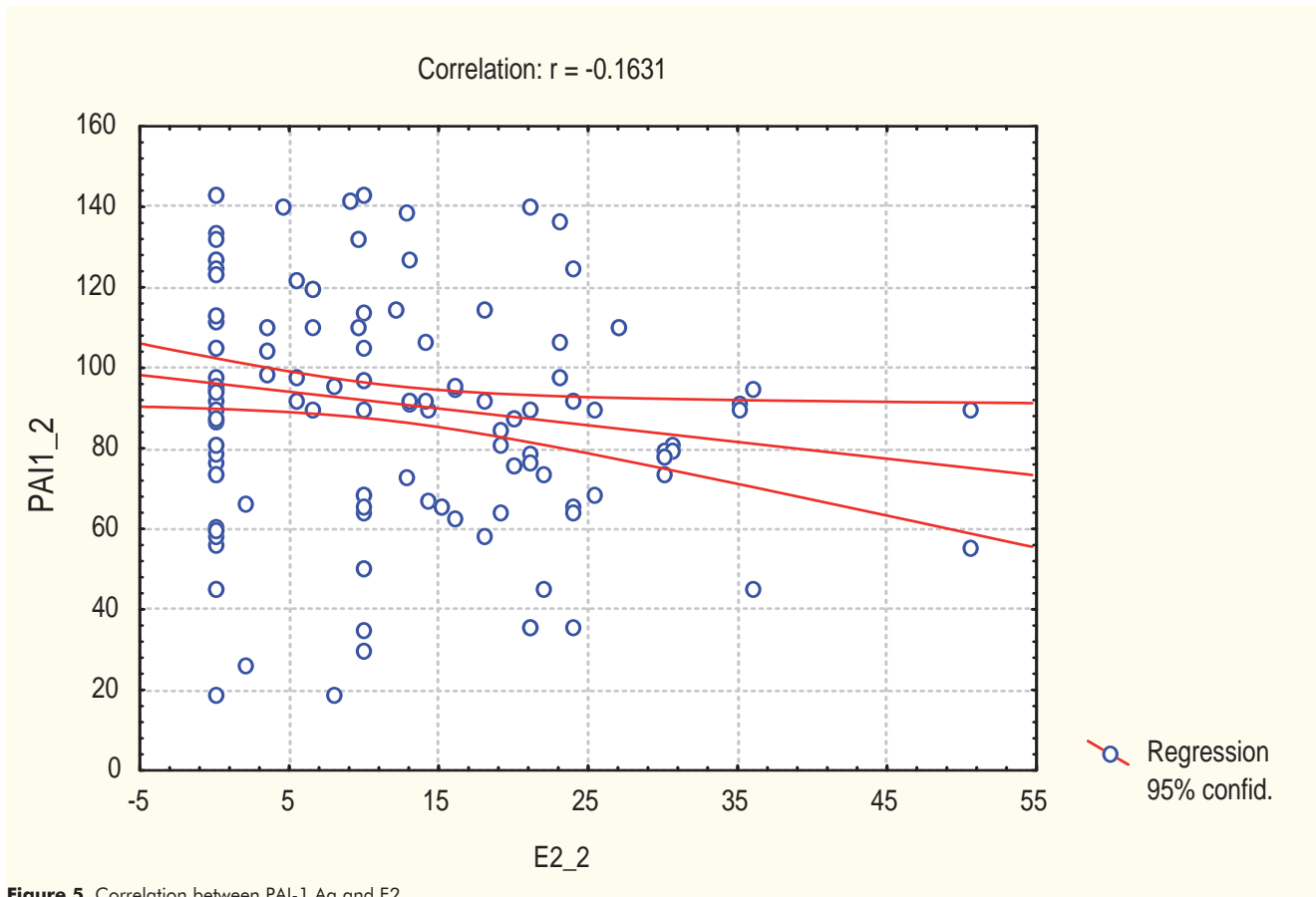


Figure 5. Correlation between PAI-1 Ag and E2



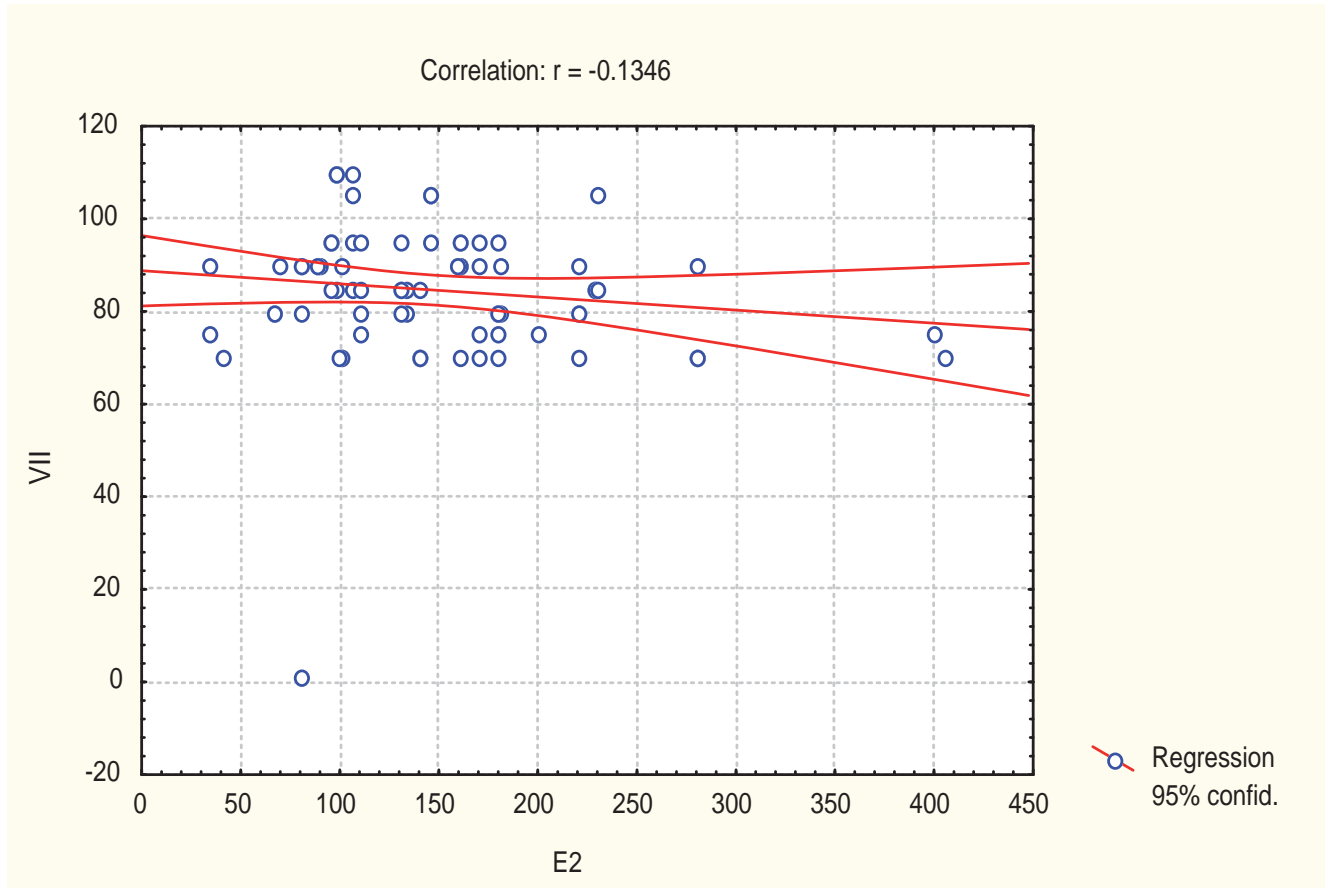


Figure 6. Correlation between factor VII and E2

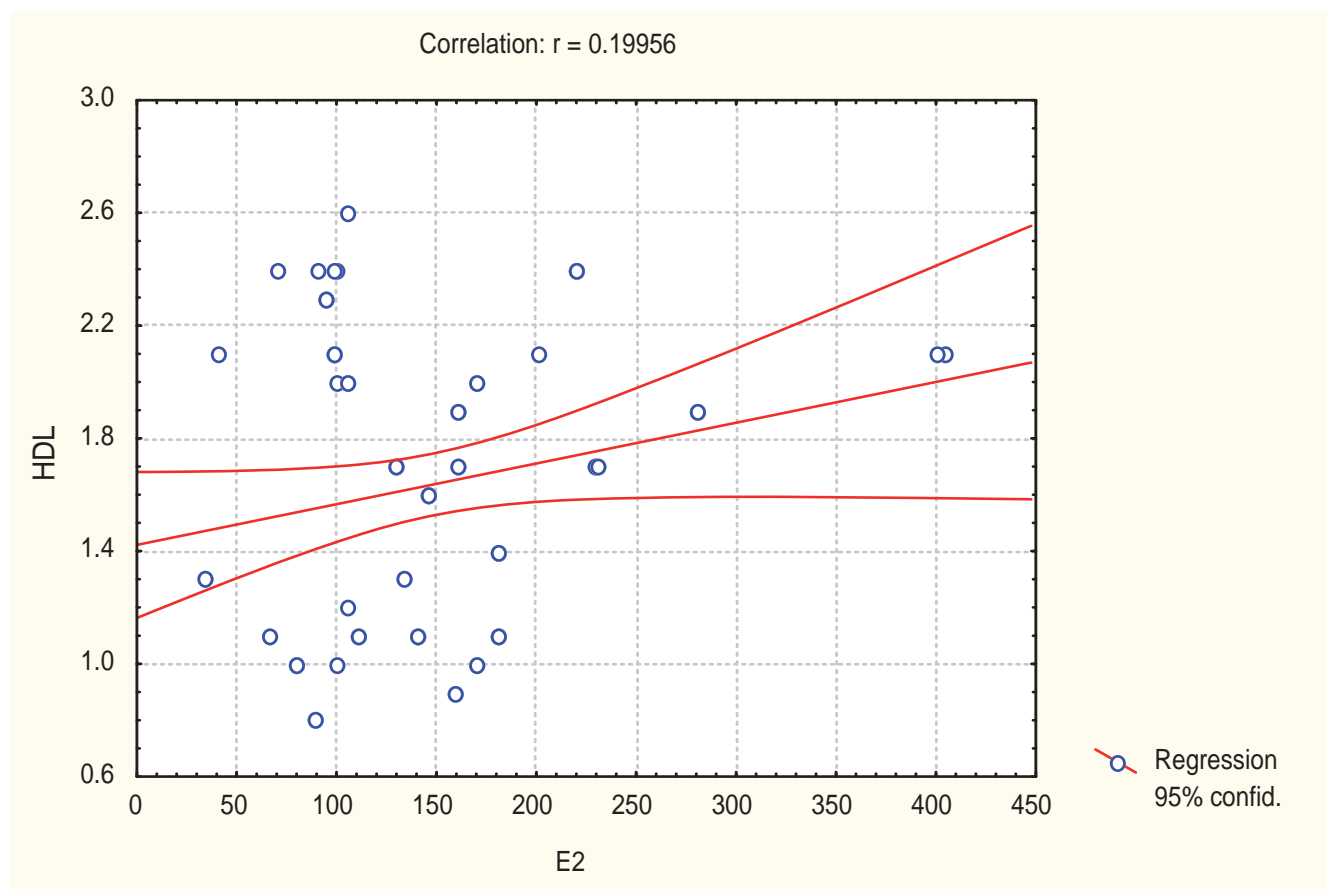
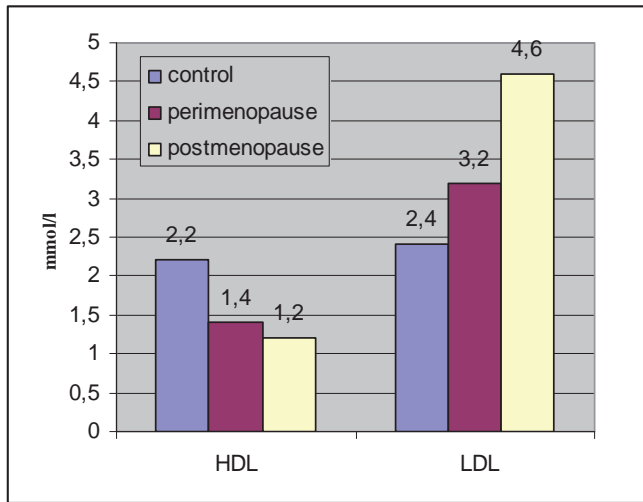


Figure 7. Correlation between HDL-C and E2



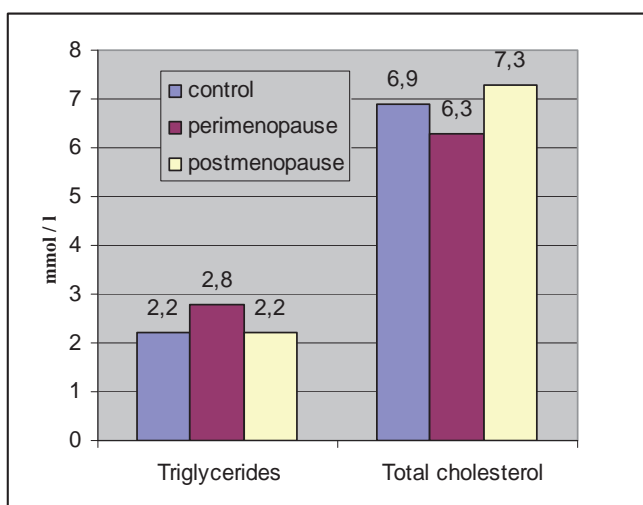
**Figure 8.** HDL-C and LDL- C levels before, during, and after menopause

those who are not receiving this kind of therapy (10). It has also been shown that fertile women have lower levels of PAI-1 than men of the same age, which is not the case with women in menopause.

Our study is in agreement with these findings. We have shown that a high E2 concentration is positively correlated with the TPA Ag level, or fibrinolytic potential, and is negatively correlated with the level of inhibitors of fibrinolysis (PAI-1).

We could conclude that E2 partially accomplishes its cardioprotective and vasculoprotective effects by increasing the fibrinolytic potential, but the mechanisms have still not been well defined.

Change in the haemostatic system poses additional risks for onset of cardiovascular disease and thrombotic complications in postmenopausal women. The increase in factor VII in postmenopausal women could be explained by changes that occur in the endothelium secondary to the absence of estrogens, whose antioxidative effects normally counteract the initial conditions that lead to the appearance of atherogenic lesions, such as increases in LDL-C and its oxidation. This most



**Figure 9.** Triglyceride and total cholesterol levels before, during, and after menopause

probably leads to activation of the coagulation process where factor VII plays a key role.

Vast numbers of studies report changes in the haemostatic system associated with advancing age, and these are in direct relation with estradiol status. Fibrinogen levels and factor VII activity (13) markedly increase in the period of postmenopause. Fibrinogen increases during aging (14) and, in women, this increase begins in the fifth decade of life (15).

In our study, we have shown that there was also a profound decrease in HDL-C concentrations and an increase in LDL-C concentrations in both perimenopausal and postmenopausal women as compared to controls. Levels of total cholesterol and triglycerides showed no significant difference with advancing age. The protective effects of estrogens in the development of atherosclerosis have been proven in numerous experimental and clinical studies (16).

Risk factors for cardiovascular disease were examined in 2873 premenopausal and postmenopausal women within a period of 20 years of the Framingham epidemiological study (17). It has been noticed that lipid profiles had an important role in the development of atherosclerotic disease. Both prior to and during menopause, levels of HDL cholesterol are higher in women than in men, but levels of LDL-C increase with menopause. They have demonstrated that the increase of cholesterol in postmenopausal women is due to an increase in the LDL-C fraction. The VLDL fraction also increases, but there is no significant change in the HDL-C fraction.

Lipid profiles in females and males of comparable age have been examined and it has been shown that levels of LDL-C, apo B and triglycerides are higher in men than in women during the fertile period. These parameters increase in menopausal women (18). Increases in LDL-C and decreases in HDL-C are risk factors for coronary heart disease. It has been reported that in women there is an increased production of apo A-1, a major HDL lipoprotein, as compared with men and that the level of apo A-1 may be increased with estrogen administration (18). Women in the fertile period have significantly lower values of LDL-C, apo B and all lipoproteins containing apo B, but they also have higher level of HDL-C and apo A-1 as well as higher percentage ratios of HDL2/ HDL3 when compared to women in menopause. Disorders of lipid profiles in perimenopausal and postmenopausal women increase the risk of coronary heart disease. Use of estrogen replacement therapy significantly decreases this risk. Namely, levels of LDL-C are significantly decreased in postmenopausal women after administration of exogenous estrogen, whereas HDL-C and apo A-1 are significantly increased (19).

## CONCLUSION

Our data suggest a significant increase in LDL cholesterol, PAI-1 Ag and factor VII, all potential arteriosclerotic and thromboembolic risk factors, in both perimenopausal and postmenopausal women compared to the control group. There is also a significant decrease in HDL cholesterol and TPA Ag during menopause. It is obvious that there was a weak positive correlation between estradiol levels and TPA Ag concentrations as well as HDL-C concentrations.

It is also apparent that there was a weak negative correlation between estradiol levels and concentrations of PAI-1 Ag and factor VII.



This study favours the view that decreases in estradiol levels seen in perimenopausal and postmenopausal women may be responsible for the increased risk of atherosclerotic and thromboembolic complications in women after menopause.

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## THE ASSESSMENT OF KINESIS-THERAPEUTIC TREATMENT USING NUMERICAL EVALUATION OF PELVIC FLOOR MUSCLE FORCES

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## PROCENA KINEZITERAPIJSKOG TRETMANA KROZ NUMERIČKU EVALUACIJU SILA PODA KARLICE

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### ABSTRACT

**Introduction:** Numerous factors lead to the dysfunction of pelvic floor muscle in women, resulting in various disturbances, of which urinary incontinence is the most significant. In addition to surgery, treatment of stress urinary incontinence may include, for instance, exercises for strengthening the pelvic floor muscle.

**Aim:** The aim of the current study was to use a vaginal dynamometer, a device for measuring pelvic floor muscle force, to compare the pelvic floor muscle force before and after a kinesiotherapy program for women who suffer from stress urinary incontinence.

**Method:** This pilot study included 50 women, aged 30-58, who suffered from urinary stress incontinence. Patients were selected using the method of controlled sample, which excluded pregnant women, patients with inflammatory processes, and malignant and respiratory illnesses. Pelvic floor muscles were strengthened by performing Kegel exercises and the Proprioceptive Neural Facilitation Spiral-dynamic technique. Pelvic floor muscle strength was measured using a vaginal dynamometer before and after the exercise. Exercise efficiency was determined based on orally reported data about incontinence (loss of urine and quality of life) and the numerical values obtained with the vaginal dynamometer.

**Results:** The difference between pelvic floor muscle force measured by a vaginal dynamometer before and after the exercise was statistically significant ( $p=0.000$ ).

**Conclusion:** The results confirm that the vaginal dynamometer provides reliable measurements. They also suggest the superiority of the newly designed device over the previously applied conventional methods of measuring pelvic floor muscle strength.

**Key words:** pelvic floor, urinary incontinence, dynamometer

### SAŽETAK

**Uvod:** Brojni cinioi štetnim delovanjem dovode do disfunkcije mišića poda male karlice kod žena, što ima brojne posledice, od kojih je najznačajnija urinarna inkontinencija. Pored hirurškog lečenja kod stres inkontinencije primenjuje se i konzervativno lečenje odnosno vežbe za jačanje mišića poda karlice.

**Cilj** Cilj rada je da se uz pomoć uređaja za merenje mišićne sile mišića poda karlice kod žena-vaginalnog dinamometra upoređi vrednost mišićne sile pre i posle sprovedenog kineziterapijskog programa kod žena koje pate od stres urinarne inkontinencije.

**Metod:** U pilot studiji 50 žena starosne dobi od 30-58 god. koje pate od stres urinarne inkontinencije su metodom kontrolisanog uzorka iz koga su isključene trudnice, osobe sa malignim i zapaljenskim bolestima, kao i one sa ozbiljnim kardiovaskularnim i respiratornim bolestima izabrane da vežbaju mišiće poda karlice pomoću Kegelovih vežbi i PNF Spiraldinamik tehnike. Snaga mišića poda karlice je merena vaginalnim dinamometrom pre i posle vežbi. Na osnovu usmeno dobijenih podataka o inkontinenciji (izveštaj o gubitku urina i kvalitetu života) i na osnovu dobijenih numeričkih vrednosti izmerenih vaginalnim dinamometrom utvrđena je efikasnost vežbi.

**Rezultati:** Razlika između vrednosti mišićne sile merene vaginalnim dinamometrom pre i posle vežbi je statistički značajna ( $p=0,000$ ).

**Zaključak:** Ova studija na osnovu dobijenih rezultata ukazuje na to da vaginalni dinamometar obezbeđuje pouzdana merenja. Iz toga proizilazi da novo konstruisan vaginalni dinamometar ima idejnih i mernih prednosti u odnosu na dosad korišćene konvencionalne metode merenja snage mišića poda karlice kod žena.

**Ključne reči:** pod karlice, urinarna inkontinencija, dinamometar

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## INTRODUCTION

Stress urinary incontinence (SUI) in women is defined as an involuntary loss of urine in cases of strain, sneezing or coughing (1). It is a very frequent disorder, increasingly affected by age and number of deliveries (2). It is a serious social and hygiene problem (3,4,5). Numerous factors contribute to SUI, and many solutions to the problem have been proposed (6). Conservative, non-surgical treatments that have been suggested include kinesis therapy, such as exercises for strengthening the pelvic floor muscle (PFM), bio-feedback, electric stimulation and vaginal cones (7,8,9). In order to decrease SUI, traditional exercises for strengthening PFM are mostly limited to Kegel exercises. They consist of static contractions of the PFM. In addition to Kegel exercises, the PNF Spiral-dynamic technique, i.e., proprioceptive neural stimulation that follows the principle of body diagonals and spiral three-dimensionality of movements, is also applied (10,11,12). Since the aim of physical therapy is to strengthen the PFM, a reliable direct measurement of muscle strength is essential for the evaluating the effects of such treatment.

So far, PFM strength has been measured using digital assessment (13,14,15) and indirect methods, such as perineometry measurement, perineal ultrasound and surface electromyography (16,17,18).

An attempt to develop a dynamometer for measuring isometric PFM force has been reported (Doumulin 2003) (19,20).

Recognising the importance of direct measurements of PFM strength in the evaluation of SUI, and the application of kinesis therapy as treatment, we decided to construct a new device that can reliably and numerically display the measured PFM strength before and after the exercises.

The aim of this paper is to describe the design of a new dynamometer that provides unique data in comparison with the previously employed measurement techniques. The device's clinical application in persons who suffer from SUI will also be discussed.

## MATERIALS AND METHODS

The study was approved by Ethics Committee and carried out at the Centre for Physical Therapy and Rehabilitation, Clinical Centre in Kragujevac during 2007–2008.

The study included 50 patients aged 30–58. The experimental group included women who had 1–3 deliveries and suffered from SUI (based on reported loss of urine and quality of life). Patients were randomly selected for measurements of PFM force using the vaginal dynamometer. After the measurements, they were exposed to exercises for PFM strengthening through the PNF Spiral-dynamic technique method and Kegel exercises. After 3 months, the control measurements were performed using the vaginal dynamometer. Pregnant women or those who suffered from inflammatory or malignant diseases of pelvic organs, or who had serious cardiologic or respiratory diseases, were not included in the study.

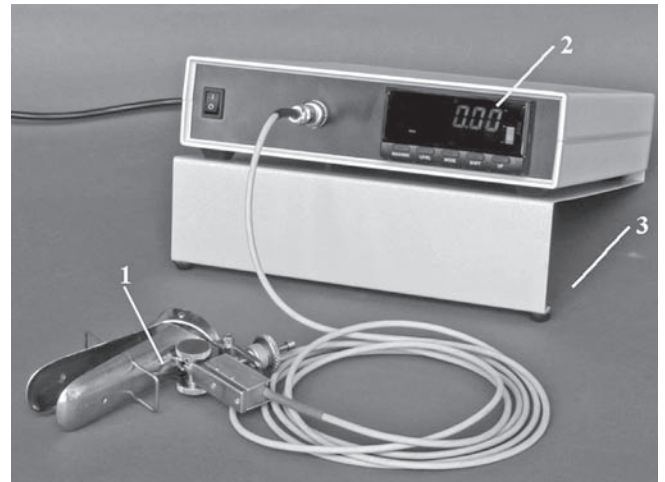
All women were interviewed about the extent of their SUI (i.e., a small level of discomfort, a small problem, a great problem, or a huge problem). Subsequently, PFM strength was measured using the newly constructed dynamometer.

Precise, numerical and reliable determination of PFM force expressed in daN (decaNewtons) is possible with the applica-

tion of a vaginal dynamometer. It was designed at the Faculty of Mechanical Engineering in Kragujevac, in collaboration with professors of the Medical and Mechanical Engineering Faculties.

The dynamometer consists of:

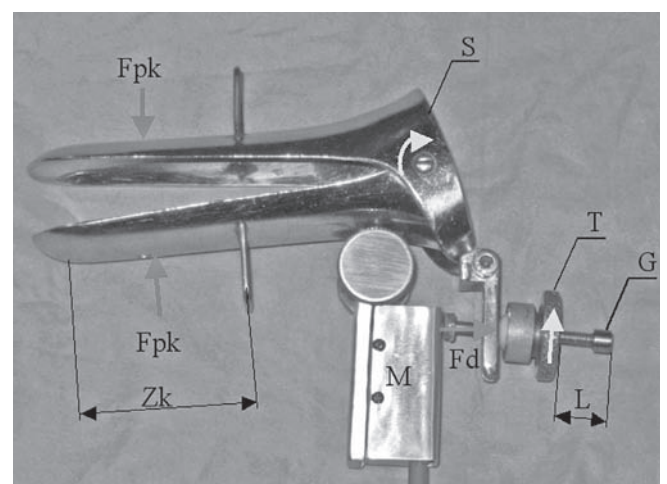
1. An instrument for measuring the PFM contraction forces with a cable (Position 1)
2. A measuring device with a display unit and analogue output for monitoring (Position 2)



**Figure 1.** Instrument for measuring the contraction forces of the pelvic floor muscles -vaginal dynamometer

The body of the instrument consists of a redesigned speculum, which is used in gynaecology, with a sensor for force measurement. This newly designed dynamometer employs the principle of measuring bands and the Winston Bridge. The force is physically transferred to the dynamometer and then transformed into an electrical signal that is proportional to the magnitude of the force.

Measurements are made in the following way: First, the methodology of applying the new device is explained to each patient. Then, the patient takes the necessary position on the gynaecological table. The instrument is inserted with closed



**Figure 2.** Instrument for measuring the contraction forces of the pelvic floor musculature S- integral composition of the speculum, M- sensor for measuring the contraction forces of the pelvic floor musculature, T- load wheel, G-limiter, Fpk- the contraction forces of the pelvic floor musculature, Fd-force on the sensor for measuring of the force, Zk-contact zone



branches up to stopper G, and the wheel T is turned to separate the branches until contact pressure between the vaginal wall and the instrument is established. When the instrument is placed, the patient initiates a static contraction, straining the PFM for 6 seconds, and PFM force (Fpk) is applied to the branches of the instrument. Thus, physical application of PFM force (Fpk) is transmitted to the dynamometer as the force Fd and turned into an electric voltage signal with a value proportional to the strength of the force (Fpk). After a 12 second pause, the procedure is repeated 5 times in order to calculate a mean value. The numerical value of the measured force is read from the display of the instrument.

Calibration is performed with a known unit of pressure (Fpk = 1 daN) that is exerted in the middle of contact zone Zk.

After the measurement of PFM force using the vaginal dynamometer and obtaining the data, the patients were either trained to exercise using the PNF Spiral-dynamic technique or taught how to perform Kegel exercises at the Centre for Physical Therapy and Rehabilitation. After the training, the patients practiced at home. They visited a physiatrist or a physical therapist at the Centre monthly to report on the regularity of practice.

After 3 months of exercise, PFM strength was measured again with the vaginal dynamometer.

## RESULTS

**Table 1** shows the values of PFM force (in daN) measured using the vaginal dynamometer before and after exercise.

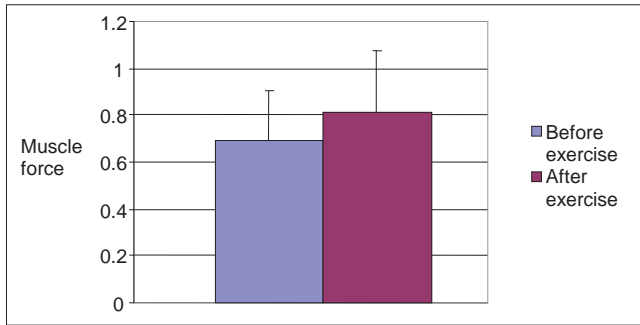
ordinal number r	age	number of deliveries	incontinence	PMF forces before exercise	PMF forces after exercise
1	43	1	yes	0,429	0,442
2	43	1	yes	0,929	1,103
3	32	2	yes	0,951	1,281
4	55	2	yes	0,352	0,547
5	50	2	yes	0,621	0,656
6	38	1	yes	0,479	0,456
7	43	1	yes	0,419	0,432
8	41	3	yes	0,475	0,513
10	38	2	yes	0,841	0,956
11	44	3	yes	0,486	0,506
12	46	3	yes	0,588	0,695
13	30	1	yes	1,098	1,252
14	33	2	yes	0,960	1,082
15	47	1	yes	0,565	0,623
16	51	3	yes	0,402	0,418
17	38	2	yes	0,746	1,272
18	39	1	yes	0,998	1,094
19	47	1	yes	0,672	0,622

ordinal number r	age	number of deliveries	incontinence	PMF forces before exercise	PMF forces after exercise
20	37	2	yes	0,645	0,641
21	49	3	yes	0,515	0,488
22	37	2	yes	0,710	0,779
23	32	1	yes	0,913	1,049
24	57	3	yes	0,537	0,473
25	52	3	yes	0,332	0,644
26	44	1	yes	0,673	0,812
27	38	2	yes	0,522	0,660
28	48	3	yes	0,440	0,582
29	50	2	yes	0,849	0,889
30	35	1	yes	0,897	0,996
31	33	1	yes	0,951	1,051
32	47	2	yes	0,584	0,748
33	46	1	yes	1,102	1,357
34	49	3	yes	0,987	1,234
35	35	2	yes	0,756	0,902
36	37	1	yes	0,646	0,790
37	56	1	yes	0,525	0,679
38	38	1	yes	0,838	0,972
39	42	2	yes	0,430	0,652
40	47	2	yes	0,510	0,672
41	39	1	yes	0,720	0,854
42	31	1	yes	0,990	1,011
43	32	1	yes	1,012	1,211
44	42	2	yes	0,692	0,785
45	49	1	yes	0,735	0,898
46	58	2	yes	0,690	0,770
47	38	1	yes	0,558	0,701
48	37	1	yes	0,910	1,120
49	32	1	yes	0,732	0,867
50	50	1	yes	0,440	0,642

**Table 2.** The analysis of PFM force values in women before and after exercise revealed a significant difference ( $p = 0.000$ ).

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	VAR00005	.6909	49	.2141	3.059E-02
	VAR00006	.8139	49	.2599	3.713E-02





**Figure 3.** Values of PFM force in women measured by a vaginal dynamometer before and after exercise

## DISCUSSION

This study showed that, in addition to surgical treatment of stress urinary incontinence, a kinesis program of pelvic floor muscle strengthening may play an important role (7,8,9). Measuring women's pelvic floor strength by using the vaginal dynamometer before and after a 3-month kinesis program revealed an increase in muscle force. Kinesis therapy is not only one form of primary prevention but also an inseparable part of treating pelvic weakness. The best known therapy is Kegel exercises,

static contractions of the pelvic floor muscle, which have been the most frequently applied technique described in the literature (6,9,10,13,15). In addition to Kegel exercises for pelvic floor muscle strengthening, we also used the PNF and Spiral-dynamic technique (11,12). The importance of kinesis therapy in the treatment of stress urinary incontinence has been emphasized in numerous studies, but the strength of the pelvic floor muscle was determined subjectively by digital palpation. A digital pelvic assessment rating scale with grades 0–5 was most often used. After a 3-month period of kinesis therapy, studies have reported an average increase of muscle strength of one grade (6,9,10,11,12,13,14,15). When measured with the vaginal dynamometer, the increase in pelvic floor muscle was 0.12 daN.

In comparison with previous reports, this study measured pelvic floor muscle strength using an instrument, the vaginal dynamometer, which provided numerical values. The results clearly point to an increase of pelvic strength after a program of kinesis therapy.

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## EFFICIENCY OF ARGON LASER TRABECULOPLASTY IN OPEN ANGLE GLAUCOMA THERAPY

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## EFIKASNOST ARGON LASER TRABEKULOPLASTIKE U TERAPIJI GLAUKOMA OTVORENOG UGLA

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### ABSTRACT

**Introduction.** Argon laser trabeculoplasty (ALT) is a method for the reduction of intraocular pressure (IOP) that involves applying a laser to the area of the trabecular meshwork of the chamber angle in patients with open angle glaucoma.

**Aims.** To evaluate the efficiency and safety of ALT in open angle glaucoma therapy.

**Material and method.** A prospective examination of 84 eyes from 49 patients who were primarily treated with medications but did not achieve sufficient control of their IOP. Prior to ALT, a detailed ophthalmology check had been performed. After the treatment, follow-up visits were scheduled at 24 hours, 1 month, 3 months, 6 months, 1 year, 2 years and 4 years. The success of the treatment was defined by  $IOP \leq 21$  mmHg, with no further progression of disc or visual field changes.

**Results.** The average value of IOP before ALT was  $25.28 \pm 1.56$  mmHg. After 24 hours, 19 eyes (23.5%) had a transitory rise in the IOP of  $< 4$  mmHg. One month after the treatment the average IOP was  $19.68 \pm 2.26$  mmHg, and 3 months later it was  $18.01 \pm 1.87$  mmHg. At 6 months it was  $17.4 \pm 1.65$  mmHg, at 1 year  $17.96 \pm 2.44$  mmHg, at 2 years  $18.22 \pm 2.65$  mmHg and at 4 years  $18.49 \pm 2.95$  mmHg. The target pressure of  $\leq 21$  mmHg was achieved after 1 month in 77.8% of the patients, after 3 months in 93.8%, after 6 months in 93.8%, after 1 year in 80.2%, after 2 years in 75.3% and after 4 years in 66.7%. Two years after the treatment, a filtering surgery was performed in one case (1.2%), due to an unreduced IOP. At the end of the fourth year after the intervention, the number of examined eyes was 73, and a filtering surgery was performed for the unreduced IOP on 8 eyes (9.9%). The average reduction in IOP one year after the intervention was  $7.32 \pm 2.84$  mmHg, after 2 years  $7.16 \pm 2.98$  mmHg, and after 4 years  $6.84 \pm 3.33$  mmHg ( $p < 0.01$ ).

**Conclusion.** ALT is a safe and efficient method for IOP reduction in patients with open angle glaucoma, which can postpone filtering surgery to a great extent.

**Key words.** Open angle glaucoma, argon laser trabeculoplasty, intraocular pressure.

### SAŽETAK

**Uvod.** Argon laser trabekuloplastika (ALT) je metoda sniženja intraokularnog pritiska (IOP) aplikacijom laserskih pečata u području trabekularne mreže komornog ugla kod pacijenata obolelih od glaukoma otvorenog ugla.

**Cilj.** Evaluacija efikasnosti i bezbednosti ALT u terapiji glaukoma otvorenog ugla.

**Materijal i metod.** Prospektivnim ispitivanjem je obuhvaćeno 84 oka, 49 pacijenta prethodno tretiranih medikamentnom terapijom kojom nije postignuta zadovoljavajuća kontrola IOP. Pre izvođenja ALT urađen je detaljan oftalmološki pregled. Nakon izvođenja intervencije kontrolni pegledi su obavljani nakon 24h, mesec dana, 3 meseca, 6 meseci, nakon 1 godine, 2 godine i 4 godine. Uspeh tretmana smo definisali kao  $IOP \leq 21$  mmHg bez dalje progresije ekskavacije papile vidnog živca i progresije ispada u vidnom polju.

**Rezultati.** Prosečna vrednost IOP pre izvođenja ALT je bila  $25,28 \pm 1,56$  mmHg. 24h od intervencije kod 19 očiju (23,5%) zabeležen je tranzitorni skok IOP koji je iznosio  $< 4$  mmHg. Nakon mesec dana od intervencije prosečna vrednost IOP je iznosila  $19,68 \pm 2,26$  mmHg, 3 meseca  $18,01 \pm 1,87$  mmHg, 6 meseci  $17,4 \pm 1,65$  mmHg, 1 godine  $17,96 \pm 2,44$  mmHg, 2 godine  $18,22 \pm 2,65$  mmHg i 4 godine  $18,49 \pm 2,95$  mmHg. Ciljni pritisak  $\leq 21$  mmHg je postignut nakon 1 meseca kod 77,8%, 3 meseca 93,8%, 6 meseci 93,8%, 1 godine 80,2%, 2 godine 75,3% i 4 godine 66,7%. Dve godine od tretmana u jednom slučaju je zbog neregulisanog IOP urađena filtraciona operacija (1,2%). Na kraju četvrte godine od intervencije broj posmatranih očiju je iznosio 73, jer je zbog neregulisanog IOP kod 8 očiju izvedena filtraciona operacija (9,9%). Prosečno postignuto sniženje IOP godinu dana od intervencije iznosi  $7,32 \pm 2,84$  mmHg, dve godine od intervencije  $7,16 \pm 2,98$  mmHg, a četiri godine od intervencije  $6,84 \pm 3,33$  mmHg ( $p < 0,01$ ).

**Zaključak.** ALT je bezbedna i efikasna metoda sniženja IOP kod pacijenata sa glaukomom otvorenog ugla koja u visokom procentu može odložiti filtracionu operaciju.

**Ključne reči.** Glaukom otvorenog ugla, argon laser trabekuloplastika, intraokularni pritisak

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## INTRODUCTION

Glaucoma is a chronic optic neuropathy that manifests with an increased intraocular pressure (IOP), cup disc ratio and paracentral scotomas in the visual field. It is progressive and often followed by an unfavourable clinical course. According to all relevant statistics, it is one of the three most frequent causes of blindness worldwide and in Serbia (10-15%). The prevalence of glaucoma is 1-2% in persons older than 40 years of age, and it progressively increases with age. Therefore, the prevalence is 3% for persons between 70 and 80 years of age.

According to the 2005 data from the Blind Persons' Society register for Serbia and Montenegro, out of 12,000 blind persons who were registered, 1,500 had been suffering from glaucoma (1). Primary prevention is not available, but due to a timely diagnosis and adequate therapy, it has been possible to slow down the clinical course of the illness and significantly lower the percentage of cases that end in blindness.

Open angle glaucoma is a multi-factorial illness, which is initiated by a number of risk factors, such as higher IOP, age, inheritance, sex, race, diabetes, hypertension, vasospasm and myopia (2,3,4,5). IOP is the most significant risk factor, and the illness itself is of a progressive nature with irreversible consequences, so the treatment has been mostly focused on IOP reduction. Prevention of the loss of visual functions by glaucoma begins with a therapy that involves efficient and energetic medications. In this case, a great deal of attention must be paid in order to determine that the therapy is safe and does not cause more damage than the illness itself. In those cases in which a satisfactory IOP has not been achieved, ALT can be conducted in order to achieve an additional reduction of IOP prior to deciding to perform a filtering surgery. In addition to this secondary role, ALT is also efficient as a primary therapy of open angle glaucoma.

ALT reduces IOP by applying a laser to the area of the trabecular meshwork of the chamber angle in patients with open angle glaucoma. The introduction of this method in practice to treat open angle glaucoma was first done by Krasnov, who in 1973 (6) performed a lasertrabeculopunctura of Schlemm's canal using a laser, but this reduction in the IOP only lasted for a short period. In 1979, Wise and Weiter achieved a consistent reduction of IOP by applying spots from an impenetrable argon laser (7). This intervention was successful in most cases, but the results have decreased over the course of time. After one year, the IOP was controlled in 67-80% cases, 5 years after the intervention in 35-50%, and 10 years after the intervention in 5-30% (8,9).

The complications from ALT are small and temporary. Early complications include transitory sight that is blurred just after the intervention and is caused by contact glass pressure and methylcellulosis, transitory laser-induced increase in the IOP and mild iritis. Quick deterioration of the visual field is rare, but it does represent a rather serious complication that can be encountered in patients with advanced glaucoma and high IOP values prior to surgery. Small peripheral anterior synechiae appeared with a large number of posterior spots in patients with a narrow chamber angle. Later complications include a gradual increase in the IOP due to a smaller effect of the ALT treatment and a decrease of the efficiency subsequent to filtering surgery. Although there are not enough data to support this thesis, it has been shown that a three-fold higher

frequency of encapsulated filtering cushion after filtering surgery has been conducted in persons who had previously undergone ALT (10).

The major aim of our work is to assess how efficient and safe Argon laser trabeculoplasty is in open angle glaucoma therapy.

## MATERIAL AND METHOD

Research conducted at the Clinic of Eye Diseases, Clinical Centre in Kragujevac in the period from January 1, 2004 to September 30, 2008 included 84 eyes from 49 patients who had been previously treated with medications and did not achieve a satisfactory control of IOP. The intervention was performed with a Zeiss Visulas 532 laser.

The inclusion criteria used in this study were, as follows: i) open angle glaucoma not treated by medications, according to the type of primary open angle glaucoma (POAG) and secondary open angle glaucoma (pseudoexfoliative glaucoma – PEX and pigmented glaucoma), ii) IOP > 22 mmHg, iii) age  $\geq$  50, iv) a cup disc ratio of 0.5 or more, v) an asymmetry of the findings between two eyes > 0.2, vi) visual acuity > 0.2 and vii) phakic eyes.

The exclusion criteria were as follows: i) patients with progression of the cup disc ratio, ii) patients with advanced damage to their visual field, iii) IOP higher than 30 mmHg, iv) patients who previously had eye surgery, such as aphakia, pseudophakia and filtering surgery, v) patients expected to undergo some sort of ocular surgical intervention, vi) corneal illnesses preventing visualisation of the trabecular meshwork of chamber angle and a precise measurement of the IOP, vii) monocular patients, viii) high myopia, ix) patients who were on systemic or local corticosteroid therapy, and x) patients with illnesses that might require a corticosteroid treatment.

Before the treatment started, a detailed ophthalmology exam was performed, which included the following: i) the history of the current illness and the prior medication therapy that was used in order to determine the best corrected visual acuity, ii) the measurement of IOP by the Goldmann applanation tonometer, iii) biomicroscopy of the anterior eye segment, and iv) gonioscopy and stereoscopy of the optic nerve head and retinal nerve fiber layer in the biomicroscope by either the indirect method, which uses an indirect fundus lens (78D or 90D) or by the direct method, which uses the Goldmann 3-mirror or visual field charting on the Humphrey automated perimeter, respectively, using the 30-2 Threshold program.

Prior to intervention, each patient received 250 mg acetazolamide per os tbl in order to prevent a laser induced-increase of IOP. The intervention was performed with a topical anaesthetic, sol tetracain 0.5%, right before the treatment. ALT was performed using Goldmann contact glass with 3 mirrors and an anti-reflective layer. Methylcellulosis was used as a medium between the cornea and the glass. Having analyzed the elements of the chamber angle, the spot application was performed. The lower 180° chamber angle was treated clockwise, at the junction of the anterior non-pigmented and the posterior pigmented part of the trabecular meshwork. Fifty spots per patient were applied. The standard parameters were a spot size of 50  $\mu$ m and an exposition of 0.1 s, while the power was individually allocated within a 600- to 1,000-mW parameter until the desired effect, in the form of gas bubbles, appeared





or the eye became bleached where the laser was applied. Patients were given another tbl of 250 mg acetazolamide in the evening, followed by topical sol dexamethasone-neomycin four times per day for seven days in order to prevent a topical inflammatory reaction, which could be proceeded with running anti-glaucoma medication therapy. Periodic check-ups were scheduled for the first 24 hours, 1 month, 3 months, 6 months, 1 year, 2 years and 4 years after the treatment. During the scheduled periodic examinations, the visual field was examined with the Humphrey automated perimeter using the 30-2 Threshold program.

The success of the treatment was defined as IOP ≤ 21 mmHg, with no further progression of disc or visual field changes and a drop in the progression in the visual field.

Statistics were calculated with the statistics software, SPSS 10.0 for Windows XP, for descriptive statistics that included absolute numbers, average value and standard deviations. The Student's T-test was used for the comparison of the average values before and after the intervention.

## RESULTS

Eighty-four eyes from forty-nine patients were analyzed. Fifty-one eyes had primary open angle glaucoma (72.6%), nineteen eyes had pseudoexfoliative glaucoma (22.6%) and four eyes had pigment glaucoma (4.8%). The average age of the patients was 64.65 ± 5.60 years (range = 54-73 years). Twenty-eight men (57.1%) and twenty-one women (42.9%) were examined. (Table 1.)

All patients had been previously treated with topical medication. Forty-eight eyes (57.1%) were treated with one medication, thirty eyes (35.7%) were treated with two medications and six eyes (7.1%) were treated with three medications. The average number of medications was 1.5 (SD 0.63). The average IOP value prior to Argon laser trabeculoplasty was 25.28 ± 1.56 mmHg (range = 23-29 mmHg). For 19 eyes (23.5%), the transitory IOP increase was < 4 mmHg. Peripheral anterior synechiae were detected in eleven eyes (13.6%), and a mild uveal reaction was detected in four cases (4.9%). One month after the intervention, the target IOP of ≤ 21 mmHg was achieved in 63 eyes (77.8%), where the average IOP value was 19.68 ± 2.26 mmHg (range = 16-24 mmHg). Three months after the treatment, the target IOP was recorded in 76 eyes (93.8%), with an average IOP value of 18.01 ± 1.87 mmHg (range = 16-23 mmHg). Six months after the treatment, the average IOP value was 17.4 ± 1.65 mmHg (range = 16-23 mmHg), and the target pressure was achieved in 76 cases (93.8%). One year after the intervention, a small decrease in the intervention efficiency was detected, with the target IOP achieved in 65 cases (80.2%) and an average IOP value of 17.96 ± 2.44 mmHg (range = 16-24 mmHg). Two years after the treatment, the average IOP value was 18.22 ± 2.65 mmHg (range = 16-24 mmHg), and the target IOP was reached in 61 eyes (75.3%). Due to an unresponsive IOP, filtering surgery was performed in one case (1.2%). At the end of the fourth year, the number of examined eyes amounted to 73, due to the fact that filtering surgery was performed on 8 eyes (9.9%) with unresponsive IOP. At this time, the average IOP value was 18.49 ± 2.95 mmHg (range = 16-24 mmHg), and the target IOP was achieved in 54 eyes (66.7%). (Table 2, Table 3.)

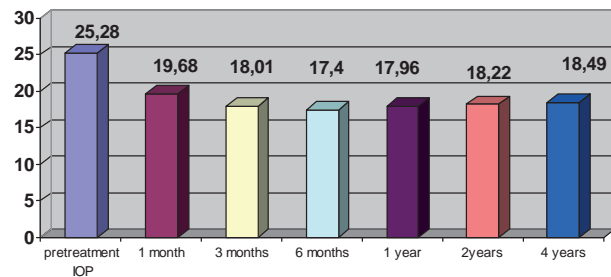
**Table 1.** Patient data

No. patients (eyes)	49 (84)
Age mean ± SD	64.65 ± 5.60
Sex	
Male	28 (57.1%)
Female	21 (42.9%)

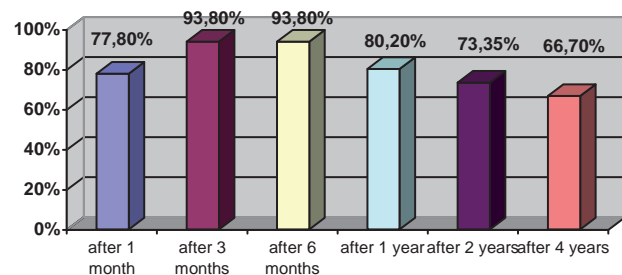
Statistically, a significant decrease in the IOP was achieved when compared to the initial values one year after the treatment (7.32 ± 2.84 mmHg), two years after (7.16 ± 2.98 mmHg) and four years after (6.84 ± 3.33 mmHg) (p < 0.001, for all).

## DISCUSSION

Many studies have proven that ALT is efficient in decreasing the IOP with open angle glaucoma. The criteria and percentage that show the success of the treatment after the first year of intervention has varied among the studies, with a range between 70-90%. Immediately after the intervention, ALT significantly reduced the IOP. Thomas et al. analyzed ALT efficiency in 1982, with a focus on patients who were on optimal drug therapy. Their study demonstrated that IOP was reduced by 6.4 mmHg (26%) five months after the treatment of 237 patients with POAG (11). In 1990, the Glaucoma Laser Trial Research Group has shown that a bigger reduction of IOP can be achieved with those patients who had ALT performed as the primary procedure. There was an average IOP reduction of 9 mmHg (33% three months after it was performed on 264 patients) (9).



**Table 2.** Effect of ALT on IOP reduction in mmHg (mean ± SD)



**Table 3.** Success rate of ALT (%)



Our research has found that the average IOP decreased by the following amounts: 1 year after treatment,  $7.32 \pm 2.84$  mmHg; 2 years after treatment,  $7.16 \pm 2.98$  mmHg and 4 years after treatment,  $6.84 \pm 3.33$  mmHg. This is in agreement with the results obtained from Thomas et al. During the first week after the treatment, no serious complications were recorded. The most serious complication was a laser-induced rise of IOP, and it was detected in 19 eyes (23.5%) but was less than 4 mmHg in all cases. Our results do not record a significant laser-induced rise of IOP, which is contrary to the results of the Glaucoma Laser Trial Group, whose results showed that there was a relatively frequent IOP rise after ALT, with a rise of more than 5 mmHg in 34% of the cases and a rise of 10 mmHg in 12% of the cases. The patients who were treated for 180° of chamber angle were the ones who had the highest laser-induced IOP rise (12). These results should be clarified before and after the surgery, using acetazolamide on the very day of surgery, as well as with an IOP time measurement. Thus, control measurements of the IOP were taken one hour after the surgery. It is important to note that the frequency and complexity of IOP increases become higher, as more energy is used when there is a 360° chamber angle treatment with a more posterior position of the spot, with a higher pigmentation of the chamber angle and with a lower presurgical chamber liquid drainage (13). The increase in the IOP is most frequent 2 hours after the surgery, although a postponed IOP increase can also occur. Therefore, close monitoring of the patient is advised for four hours after the intervention. The mechanism behind the laser-induced increase in IOP has not been fully clarified, but it is assumed that it appears as a consequence of the trabecular meshwork being swollen or as an obstruction of trabeculotomy swelling by debris. Topical use of corticosteroids cannot prevent it, nor can synthesis inhibitors of prostaglandins, while the use of synthesis blockers of the aqueous humour and  $\alpha$ -2 agonist reduce the incidence of a laser-induced rise of IOP in almost 2/3 of all cases (14).

Peripheral anterior synechiae are present in a high percentage after ALT, but their appearance is of little clinical importance and has no influence on the reduction of IOP. In 13.6% of our cases, they appeared when higher energy was used and at more posterior spots. Post-laser uveitis is mild and rare. In our study, it appeared in 4.9% of all cases and was successfully treated with topical corticosteroid therapy.

There was also a positive effect that was noted with diurnal fluctuations of IOP in successfully treated patients (15).

Many studies have proven that the ALT effect decreases when IOP is reduced. Schwartz et al. have proven that the treatment was successful in 77% of patients for two years after the treatment but that the success decreased to 46% five years after the treatment (16). In 1996, Weireb et al. showed that ALT was efficient in 50% of the cases in a five-year study, with a decrease rate of 6-10% annually (17). Spaeth and Baez have come to the conclusion that only one-third of their patients displayed a satisfactory IOP reduction five years after the intervention. Efficiency decreases mostly during the first year and then gradually decreases by 10% annually (18). Our research has shown that one year after the intervention, the target IOP was achieved in 80.2% of patients, 2 years after the intervention in 75.3% and 4 years after in 66.7%, which is in agreement with previous data. Since the selection of patients does affect the success of the treatment, one of the criteria for inclusion in this study was an age of  $\geq 50$ . Persons who are younger than 40 years show a weaker effect on IOP reduction, have stronger post surgical inflammation and paradoxically have a prolonged IOP increase (19). The disparities due to age can be explained by the fact that age mellows the walls in Schlemm's canal and the trabeculoma, which responds better to the tightening of the inner trabecular ring after ALT. The Advanced Glaucoma Intervention Study (AGIS) (20) has proven that unsuccessful ALT correlates with a younger age and a larger presurgical IOP value.

Our study has shown that ALT is a safe and effective method that can achieve a satisfactory reduction of the IOP in patients with open angle glaucoma who have not had success with drug therapy to target and reduce the IOP. The method is a simple out-patient procedure, which does not have any significant or long-lasting side effects or complications. ALT can postpone the need for filtering surgery for a high percentage of patients. After four years in our study, filtering surgery was only performed in eight cases (9.9%). Any undesired ALT side effects weaken over the course of time and limit the repetition of the treatment for one more application to the remaining 180° of the chamber angle due to structural changes in the trabecular meshwork chamber angle.





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All illustrations (photographs, graphs, diagrams) will be considered as figures, and numbered consecutively in Arabic numerals. The number of figures included should be the least required to convey the message of the paper, and no figure should duplicate the data presented in the tables or text. Figures should not have titles. Letters, numerals and symbols must be clear, in proportion to each other, and large enough to be readable when reduced for publication. Figures should be submitted as near to their printed size as possible. Figures are reproduced in one of the following width sizes: 8 cm, 12 cm or 17 cm, and with a maximal length of 20 cm. Legends for figures should be given on separate pages.

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Both letters concerning and those not concerning the articles that have been published in *Medicus* will be considered for publication. They may contain one table or figure and up to five references.

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All manuscripts will be carefully revised by the publisher desk editor. Only in case of extensive corrections will the manuscript be returned to the authors for final approval. In order to speed up publication no proof will be sent to the authors, but will be read by the editor and the desk editor.





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